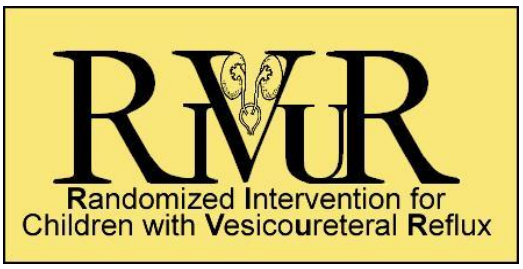

Official Protocol and Manual of Procedures

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Data Collection Forms

ADJ	Endpoints Adjudication form
AEF	Adverse Events Form
BDF	Baseline Demographic Form
BMH	Baseline Medical History Form
BSR	Blood Specimen Results Form
CLR	Central Lab Blood Results Form
CMF	Concomitant Medication Form
CSL	Central Lab Specimen Shipping Form
DDF	Drug Distribution Form
DMF	DMSA Results Form
DSF	DMSA Sedation Form
DSS	DMSA Scan Shipping Form
DVQ	DV Questionnaire
ERF	Eligibility and Randomization Form
ESD	Endpoint Source Documentation Cover Sheet
EXF	Exit Form
FDA 3500A	Medwatch FDA 3500 A Form
FUP	Protocol Follow-up Contact Form
ICT	Informed Consent Tracking Form
LIQ	LIA Questionnaire
MCA	Medical Care Abstraction Form
MCN	Medical Care Notification Form
MDD	Medication Dispensing and Dosing Form
MDL	Medication Distribution Log
MDL-P	Medication Distribution Log – Pharmacy
MRF	Medication Return Form
NIDDK-BSL	NIDDK Genetics Repository Blood Shipping Log
NIDDK-USL	NIDDK Biosample Repository Urine and Blood Shipping Log
PCF	Participant Contact Form
PEF	Physical Exam Form
PSL	Participant Screening Log
RCF	Record of Contacts Form
RFF	RIVUR Follow-up Form
RSL	Rectal Swab Shipping Log
RSR	Rectal Swab Results Form
SCF	Specimen Collection Form
URF	Ultrasound Results Form
USR	Urine Specimen Results Form
VRF	VCUG Results Form
VSF	VCUG Sedation Form
VUS	VCUG/Ultrasound Scan Shipping Form
FSS	FDA Signature Sheet
ITL	Initials and Training Log

PROTOCOL

*R*ANDOMIZED *I*NTERVENTION FOR CHILDREN WITH *V*ESICO*U*RETERAL *R*EFLUX
(RIVUR)

A Randomized, Double-blind, Placebo-controlled Trial of Antimicrobial Prophylaxis in Children with Vesicoureteral Reflux and Urinary Tract Infection

Funded by the National Institute of Diabetes and Digestive and Kidney Diseases
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I. SUMMARY

This multicenter, randomized, double-blind, placebo-controlled trial is designed to determine whether daily antimicrobial prophylaxis is superior to placebo in preventing recurrence of urinary tract infection (UTI) in children with vesicoureteral reflux (VUR). The basic eligibility criteria are: (1) age at randomization of at least 2 months, but less than 6 years, (2) a diagnosed first or second febrile or symptomatic UTI ($_{F/S}$UTI) within 112 days prior to randomization that was appropriately treated, and (3) presence of Grade I-IV VUR based on voiding cystourethrogram (VCUG). Children with co-morbid urologic anomalies, history of allergy to the study intervention, and other conditions or chronic diseases that might interfere with completing the study protocol will be excluded.

Patients will be randomly assigned to treatment for 2 years with daily antimicrobial prophylaxis (trimethoprim-sulfamethoxazole) or placebo. The study is designed to recruit 600 children (approximately 300 in each treatment group) over an 18-24 month period. The protocol will encourage prompt evaluation of children with UTI symptoms and early therapy of culture-proven UTIs. It is expected that approximately 10% of children will have to discontinue study medication due to allergic reactions. Assuming a 20% placebo event rate and 10% non-compliance rate, the study has 83% power to detect an absolute 10% event rate in the antimicrobial prophylaxis group. If the placebo event rate is instead 25%, power is 97% to detect an absolute 10% event rate in the treated group, even if non-compliance is as high as 15%.

The primary endpoint is recurrence of $_{F/S}$UTI. In addition, patients will be evaluated for secondary endpoints related to renal scarring and antimicrobial resistance. Scarring will be determined based on renal scintigraphy by ^{99m}Tc dimercaptosuccinic (DMSA) scan. Quality of life, compliance, safety parameters, utilization of health resources, and change in VUR will be assessed periodically throughout the study.

II. BACKGROUND AND SIGNIFICANCE

The Link between Urinary Tract Infection and Vesicoureteral Reflux: Contemporary Issues and Study Design

UTI is one of the most common serious bacterial infections during childhood [1]. Estimates of the cumulative incidence of UTI in children under age 6 years (3-7% in girls and 1-2% in boys) suggest that between 70,000 to 180,000 of the annual US birth cohort will have a UTI by age 6 [2]. UTIs have been considered to be the principal cause of permanent renal parenchymal damage and scarring in children, especially those with VUR [3]. VUR results in urine passing up the ureter in a retrograde fashion. The extent of passage up the ureter is graded, with grades III, IV, and V being defined by progressive dilatation and distention of the renal pelvis [3, 4]. Since VUR is found in 30% to 40% of children with a UTI, the current standard of care is to perform an imaging procedure to assess the presence and extent of reflux [5, 6]. This strategy is dependent upon the hypothesis that reflux, especially of higher grades, increases the risk of renal scarring, with associated sequelae in later life of proteinuria, hypertension, eclampsia and end-stage renal disease (ESRD) [2, 5, 7-9].

This thesis has recently been challenged by long-term studies that show that renal scarring can occur in children without VUR, and that renal scarring is not common in children with even high degrees of reflux [1, 10]. Further, monogenic (and even polygenic) conditions result in reflux and progressive renal damage, often as a component of an identified syndrome; these can be viewed as separate from primary reflux [11, 12]. Analysis of dialysis and transplant registries suggest that the efforts to diagnose and treat children with VUR since the 1960's have not been associated with a reduction in the fraction of cases of end-stage renal failure attributable to reflux nephropathy [1, 5]. More importantly, studies comparing the effectiveness of combined surgical correction and antimicrobial prophylaxis to antimicrobial prophylaxis alone have demonstrated no difference in rates of renal scarring [1, 2, 5, 9, 10, 13]. Other concerns about current diagnostic and therapeutic strategies include the cost and potential psychological harm of studies to detect VUR [5,10,13,15] and the development of antimicrobial resistance with long-term prophylactic antibiotic use [16,17]. Doubts have arisen concerning the role of VUR in renal scarring and the efficacy of therapeutic strategies compared with prompt evaluation of urinary symptoms and early treatment of confirmed UTI [2, 7, 8, 14].

Because of the low prevalence of scarring, the cost of identification of VUR, and the potential problems of long-term antimicrobial prophylaxis and/or anti-reflux surgery, there exists a real need for a carefully designed and sufficiently large clinical trial to assess the effectiveness of current evaluation and therapeutic strategies [1, 15]. In our current trial, we propose a multi-center, randomized, placebo-controlled, double-blind study to determine whether, in the setting of prompt evaluation of UTI symptoms and early therapy of culture-proven UTI, daily antimicrobial prophylaxis is superior to daily placebo in preventing recurrent UTI and renal scarring in children aged from 2 up to 72 months diagnosed with grades I-IV VUR, following an initial episode of UTI [11].

II.A. Background

Studies for more than 50 years have suggested a link between recurrent UTI, VUR and renal parenchymal scarring [3, 4, 7-9, 16]. This scarring is associated with proteinuria,

hypertension, failure of renal mass to grow, progression to chronic kidney disease (CKD), and ultimately to end-stage renal disease requiring renal replacement therapy [4, 17-19]. Under this model of chronic renal failure, either long-term antimicrobial prophylaxis administration or anti-reflux surgery (such as ureteral reimplantation or endoscopic injection of a biocompatible material to diminish the size of the lumen of the ureterovesical orifice) or both have been utilized to prevent the damage related to an inflammatory response after retrograde reflux of infected urine to the ureter to the renal pelvis.

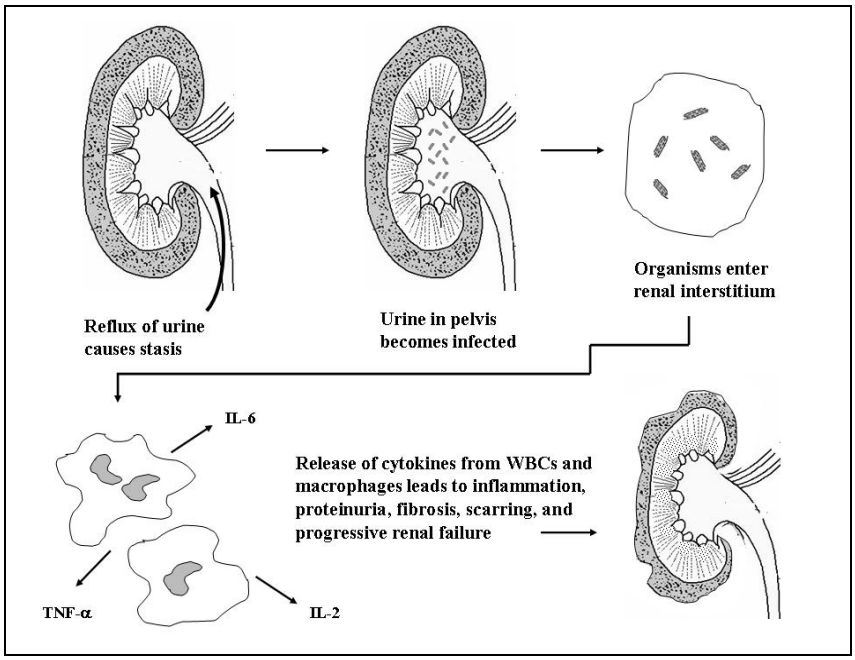


Figure 1. Theoretical model showing how urinary stasis caused by VUR leads to bacterial growth in the renal parenchyma. Macrophages and leukocytes migrate to the interstitium and secrete pro-inflammatory cytokines, resulting in fibrosis and scarring with a progressive decline in renal function and the development of proteinuria and hypertension. In reality, only a minority of children with primary VUR develop scarring.

Several findings have emerged which question the validity of this paradigm. First, review of studies that form the basis for our current strategies for preventing UTI- and VUR-related renal scarring reveals an absence of strong supportive evidence, with few if any randomized controlled trials [5, 10, 13, 15, 20]. Second, antimicrobial prophylaxis has been shown to be superior to placebo in terms of prevention of recurrent infection in only a limited fashion, and the value of anti-reflux surgery is even less certain [1, 2, 5]. The finding of renal scarring in children with recurrence of UTIs without VUR raises issues concerning the model [1, 10]. Long-term studies have shown that the proportion of children receiving antimicrobial prophylaxis or surgery who develop new scarring is actually quite low, and most children do not enter the pathway toward chronic kidney disease [1, 4, 5, 9].

Additional considerations include the fact that a certain number of children with VUR and recurrent UTIs will have chromosomal monogenic or polygenic conditions which may include embryonic malformation of the kidney, renal hypoplasia, dysplasia or obstruction [11, 12]. It needs to be determined whether the child with a neurogenic bladder and/or a myelomeningocele who develops evidence of progressive chronic kidney failure should be

considered as part of, or apart from, the UTI-VUR scarring model. Antimicrobial resistance in the patient and the community raises concerns about the safety of antimicrobial prophylaxis [21-23].

II.B. Vesicoureteral reflux (VUR)

VUR, retrograde urine flow from the bladder to the ureters, is the most common functional abnormality of the urinary tract in children [5, 10]. Primary VUR is characterized by short mucosal tunnel length, as opposed to secondary VUR, in which reflux is the result of increased bladder pressure from a neurogenic bladder, outlet obstruction or other vesicular anomalies. This study will address only primary reflux.

Over the past 3 decades, it has become apparent that approximately 30 to 40 percent of children investigated by imaging studies after a UTI show evidence of VUR [4, 6, 9]. An international grading system of reflux has been established which proceeds from grade I (reflux up a non-dilated ureter) to grade V (massive reflux with marked ureteric dilatation and distention of the pelvis with concavity of the papillae or papillary flattening). These grades are well described and involve increasing degrees of reflux, dilatation and cupping of the papillae [3, 4, 6, 9, 18].

VUR is also seen in asymptomatic family members at rates of from 20% to nearly 50% penetrance. This reflux is found in successive generations without particular influence of consanguinity. Other genetic conditions, to be discussed below, are associated with reflux and recurrent UTIs [19].

Another issue for consideration is that primary reflux may be discovered in a prenatal ultrasound or after an infection [8, 14, 22]. Because our interest is in patients with primary rather than secondary reflux, the timing of the discovery of reflux is less important. Put differently, all primary reflux exists on an embryologic basis [12, 14]. The main differences between pre- and post-natal disease are therapeutic approaches, including the choice of antimicrobials, the organisms encountered, and a greater spontaneous remission rate in younger children.

Reflux nephropathy is an appreciable cause of progressive renal failure leading to renal replacement therapy. The fact that the incidence of ESRD secondary to reflux nephropathy is unchanged from the1950's and 1960's probably indicates that many genetic and secondary causes of reflux are included in cases of reflux nephropathy. Thus, the model of infection, detection of reflux, and treatment is based upon many older studies that are smaller, non-randomized, and often include secondary reflux.

Although numerous studies have examined the importance of anti-reflux surgery, only a few studies are of sufficient length and size to permit valid statistical analysis [5, 10, 13]. In general, these studies have examined open vesicoureteric reimplantation and have not evaluated endoscopic ureteral surgery.

The International Reflux Study and other randomized controlled trials that compared combined surgery and antimicrobial prophylaxis to antimicrobial prophylaxis alone also raised doubts about this model. If VUR contributed significantly to the development of renal

scarring from UTI, then in those trials surgical correction should have decreased renal scarring compared with antimicrobial prophylaxis alone. However, the several trials testing this hypothesis all showed no incremental difference in rates of renal scarring with surgical correction and antimicrobial prophylaxis compared with antimicrobial prophylaxis alone [17, 18, 22, 24, 25]. Because none of these studies included a placebo or "observation only" arm, the question has also been raised as to whether surgery or antimicrobial prophylaxis has any effect on renal scarring in children with VUR diagnosed following a UTI.

II.C. Role of infection and VUR in scarring

At least 1% of boys and 3-5% of girls will experience at least one UTI during childhood; of these 30-50% are likely to have a recurrence [8]. Permanent renal scarring after pyelonephritis is detected 5-20% of the time when children are evaluated with intravenous urography and up to 40% of the time when evaluated by a DMSA scan [1, 5]. The finding of scarring increases with each episode of pyelonephritis [16]. The conventional view is that the incidence of scarring falls after the 5^{th}-7^{th} birthday, even with new infections, but in a large study by Benador *et al.* the frequency of scarring was the same in children aged 1-5 years as it was in children over 5 years [24].

Rushton *et al.*, in a now classic study, emphasized that new renal scars form less frequently in kidneys with VUR than those without [25]. In a meta-analysis of randomized, controlled trials of antimicrobials and anti-reflux surgery for VUR, Wheeler *et al.* concluded that, "it is uncertain whether the identification and treatment of children with VUR confers clinically important benefit."[10, 13]. It also appears that scarring may be identical in refluxing and non-refluxing units [3, 10, 13], challenging routine initiation of antibacterial prophylaxis following detection of VUR in all patients[26].

Another major problem is the lumping of cases with secondary reflux and genetic causes along with cases of children with UTI and scarring. A number of malformation syndromes, some with a recognizable inheritance pattern, can be associated with VUR, infection and scarring [11, 12]. Among these are VATER-VACTERL (vertebral, anal, cardiac, tracheoesophageal, renal, limb) syndrome and other syndromes with a variety of renal malformations, including renal agenesis, dysgenesis, horseshoe kidney, a duplex pelvis, hydronephrosis, and cloacal anomalies [11, 12]. Some of these disorders are chromosomal and others involve mutations in developmental genes. (Table 1, 2) In a series of 317 children with anorectal malformations, 138 had associated renal anomalies and 27 had VUR. Mutations of developmental genes, including PAX2, EYE1, and WT-1, can result in syndromes with reflux, scarring, and reflux nephropathy [11].

Table 1. Representative syndromes that may display VUR, scarring, recurrent infection and progressive renal disease [10, 13]

1. VATER - VACTERL association
2. Townes-Brock syndrome (*SALL1* mutation)
3. Cat eye syndrome (tetrasomy, chromosome 22)
4. Casamassima - Morton-Nance syndrome
5. Renal coloboma syndrome (*PAX2* mutations)
6. Branchio-oto-renal syndrome (*EYE1* mutation)
7. Frasier syndrome (*WT1* mutation)

Table 2. Renal and bladder variants resulting in VUR [10, 13]

1. Renal dysplasia
2. Renal hypoplasia
3. Obstructive uropathy
4. Bladder changes in function
5. Bladder changes in neurologic status
6. Bladder exstrophy

II.D. The characterization of scarring

Renal scarring is the consequence of focal areas of inflammation with massive cytokine release from tissue macrophages and lymphocytes [5]. Fibrosis is another post-infection finding. Other features are renal cortical thinning, and evidence of microalbuminuria [1, 13]. In all series a small number of children go on to have significant hypertension and end-stage renal disease.

II.E. Background to therapy

The use of antimicrobials to reduce recurrent and/or chronic UTIs dates back to the 1940's and 50's. The now classical studies of Jean Smellie and her colleagues form the most compelling reason to consider antimicrobial prophylaxis [6-9, 13, 16, 18]. The goals of this antimicrobial therapy and prophylaxis are: (a) prevent or reduce the number of recurrent infections; and (b) reduce the incidence of scarring. Again, this set of assumptions has come under criticism because of many of the facts listed previously (Table 3).

Table 3. Issues difficult to reconcile with the UTI-VUR Model [10, 13]

1. The percent of patients with recurrent UTI and reflux who develop scarring is quite small.
2. In one small trial comparing prophylaxis with no therapy for recurrent UTI, no significant differences in risk for UTI or renal damage were found.
3. Most children with even high grade VUR do not develop renal scarring.
4. Patients without VUR who have recurrent UTIs can develop scars.
5. The percent of patients who require renal replacement therapy (dialysis and/or renal transplantation) for reflux nephropathy has not changed since the 1960's.
6. Assuming a UTI rate of 20 percent for children with VUR on antimicrobials for 5 years, nine reimplantations would be required to prevent one febrile UTI.
7. Most trials evaluating the value of antimicrobials or surgery (open or endoscopic) are statistically underpowered and valid conclusions are impossible.
8. Many older studies also contain patients with secondary causes of VUR and genetic syndromes.
9. The increasing emergence of organisms resistant to standard antibiotics is rising, making prophylaxis increasingly difficult to justify.
10. In a Cochrane analysis based on 10 trials involving 964 evaluable children, the authors indicated that it was uncertain whether the identification and treatment of children with VUR conferred any benefit.

II.F. Background to Imaging Studies

A number of imaging techniques have been utilized to evaluate the child with a UTI. Radiographic VCUG remains the gold standard for identification and evaluation of VUR. Renal ultrasound; identifies hydronephrosis but is insensitive to identifying renal scarring. A number of procedures and tests have been used to try to localize the site of UTI to the upper (acute pyelonephritis, or APN) or lower (cystitis) urinary tract. An acute phase response consisting of elevated peripheral white blood cell (WBC) count, erythrocyte sedimentation rate and C-reactive protein were used in several studies to indicate infection of the upper urinary tract. However, as noted in a review article by Rushton and in editorials by Andrich and Majd, Conway, and Hellerstein, children who have a first UTI accompanied by fever and toxicity cannot be diagnosed reliably as having APN based on clinical signs and symptoms or laboratory parameters alone [27, 28]. Currently DMSA scintigraphy has emerged as the imaging agent of choice for the detection and evaluation of APN and renal cortical scarring in children. Using strict histopathologic criteria in the refluxing infected piglet model, DMSA renal scans have been found to be highly sensitive and specific for the detection and localization of APN [28, 29]. The DMSA scan also has shown higher sensitivity and specificity than intravenous pyelography (IVP) in documenting renal scars in several clinical studies, and has shown good correlation with histopathology in animal data [30-34]. Consequently, DMSA renal scintigraphy provides a unique opportunity to study the progression of renal damage and functional loss from the initial insult of APN to the subsequent development of irreversible renal scarring [25]. Accordingly, DMSA renal scanning is considered to be the "gold standard" for identifying renal parenchymal changes, and is recommended as the primary study for diagnosis of APN and renal scarring [27, 28, 35, 36]. As such, DMSA renal scans will be used in the NIH RIVUR study as the outcome measurement for the detection and semi-quantification of both preexistent and newly acquired renal parenchymal damage associated with UTIs in children with Grades I-IV VUR.

II.G. Potential harm of current management of VUR

There are concerns about the potential harm of current diagnostic tests and therapeutic approaches. The tests for defining reflux - its nature and extent - include voiding cystourethrography and radionuclide cystography.

Major concerns are as follows:

A. Imaging – Problems include cost and the long-term impact of repeated exposure to ionizing radiation.
B. Antimicrobials - the daily administration of an antimicrobial is problematic for several reasons:
    1. Strains of common urinary tract pathogens are becoming increasingly resistant to traditional agents employed in treating UTIs [1, 21].
    2. Resistance leads to the use of other agents and classes of antimicrobials, which may be costlier, are not fully tested in younger children, may be excreted in sites other than the renal parenchyma, and have limited antibacterial spectra [19].
    3. Questions remain about the optimal length of antimicrobial prophylaxis and the need for/frequency of urine culturing [5, 19].

C. Length of follow-up - this is a complex issue with a myriad of unanswered questions [2]. After infancy, boys experience far fewer recurrences of UTI. In general, new scarring does not occur after age 5-7 years, but as noted, can occur in the absence of VUR. Does the risk of antimicrobial resistance outweigh the possibility of infection and the even smaller risk of scarring? [1, 5].
D. Psychological - the process of inserting a urinary catheter into the urethra of a young child, followed by putting the child under an X-ray machine on a hard table, is clearly a source of psychological stress and the cause of tears, nightmares, and retained memories. If these tests are of only marginal value, or no value, then perhaps they should not be performed [1, 10, 13, 37].

II.H. Need for a well-designed study

To date, a small number of studies in children and numerous larger studies in adults have indicated that antibacterial prophylaxis can reduce the number of recurrent UTIs [5, 10, 13]. While this could indicate that randomized, prospective, placebo-controlled trials (in children with VUR diagnosed following UTI) are not indicated, this is not the case. As succinctly stated by J. Craig in his commentary on clinical trials in children, "We do not simply need more studies. We need the right studies done right."[15]. In order to accomplish this charge, children with a resolved first or second febrile or symptomatic UTI who have grades I-IV VUR will be randomized to receive placebo or an antimicrobial prophylaxis with a primary endpoint of recurrent UTI and a secondary endpoint of renal scarring. Children to be studied are those with primary VUR diagnosed following the occurrence of a first or second UTI. We anticipate enrolling and randomizing 600 children to antimicrobial prophylaxis and placebo treatment arms. Children with obstruction, genetic syndromes, chromosomal syndromes, and complex anomalies that influence bladder function and urinary flow will be excluded, in part because many of these children have secondary or obstruction-related reflux [11, 12]. Each child will be followed for at least 2 years, and both infection rates and scarring will be monitored. Such a study should have the statistical power to answer whether antimicrobial prophylaxis protects against these outcomes.

Because of the frequancy of UTIs in children, there is a need for a well-designed and appropriately powered study that can determine the value of antimicrobial prophylaxis on the recurrence of UTI and on the incidence of renal scarring [1, 15]. Because the currently recommended follow-up (repeated urine cultures, renal and genitourinary imaging, antimicrobial therapy and prophylaxis, as well as other factors including cleanliness, adequate bladder and bowel emptying, and compliance with protocols) are expensive (in terms of time, attention to detail, and cost) and cumbersome, these recommendations should be evidence-based [26].

III. STUDY DEFINITIONS

III.A. Febrile UTI ($_F$UTI)

$_F$UTI requires the presence of (1) fever, (2) pyuria based on urinalysis, and (3) culture-proven infection with a single organism. Specifically, the study definition of $_F$UTI requires:

I. Fever[1]
- Documented temperature of at least 100.4 °F or 38°C, measured anywhere on the body either at home or at doctor's office

AND

II. Pyuria on urinalysis
- $\geq$10 WBC/mm^3 (uncentrifuged specimen) OR
- $\geq$5 WBC/hpf (centrifuged specimen), OR
- positive leukocyte esterase on dipstick

AND

III. Culture proven infection with a single organism
- $\geq 5 \times 10^4$ CFU/mL (catheterized or suprapubic aspiration urine specimen) OR
- $\geq 10^5$ CFU/mL (clean voided specimen).

III.B. Symptomatic Non-febrile UTI ($_S$UTI)

$_S$UTI requires the presence of (1) urinary tract symptoms, (2) pyuria on urinalysis, and (3) culture-proven infection with a single organism. Specifically, the study definition of $_S$UTI requires:

I. Symptoms[1]
- Suprapubic, abdominal, or flank pain or tenderness, or urinary urgency, frequency, or hesitancy, or dysuria, or foul smelling urine, or in infants $\leq$ 4 months old, failure to thrive, dehydration, or hypothermia

AND

II. Pyuria on urinalysis
- $\geq$10 WBC/mm^3 (uncentrifuged specimen) OR
- $\geq$5 WBC/hpf (centrifuged specimen), OR
- positive leukocyte esterase on dipstick

AND

III. Culture proven infection with a single organism
- $\geq 5 \times 10^4$ CFU/mL (catheterized or suprapubic aspiration urine specimen) OR
- $\geq 10^5$ CFU/mL (clean voided specimen).

III.C Febrile or Symptomatic UTI ($_{F/S}$UTI)

As defined above in sections III.A and III.B.

[1] Must occur within ± 24 hours of intitiating workup for UTI.

III.D. Index UTI

UTI that leads to VCUG and patient recruitment for the study. The index UTI may be either:

(1) The participant's first febrile or symptomatic UTI

OR

(2) The participant's second UTI which is either febrile or symptomatic, and where the first UTI did ***NOT*** result in the patient being placed on antimicrobial prophylaxis.

The date of diagnosis for the index UTI is the date that the urine specimen that resulted in a positive culture was collected.

III.E. Recurrence of UTI

Infection more than 14 days after end of appropriate treatment of a UTI, or following a negative urine culture, or infection with a new organism.

III.F. Persistent UTI

Evidence of infection within 14 days after end of treatment of a UTI, in the absence of an intermediate negative urine culture (indicating that the treated UTI was never resolved).

III.G. Vesicoureteral reflux

VUR is defined as the retrograde flow of urine from the bladder up the ureter. It may or may not reach the level of the renal pelvis producing dilation of the upper urinary tract (see figure 4, section VI.B.2.d.ii.)

III.H. Renal scarring (DMSA)

Renal scarring will be defined as decreased uptake of tracer associated with loss of contours or cortical thinning. In order to quantify the extent of renal scarring, each kidney will be divided into 12 segments and a five level grading system will be applied. Severe scarring will be defined as the presence of grades 3 or 4 scarring on at least 1 kidney (see figure 2, section V.C.1.).

III.I. Dysfunctional voiding

A dysfunctional voiding symptoms score (DVSS) of more than 6 in female and more than 9 in male children $\geq$3 years of age or older using a standardized scale [38].

III.J. Chronic constipation in the toilet trained child, as defined by the Paris Consensus on Childhood Constipation Terminology

According to the Paris Consensus on Childhood Constipation Terminology (PACCT) [39], chronic constipation in the toilet trained child is defined as:

The occurrence of 2 or more of the following during the last 8 days in the toilet-trained child

- Frequency of bowel movement < 3 / week
- More than one episode of fecal incontinence / week
- Large stools in the rectum or palpable on abdominal examination
- Passing of large stools that may obstruct the toilet

- Display of retentive posturing and withholding behaviors
- Painful defecation

III.K. Treatment failure:

Treatment failure is defined by:

(1) In any participant:

- Occurrence of 2 recurrent $_{F}$UTIs or a total of 4 recurrent $_{F/S}$UTIs within the study period, OR
- Interim 12-month scan shows new or worsening scarring at a site different from the index APN or worsening scarring evidenced by extension of a preexistent scar seen on the baseline DMSA scan (note, the interim scan may serve as the outcome DMSA scan in these participants)

OR

(2) In children with baseline scarring grade 3 or higher:

- Children whose initial DMSA scan shows grade 3 or higher scarring in either kidney will have a repeat DMSA performed at the time of any recurrent $_{F}$UTI; if additional renal segment involvement is observed (APN or scar) compared with the baseline scan, then the child will be categorized as treatment failure and have an outcome DMSA scan at approximately 4 months following the $_{F}$UTI. If no additional renal segment involvement is observed, the child will continue in the study as assigned.

III.L. Appropriately treated UTI

Treatment for UTI will be considered appropriate if antibiotic therapy continues for a minimum of 7 days and:

1) There is documented sensitivity of the organism to the antibiotic used for treatment OR
2) There is a documented test of cure (negative urine culture) 1-14 days after completion of therapy.

III.M. Society of Fetal Urology (SFU) grading of hydronephrosis

Grade 0 - No hydronephrosis, intact central renal complex.
Grade 1 - Only renal pelvis visualized. Dilated pelvis on ultrasound.
Grade 2 - Moderately dilated renal pelvis and few calyces seen.
Grade 3 - Hydronephrosis with nearly all calyces seen. Large renal pelvis and good parenchymal.
Grade 4 - Hydronephrosis with nearly all calyces seen and parenchymal atrophy or thinning.

III.N. Study Medication

The term ‘study medication’ refers to both the study antimicrobial prophylaxis (TMP/SMZ) and placebo.

IV. STUDY HYPOTHESES

IV.A. Primary Hypothesis

IV.A.1. Recurrence of $_{F/S}$UTI

Hypothesis 1a. The proportion of children with a recurrence of $_{F/S}$UTI will be lower among those in the antimicrobial prophylaxis group than in the placebo group.

IV.B. Secondary Hypotheses

IV.B.1. Recurrence of $_{F/S}$UTI

Hypothesis 1b. The time to first recurrence of $_{F/S}$UTI will be shorter in the placebo group than in the antimicrobial prophylaxis group.

IV.B.2. Renal scars

For most participants, the incidence and extent of renal scarring will be determined 24 months after the index UTI using a DMSA scan. For children who meet criteria for "Treatment Failure," renal scarring will be determined based on the outcome DMSA scan. This outcome scan will be performed approximately 4 months following classification as treatment failure based on recurrent UTI or the interim scan if treatment failure is based on new or worsening scarring assessed on this DMSA scan.

Hypothesis 2a. The proportion of children with any renal scarring identified on the outcome DMSA scan will be lower among those in the antimicrobial prophylaxis group than in the placebo group.

Hypothesis 2b. The proportion of children with *severe* renal scarring identified on the outcome DMSA scan will be lower among those in the antimicrobial prophylaxis group than in the placebo group.

IV.B.3. Treatment Failures

A composite outcome of treatment failure is derived from the frequency and rate of $_{F/S}$UTI reoccurrence or identification of new or worsening renal scarring.

Hypothesis 3. The proportion of children classified as treatment failures will be lower among those in the antimicrobial prophylaxis group than in the placebo group.

IV.B.4. Antimicrobial resistance

Continuous exposure to antimicrobial prophylaxis is predicted to alter the microbial flora in the urine and stool of treated children.

Hypothesis 4a. The proportion of children who develop stool E. coli resistant to TMP/SMZ will be greater in the antimicrobial prophylaxis group than in the placebo group.

Hypothesis 4b. The proportion of children with recurrent $_{F/S}$UTI caused by TMP/SMZ-resistant organisms will be greater in the antimicrobial prophylaxis group than in the placebo group.

V. STUDY ENDPOINTS

V.A. Overview of Primary and Secondary Endpoints

The primary endpoint to evaluate treatment efficacy is recurrence of $_{F/S}$UTI. The proportion of participants who have at least one such recurrent $_{F/S}$UTI will serve as the primary analysis variable. Efficacy with respect to UTI will also be assessed based on analysis of time to recurrent $_{F/S}$UTI. Renal scarring is a secondary outcome measure. The proportion of participants who have any renal scars assessed on the outcome DMSA scan will serve as the principal analysis variable for scarring. The proportion with *severe* scarring will also be evaluated. Treatment failures and the development of antimicrobial resistance will also be measured as secondary outcomes.

V.B. Primary Endpoint

V.B.1. Recurrence of $_{F/S}$UTI

Suspected recurrent UTI events will be reviewed and adjudicated to determine if they meet the RIVUR criteria for a primary endpoint. The definition of recurrent $_{F/S}$UTI requires the presence of (1) fever or urinary tract symptoms[2], and (2) pyuria based on urinalysis, and (3) culture-proven infection with a single organism. A UTI will be defined as recurrent only if its onset occurs more than 2 weeks from the last day of appropriate treatment for the preceding UTI or following a negative urine culture, or it is an infection with a new organism.

V.C. Secondary Endpoints

V.C.1. Renal Scarring

The incidence and extent of renal scarring will be determined 24 months after the index UTI using DMSA scan in most participants. Children who are deemed "treatment failures" will have the outcome scan used to assess the scarring endpoint at an earlier time point. The outcome scan will be performed at approximately 4 months following the recurrence of UTI that leads to classification as treatment failure and study treatment discontinuation. In children who meet treatment failure criteria based on the interim 12-month scan, this scan may provide the basis of the outcome assessment. Renal scarring will be defined as decreased uptake of tracer associated with loss of contours or cortical thinning. In order to quantify the extent of renal scarring, each kidney will be divided into 12 segments and a five level grading system will be applied (Figure 2). Severe scarring will be defined as the presence of grades 3 or 4 scarring on at least one kidney.

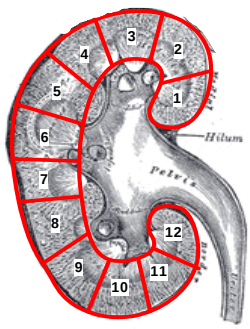


Figure 2 Grading system for characterizing extent of renal scarring

Grade	Description
0	No kidney segments affected
1	1-2 kidney segments affected
2	3-4 kidney segments affected
3	>4 kidney segments affected
4	Global atrophy characterized by a diffusely scarred and shrunken kidney.

[2] Either fever or symptoms must occur within ± 24 hours of initiating workup for UTI.

The renal scarring evaluations will be performed by central readers who are masked to treatment assignment. The principal analysis variable for scarring will be the proportion of participants having any scars on the outcome evaluation scan. Baseline scans will be used to demonstrate initial balance in treatment assignment.

V.C.2. Treatment failures

In any participant, the occurrence of two $_{F}$UTIs **or** a total of four $_{F/S}$UTIs during the study period **or** an interim 12-month scan showing new scarring at a site different from the index APN or worsening scarring evidenced by extension of a preexistent scar seen on the baseline DMSA scan will be classified as a treatment failure. In treatment failure cases where new or worsening scarring is observed on the 12-month DMSA scan, the interim scan may serve as the outcome DMSA scan.

Children whose baseline DMSA scan shows grade 3 or higher scarring in either kidney will have a repeat DMSA performed at the time of any recurrent $_{F}$UTI. If additional renal segment involvement is observed in comparison with the baseline scan, these children will also be categorized as treatment failure, be offered or referred to usual clinical care and have an outcome DMSA scan at approximately 4 months following the $_{F}$UTI. If no further damage is apparent, they will continue in the study as assigned.

V.C.3. Antimicrobial resistance

The presence of resistance to TMP/SMZ will be determined using Kirby Bauer disk diffusion on Mueller Hinton agar w/ 5% sheep blood using Clinical and Laboratory Standards Institute (CLSI) methods. In children who have met criteria for treatment failure, an outcome rectal swab will be obtained at the time study medication is permanently discontinued. Otherwise, the outcome swab will be collected at the study exit visit. The study endpoint of presence of E. coli resistant to TMP/SMZ will be based on these outcome swabs. Children who meet treatment failure criteria will also have a 24-month swab for use in a secondary outcome analysis.

The study endpoint of recurrent $_{F/S}$UTI caused by TMP/SMZ- resistant organisms will be based on antimicrobial susceptibility testing completed in conjunction with the urine culture diagnostic of the $_{F/S}$UTI.

VI. EXPERIMENTAL DESIGN AND METHODS

VI.A. Study Population

Six hundred boys and girls at least 2 months but less than 6 years of age with VUR will be recruited following diagnosis of first or second $_{F/S}$UTI

VI.A.1 Eligibility

The eligibility criteria are defined to reflect the typical patient population with VUR for whom antimicrobial prophylaxis is considered standard of care.

VI.A.1a. Inclusion Criteria

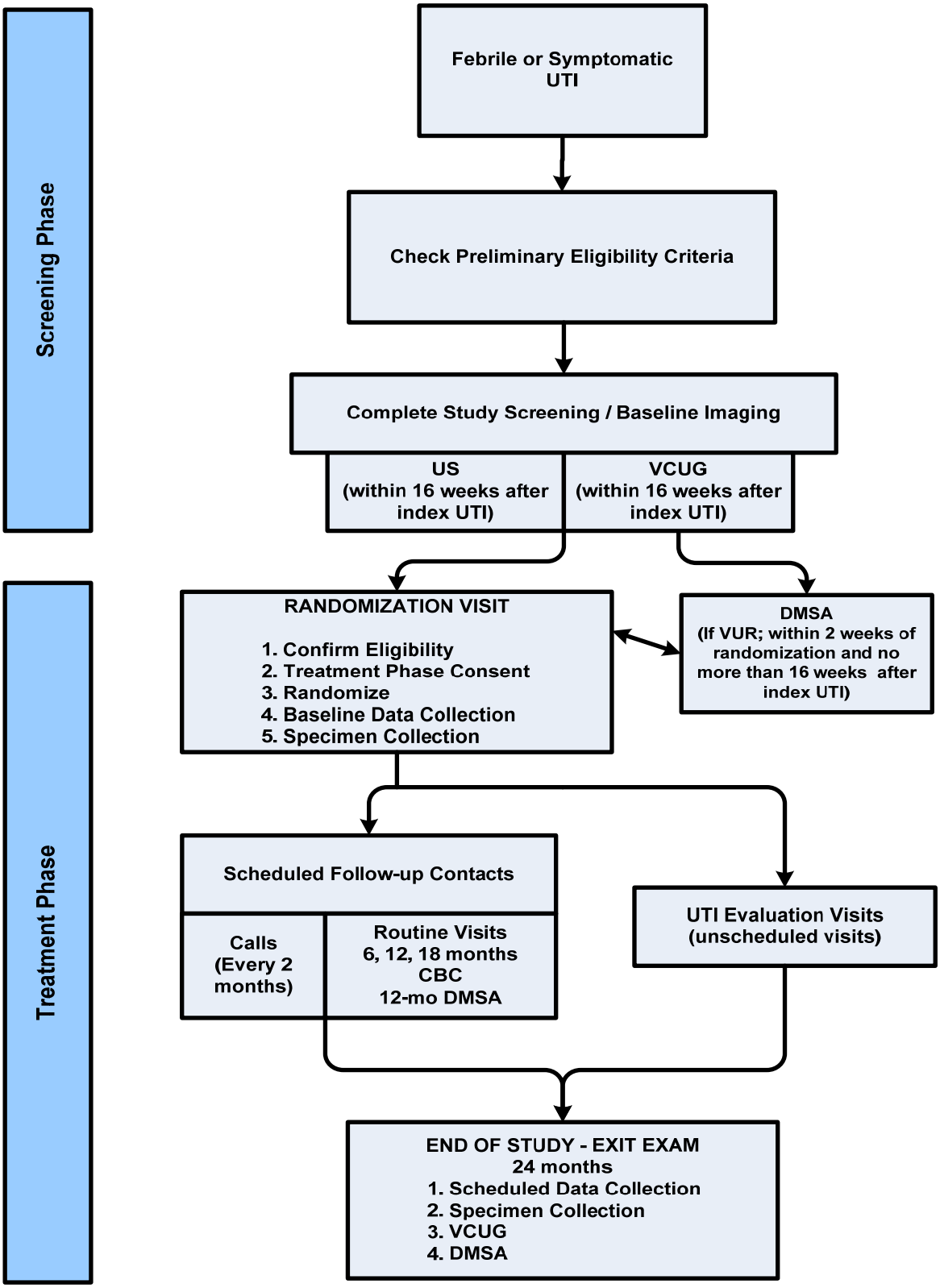
- Age at randomization: at least 2 months, but less than 6 years of age. Note that children as young as 1 month may be screened for the study.
- Diagnosed first or second $_{F/S}$UTI within 112 days prior to randomization
- Presence of Grade I- IV VUR based on radiographic VCUG performed within 112 days after diagnosis of index UTI.
- Appropriately treated index $_{F/S}$UTI

VI.A.1.b. Exclusion Criteria

- Index UTI diagnosis more than 112 days prior to randomization
- History of more than two UTIs prior to randomization
- For patients less than 6 months of age at randomization, gestational age less than 34 weeks
- Co-morbid urologic anomalies
    - Hydronephrosis, SFU Grade 4 (see section III.M.)
    - Ureterocele
    - Urethral valve
    - Solitary kidney
    - Profoundly decreased renal size unilaterally on ultrasound,(based on 2 standard deviations below the mean for age and length) performed within 112 days after diagnosis of index UTI
    - Multicystic dysplastic kidney
    - Neurogenic bladder
    - Pelvic kidney or fused kidney
- Known sulfa allergy, inadequate renal or hepatic function, G6PD deficiency or other conditions that are contraindications for use of TMP/SMZ
- History of other renal injury/disease
- Unable to complete the study protocol
- Congenital or acquired immunodeficiency
- Underlying anomalies or chronic diseases that could potentially interfere with response to therapy such as chronic gastrointestinal conditions (i.e., malabsorption, inflammatory bowel disease), liver or kidney failure, or malignancy.
- Complex cardiac disease as defined in the Manual of Procedures.
- Any known syndromes associated with VUR or bladder dysfunction (see Table 1)
- Index UTI not successfully treated
- Unlikely to complete follow-up
- Family history of anaphylactic reaction to sulfa medications

VI.B. Recruitment and Follow-Up Schedule

Figure 3. Flow Diagram for Recruitment and Follow-up



VI.B.1. Recruitment

Investigators at or affiliated with one of five Clinical Treatment Centers will enroll children with VUR in the study, following an episode of $_{F/S}$UTI. Children will be recruited from two different sources: primary care sites (Pathway 1) and subspecialty care sites (Pathway 2). Recruiting from both primary and sub-specialty care sites will (1) enhance generalizability of study findings by enrollment of children with a broader spectrum of severity of illness; (2) reduce the likelihood of selection bias; and (3) increase the chances of adoption of study results in all settings where patients with UTI and VUR seek medical care.

Primary (Acute) Care Sites (Pathway 1)

Parents of children seen in primary care offices, pediatric urgent care clinics, and emergency departments of participating institutions with their first or second $_{F/S}$UTI, will be invited to have their child participate in the study. Children will enter the screening phase of the study (see figure 3 above), during which their eligibility will be confirmed and baseline radiology studies, including a VCUG to determine the presence of VUR and a renal ultrasound will be performed. Children who meet the inclusion criteria and whose baseline radiology studies do not reveal any exclusion criteria will advance to the treatment phase of the study and be randomized to long-term administration of antimicrobial prophylaxis or placebo. All other children will be discharged from the study and managed by the primary care provider according to that provider's usual standard of care.

Subspecialty (Referral) Care Sites (Pathway 2)

Children referred to urologists or nephrologists at participating institutions who have been previously diagnosed and appropriately treated for a first or second $_{F/S}$UTI, and who are found to have VUR will also be eligible for enrollment in the study.

From previous studies with children of this age group with $_{F}$UTIs, a 50-75% consent rate is expected. Retention is expected to be high due to the involvement of investigators at the time of acute illness (Pathway 1), referral of the individual child to the Urology or Nephrology Clinic (Pathway 2), and telephone calls every 2 months.

VI.B.2. Screening Visit.

VI.B.2.a. Preliminary Eligibility Criteria

There are certain broad inclusion and exclusion criteria that will be used to initially identify a potential child for a more complete eligibility screening. Only children with grade I to IV VUR and a first or second UTI will be eligible. Children will be eligible for screening from age 1 month (30 days) to 71 months (age eligibility at randomization will be at least 2 months [60 days], but less than 6 years). Children must have been previously diagnosed with first or second $_{F/S}$UTI within 112 days of study randomization to be eligible for the RIVUR protocol.

VI.B.2.b. Consent

The parents or legal guardians of children diagnosed with their first or second UTI and with Grades I-IV VUR will be approached for consent for enrollment and randomization into the treatment phase of the study.

VI.B.2.c. Treatment for the index UTI

In order to be eligible for the treatment phase of the study, children diagnosed with first or second $_{F/S}$UTI in the screening phase of the study will have to receive appropriate treatment for the index UTI episode. In all instances, this will require treatment for a minimum of 7 days with an effective drug for the causative organism. If adequate susceptibility is documented, a repeat urine culture will not be obtained. If available, information regarding duration of fever prior to initiation of antimicrobial therapy will be collected, as well as time to defervescence. Children initially treated as inpatients or outpatients will both be eligible for enrollment in the study.

VI.B.2.d. Imaging Studies

Children enrolled in the screening phase of the study (both Pathways) will have a renal/bladder sonogram and a VCUG performed within 16 weeks (112 days) of diagnosis of the index UTI. Children who have a normal VCUG or Grade V will not be enrolled in the treatment phase of the study. Their care will be coordinated by the primary care provider or pediatric urologist/nephrologist. Those diagnosed with VUR Grades I-IV will have a DMSA scan performed within 2 weeks following randomization and no more than 16 weeks (112 days) following diagnosis of the index UTI.

VI.B.2.d.i. Renal/Bladder Sonogram

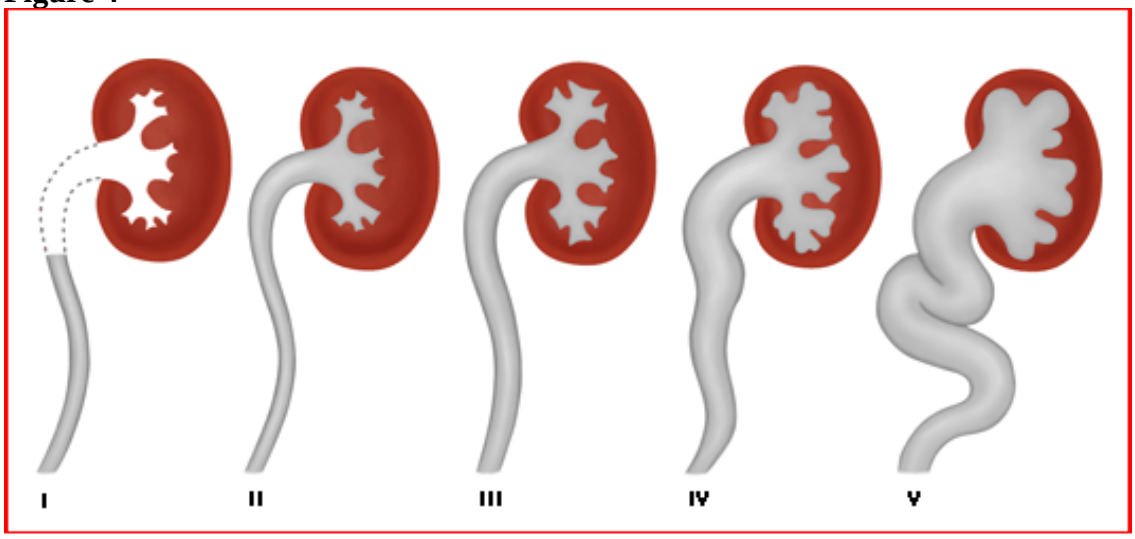
All patients will be evaluated within 16 weeks (112 days) after diagnosis of the index UTI with a renal/bladder sonogram. This study will be performed to screen for obstruction or other anatomic abnormalities of the urinary tract, such as ureteropelvic junction obstruction, a posterior urethral valve, or hydronephrosis associated with an ectopic ureter or ureterocele.

VI.B.2.d.ii. Voiding Cystourethrogram (VCUG)

A contrast VCUG will be obtained within 16 weeks (112 days) after diagnosis of the index UTI. This study is conducted in all young children diagnosed with a first or second $_{F/S}$UTI to identify and grade the severity of VUR. Morphological abnormalities of the bladder and the appearance of the urethra will be noted. VUR will be graded according to the five-grade system of the International Reflux Study Group (see figure 4 below): Grade I, reflux into ureter only; Grade II, reflux into ureter, pelvis and calyces without dilation; Grade III, mild to moderate dilation and/or tortuosity of the ureter and moderate dilation of the renal pelvis but little or no blunting of the fornices; Grade IV, moderate dilation and/or tortuosity of the ureter and moderate dilation of the renal pelvis and calyces; and Grade V, gross dilation and tortuosity of the ureter and gross dilation of the renal pelvis and calyces [28, 31].

Sedation during performance of VCUG is neither expected nor required as part of this trial. Institutional policies on sedation (see Appendix B) will not be modified for study participants. However, for children in which sedation is used, detailed information including the type and dosage will be recorded as study data.

Figure 4



International classification of vesicoureteral reflux (VUR) Modified from International Reflux Committee. Medical versus surgical treatment of primary vesicoureteral reflux. Pediatrics 1981; 67:392.

Results of the VCUG will be initially interpreted at participating institutions; the digital image will be acquired for verification of the degree of VUR by two reference radiologist investigators on the Imaging Studies Reading and Classification Committee.

VI.B.2.d.iii. DMSA Renal Scans

All children enrolled in the study will have a DMSA scan within 2 weeks following randomization and no more than 16 weeks (112 days) after the index UTI, to determine the presence of cortical defects. Patients will be injected with a dose of 5 mCi ^{99}TcDMSA per 1.73 m^2 body surface area (minimum dose 1 mCi) VI. High-resolution magnified images of the kidney will be obtained, including posterior and both right and left posterior oblique projections using a gamma-camera-computer system equipped with a high resolution parallel collimator, between 2-4 hours following injection. Right to left relative function will be calculated by the ratio of right kidney to left kidney counts obtained from the posterior views after background correction. The results will be described quantitatively as the percentage uptake in the right kidney vs. left kidney. Absolute uptakes will not be obtained. Cortical defects at this early DMSA will be defined as focal or diffuse decreased uptake of DMSA with/without loss of contours or cortical thinning with decreased volume. Using criteria established by Majd, defects will be classified as APN or preexistent renal scarring [28, 35]. These cortical defects will be assessed semi-quantitatively by dividing the renal cortex into 12 equal segments. The number of renal parenchyma segments affected will be determined. These evaluations will be made by two reference nuclear medicine investigators on the Imaging Studies Reading and Classification Committee.

A final outcome DMSA scan will be administered at the 24-month visit or 4-months after meeting treatment failure criteria. To insure participant safety, an interim DMSA scan will be performed at the 12-month follow-up visit to evaluate scarring.

Sedation during performance of DMSA scans is neither expected nor required as part of this trial. Institutional policies on sedation (see Appendix B) will not be modified for study participants. However, for children in which sedation is used, detailed information including the type and dosage will be recorded as study data.

VI.B.3. Treatment Phase

VI.B.3.a. Study Visit 1 - Baseline Evaluation and Randomization

Children who meet eligibility criteria and whose parents consent to participate in the study will advance to the treatment phase of the study.

VI.B.3.a.i. Baseline evaluation

Demographics, family history (e.g., VUR, APN, renal scarring), past medical history and selected clinical characteristics will be entered in electronic case report forms (eCRFs). Optional paper CRFs will be available. Entry examination at the time of randomization will include a general physical examination, blood pressure, height or length, weight, relevant medical history and regular medications used. For children who are toilet/potty trained, there will be an evaluation for voiding dysfunction based on the dysfunctional voiding system score developed by Farahat et al, and an assessment for constipation using definitions published by the PACCT Group [38, 39]. Baseline blood specimens (5 ml from children who weigh less than or equal to 20 lbs, and 10 ml from children who weigh more than 20 lbs), urine specimens, and rectal swabs or stool samples will be collected at this time. If blood for the genetics repository is not collected at baseline, it may be collected during a later blood draw. These samples will be tested, stored, or shipped to a central laboratory or repository as appropriate. A sample of these specimens will be processed as blind replicates for quality assurance. The rectal swabs or stool samples will be analyzed at a central lab to determine antimicrobial resistance (TMP/SMZ-resistant *E. coli*, and other organisms). Genetic samples from patients with appropriate consent will be sent to the NIDDK genetic repository for use in future genetic studies. A baseline DMSA renal scan will be performed within 2 weeks following randomization and no more than 16 weeks following the diagnosis of index UTI. A quality of life and resource utilization instrument will be administered at the baseline evaluation. Parents will be provided with tools to report relevant study-related variables.

VI.B.3.a.ii. Randomization

The Data Coordinating Center (DCC) will prepare computer-generated blocked randomization tables for allocating participants to daily antimicrobial prophylaxis or placebo. Long-term antimicrobial prophylaxis therapy will consist of trimethoprim/sulfamethoxazole (TMP/SMZ) at a trimethoprim dose of 3 mg/kg/day administered orally once a day. The study medication will be prepared centrally for all participating institutions. Investigators at each participating institution will be blinded to study medication assignment. The investigator at each participating institution, or the respective institution's central pharmacy, will be responsible for dispensing coded study medication, in order to preserve study blinding. An attempt will be made to have a central pharmacy contracted by the Data Coordinating Center maintain drug accountability records for all participating sites.

VI.B.3.b. Follow-up evaluations

VI.B.3.b.i. Monitoring and evaluations during subsequent episodes of fever

Parents will be educated at the time of their child's enrollment in the study about the potential sequelae of untreated UTI and the benefits of prompt and adequate treatment. They will be instructed to (1) contact primary care providers and study personnel in the event of intercurrent febrile illness, (2) have their child evaluated within 24-48 hours and (3) have a urine specimen obtained to evaluate for the presence of UTI. Additionally, a recent history of fever or other signs or symptoms compatible with UTI will be identified by information obtained during study-initiated phone calls every 2 months. The research nurse or the PI at each participating site, through a study-dedicated cellular phone or hospital-based beeper, will be available to parents of enrolled children. Primary care providers will be reminded through regular communication and letters about their patient's participation in the study. Specimens for culture will be obtained at the time of febrile illnesses and when children have symptoms localized to the urinary tract. Stringent criteria for recurrent $_{F/S}$UTI will be identical to those used at study entry. Patients with reinfections will be treated with effective antimicrobial therapy as outlined previously and will continue in their study-assigned treatment group until they complete the study protocol or meet treatment failure criteria.

VI.B.3.b.ii. Routine follow-up phone contacts and clinic visits

Parents will be contacted by phone every 2 months to ascertain side effects, intercurrent illnesses, and medication compliance, and children will be seen at routine follow-up visits at 6, 12, 18 and 24 months. Follow-up contacts and visits will continue through 24 months, regardless of medication compliance. The target date of these visits or phone interviews will be determined by the date of randomization. All interviews and clinic exams will be made within 10 days of the target date. If the follow-up schedule must be changed due to illness, geographic relocation or extended vacation, procedures will be followed to document the change in schedule. If a patient misses an appointment, a study coordinator will contact his/her family by phone or mail to inquire about intercurrent illnesses. Blood will be collected for local assessment of CBC at baseline, each bi-annual follow-up visit, and the study exit visit. Stool cultures or rectal swabs will be obtained at baseline, 24-month study exit and when treatment failure criteria are met. Study medication administration will be reviewed at the time of phone contacts and routine follow-up visits. Quality of life assessments will be collected at the baseline, 12- and 24-month clinic visits. DMSA scans will be administered at the 12- and 24-month visits in all participants except those who have had an outcome scan 4-months after meeting treatment failure criteria. Information on all medical visits and procedures that occur during the follow-up period, including resource utilization, will be obtained.

Urine specimens will be collected at the exit visit for storage at the repository.

A 5-10 ml (age-appropriate) blood specimen will be collected at 24-months for analysis and submission to the NIDDK specimen repository. A sample of these specimens will be processed as blind replicates for quality assurance.

VI.B.3.b.iii. Interim (12-month) DMSA scan

A DMSA scan will be obtained at 12-months post-randomization. This scan is recommended by the RIVUR Data and Safety Monitoring Board (DSMB) to insure participant safety during the trial. The rationale is as follows:

> The recommendation of the DSMB of the RIVUR study to include an interim DMSA scan is based on safety rather than experimental benefit. The assumption that there is no significant incidence of renal damage in the absence of clinically apparent UTI in children with VUR is unproven. Since the development of renal scarring in a child with VUR would prompt potential shift in therapy, this information should be made available to the investigators and thereby to the patients and families. The principle rationale for this recommendation is for safety to limit the risk of renal scarring.
>
> Recognizing the safety issues, there are study issues that may have sufficient weight to further justify use of the interim DMSA scan, which is in some practices, part of routine clinical care. To have confirmation of normal kidneys, or the converse, to know that renal injury has been sustained, will permit more solid conclusions relating the consequences of clinical VUR. This will serve the study patient as well as other patients with VUR in significant ways. The impact of VUR on renal health continues to be hotly debated and clinical practice remains highly variable, essentially unchanged from the report of 1992 by Elder, et al.[40], despite the promulgation of the AUA Clinical Guidelines. This reflects the variable interpretation of the data on VUR. While it has been reported that there is no clinical benefit to prophylactic antibiotics, the general clinical consensus is that these should be used. This is due to empirical evidence founded on clinical practice, yet may not be apparent in controlled trials. The importance of clinical trials such as the RIVUR, however, is so significant that it will impact thousands of patients in the near future and confidence in this study must be high in order for it to effect a real and rational change in clinical practice.
>
> This is an extremely important study that will have significant impact on the clinical management of patients, including infants, for years to come who have vesicoureteral reflux. The use of DMSA scanning is a well accepted standard of care in these children in order to determine the presence and severity of renal damage due to VUR. To in any way suggest that the DMSA scan is experimental is entirely without clinical basis for an imaging modality that has been used and studied for over 20 years. DMSA scanning has been shown to be superior to ultrasound and IVP in determining the presence and extent of renal scarring, which is the principle clinical factor that relates to the impact of VUR.
>
> In summary, the recommendation of the RIVUR DSMB is that an interim DMSA scan be obtained in all patients in order to maintain assurance of the safety of this clinical approach to VUR, as well as to permit confident assertion that either prophylactic antibiotics, or the absence of prophylactic antibiotics is a safe management option in patients with VUR.

VI.B.4. Procedures for treatment failure

All children categorized as meeting treatment failure criteria (see section V.C.2) will

discontinue study medication, be offered or referred to usual clinical care, undergo a DMSA scan at 4 months post failure unless the interim 12-month scan is appropriate for use as the outcome scan, and continue follow-up until the 24-month exit. An outcome rectal swab will be collected at the time study medication is discontinued as well as at the 24-month exit visit. Episodes of asymptomatic bacteruria (positive urine culture in the absence of pyuria or other urinary symptoms) identified through routine study follow-up will not be considered reinfections or treated with antimicrobials, except when indicated by an alternative source of fever (e.g., otitis media).

VI.B.5. Assessment of compliance

Parents will be reminded about the importance of daily administration of study medication at each scheduled telephone contact and every 6 months at routine follow-up visits. Also, parents will be asked to bring to clinic visits all used and unused bottles of study medication to determine compliance. Compliance data from patient diaries and interviews will be collected by the Study Coordinators at scheduled follow-up visits and used to measure compliance with administration of study medication.

In order to obtain endpoint data for analysis, follow-up visits will continue through 24 months post randomization, regardless of compliance.

VI.B.6 Assessment of new urinary tract infections (primary endpoint)

Clinical data identifying the potential occurrence of a urinary tract infection will be collected through timely medical records abstraction of all medical care visits, including hospitalizations that occur during the study follow-up period. An adjudication committee (UTI Classification Committee) will review these data and provide determination of whether the criteria for the RIVUR primary endpoint are met as well as date of event and other data. These adjudicated data will be used to determine the primary endpoint of the trial.

VI.B.7. Assessment of reflux resolution: VCUG (24 months)

A radiographic VCUG will be repeated at 24 months to determine persistence/resolution of VUR. Results of the VCUG will be interpreted at participating institutions, and a digital image will be sent to the RIVUR reference radiologists for verification of the degree of VUR.

VI.B.8. Assessment of renal scarring: DMSA scans (12-month visit and 24-month visit or 4-months post treatment failure)

Interim and outcome DMSA renal scans will follow the same procedures and standards of the baseline scan. Interim DMSA scans will be performed at 12 months, unless patients meet criteria for treatment failure prior to 12 months. For patients who experienced treatment failure within the first 18 months of the study, the outcome DMSA scan will be done 4 months after the treatment failure infection. In children who meet treatment failure criteria based on the interim 12-month scan, this scan may provide the basis of the outcome assessment. Otherwise, for all other patients, the outcome DMSA scan will be obtained at 24 months following entry into the study. An outcome measure will be evidence of renal parenchymal scarring, defined as decreased uptake of DMSA associated with loss of contours or cortical thinning with decreased volume. The proportion of children with renal scarring in each treatment group will be compared. However, severity of damage will also be measured. This will be assessed semi-quantitatively by measuring the number of renal segments involved. The severity will be classified as none (0 segments), mild (1-2 segments),

moderate (3-4 segments), severe (>4 segments), or global atrophy (diffusely scarred, shrunken kidney). The standardized grading systems will be used by the reference nuclear medicine investigators without knowledge of clinical events or treatment arm. Final diagnosis of disagreements in interpretations will be reconciled by an adjudication process. A sample of scans (early and late/outcome) will be reviewed by each observer at a later time. Intra-observer agreement will be assessed for these observations.

VI.B.9. Alert notification

Primary care providers will be notified of clinically significant findings identified at the study follow-up visits.

VI.B.10. Table 4. Summary of Observations and Procedures

Study Month Type of Contact	**-2 to 0 Pre-Randomizatiion activities**	**0 (Visit) Randomization/ Baseline**	**6 month (Visit) Follow-up**	**12 month (Visit) Follow-up**	**18 month (Visit) Follow-up**	**24 month (Exit Visit) Follow-up**	**Every 2 months (Phone) Follow-up**
Ultrasound	X*						
Contrast VCUG	X*					X	
Informed Consent	X						
DMSA	X**			X		X***	
Detailed Medical History	X						
Interim History		X	X	X X X			
Physical Examination	X	X	X	X X X			
Questionnaires							
Dysf Void Symp Score and PACCT (age≥3)		X		X X			
Parent Diary†		X	X	X X X			
QOL assessment		X		X X			
Randomization		X					
Study medication dispensation		X	X	X X			
Study medication Accountability		X	X	X X X			
Urine tests							
Urinalysis		X				X	
Culture		X††				X††	
Microalbumin/ Creatinine		X				X	
Urine for central Repository		X				X	
Blood tests							
CBC with diff		X	X	X X X			
Creatinine, lytes,		X				X	
Cystatin C		X				X	
Blood for central Repository§		X				X	
Rectal Swabs†††		X				X	
Telephone Follow-up							X

* Screening ultrasound and VCUG may occur any time within 16 weeks following the index UTI and prior to randomization

** Screening DMSA may occur within 2 weeks following randomization and no more than 16 weeks after the index UTI

*** 24 month DMSA scan may not occur if a study outcome scan has already been obtained.

† Paper or web-based data collection

†† If urinalysis is positive, culture is obtained

††† Rectal swabs will also be collected when participants meet treatment failure criteria

§ If blood for the genetics repository is not collected at baseline, it may be collected during a later blood draw

VI.C. Human Subject Issues

VI.C.1. Rationale for Placebo-controlled Trial

The use of antimicrobial prophylaxis in children with VUR is principally based on the association between VUR and renal damage ("reflux nephropathy"). Hypertension and chronic renal failure are potential sequelae of reflux nephropathy. In addition, VUR is believed to place children at risk for the morbidity of recurrent UTIs. Accordingly, long-term administration of antimicrobial prophylaxis is based on the assumption that it prevents UTIs that cause renal damage. Children typically receive antibiotic prophylaxis until the VUR spontaneously resolves or is operatively corrected. This strategy necessitates periodic VCUGs to determine if VUR has resolved.

Despite the widespread use of antimicrobial prophylaxis in children with VUR, poor evidence exists of the beneficial effects of this strategy. Randomized trials showing a benefit of antimicrobial prophylaxis in preventing renal injury have not been conducted. Current management strategies are based on observational studies demonstrating a low rate of disease progression (i.e., new renal damage) in children treated with antimicrobial prophylaxis. In addition, there is evidence that prophylactic antibiotics prevent UTIs in children, although this has not been demonstrated in children with VUR. The current strategy is financially costly, leads to patient morbidity due to repeated VCUGs (psychological trauma and radiation burden), surgical procedures, and side effects from antimicrobial prophylaxis (allergic reactions and selection of resistant organisms).

Along with the paucity of evidence supporting the use of antimicrobial prophylaxis, additional compelling arguments indicate that this practice may not be necessary. First, convincing evidence exists that many children with reflux nephropathy are born with abnormal kidneys, and thus postnatal intervention may not influence outcomes, assuming no additional postnatal damage. Inclusion of these children might have introduced bias in previous reports of VUR outcome by attributing this prenatal damage to postnatal infections. Second, current increased awareness of UTI generally results in prompt antibiotic treatment, further reducing the likelihood of renal damage from delayed therapy. Third, this more aggressive screening and early identification of children with UTI, probably results in the identification of young children with VUR who have milder disease (i.e., less severe VUR and less severe renal damage)

The uncertainty regarding the need for antimicrobial prophylaxis in children with VUR is reflected in expert opinion. European guidelines for the management of VUR do not recommend antimicrobial prophylaxis for children with grade I or II VUR [41]. Many clinicians in the US do not prescribe antimicrobial prophylaxis for children with grade I VUR. A number of authorities have independently recommended that antimicrobial prophylaxis for children with VUR be evaluated in a randomized, placebo-controlled study.

VI.C.2. Consent Procedures

Following an initial episode of UTI, children with VUR will be recruited into the study from two different sources, primary care sites and subspecialty care sites. Informed consent will be obtained for each study participant successfully screened from both pathways at an appropriate point in the screening process. The consent document, acquired from participants' parent(s) or legal guardian before the child is enrolled in the study, will describe

potential risks and benefits of study participation as well as the responsibilities of the study participants, parents or legal guardians, and investigators, as well as give the parents/guardians an opportunity to consent or decline to collection and storage of DNA specimens. This consent document will be written in language understandable to the adult providing consent as the child's responsible representative.

VI.C.3 Compensation

A small monetary compensation for their time and effort will be provided for study participants' parents or legal guardians at each study-related randomization and semiannual follow-up visit.

VI.C.4. Potential Risks

VI.C.4.a. Placebo Arm

If daily antimicrobial prophylaxis is protective against recurrence of UTI and renal scarring, then children in the placebo group will be exposed to a higher risk of recurrent UTI and renal scarring.

VI.C.4.b. Antimicrobial Prophylaxis Arm:

If antimicrobial prophylaxis induces the development of resistant organisms, then children in the antimicrobial prophylaxis group will be exposed to a higher risk of developing UTI with a resistant pathogen, which may require treatment with intravenous antimicrobials.

TMP/SMZ is commonly used for UTI prophylaxis and has an established record of safety in children. Nevertheless, participants may have adverse reactions to the antimicrobial prophylaxis or placebo used in this study. TMP/SMZ may cause allergic reactions that range from mild (skin rash) to severe (Stevens-Johnson Syndrome), although severe reactions are extremely rare. Other potential side effects of TMP/SMZ include sun sensitivity, recurrent vaginitis, granulocytopenia, and dizziness.

VI.C.4.c. Risks: Radiographic Studies

VI.C.4.c.i. VCUG

A VCUG is a standard procedure following a first or second UTI in a child. It is also standard to perform a VCUG to document resolution of VUR prior to discontinuation of antimicrobial prophylaxis. A VCUG requires urethral catheterization and filling of the bladder with contrast material, both of which can be uncomfortable to children.

The radiation exposure from a VCUG, expressed as effective dose equivalents, is between 79 and 190 mrem (versus 300 mrem for natural background radiation per year at sea level).

VI.C.4.c.ii. DMSA

A DMSA scan requires placement of a peripheral IV catheter and infusion of a radioisotope. IV placement can be painful for children and IVs can be dislodged and result in infusion into soft tissue (infiltrates).

The radiation exposure from a DMSA scan, expressed as effective dose equivalents is between 69-155 mrem (versus 300 mrem for natural background radiation per year at sea level).

VI.C.4.d. Blood Draws

Blood draws may cause mild pain, bleeding, or bruising. Fainting and infection are rare complications.

VI.C.4.e. Confidentiality

There is minimal risk for loss of confidentiality.

VI.C.5. Potential Benefits

VI.C.5.a. Placebo arm

Children in the placebo group by not being exposed to low daily doses of antimicrobials for long periods of time, may be less likely to become colonized (nasopharyngeal and rectal) with resistant pathogens, which may in turn result in infections (UTIs, acute otitis media, sinusitis) that would require further antibiotic treatment. In addition, these subjects will not experience potential allergies and adverse events associated with antimicrobial prophylaxis.

VI.C.5.b. Antimicrobial Prophylaxis arm

If daily antimicrobial prophylaxis is protective against recurrence of UTI and renal scarring, then children in the antimicrobial group may benefit from an intervention expected to prevent break-though reinfections and subsequent renal scarring.

VI.C.5.c. DMSA

Early detection of renal cortical defects by DMSA scans results in close prospective monitoring with early identification of recurrences, reducing or preventing further scarring of the renal parenchyma.

VI.C.5.d. Laboratory tests

These tests will yield additional information, such as the presence of urine microalbumin allowing for early detection of potentially progressive renal damage.

VI.C.6. Protection against Potential Risks

VI.C.6.a. Protections against Risks to Study Participants

VI.C.6.a.i. Placebo arm

The protocol may minimize the risk of recurrent UTI causing renal scarring in patients in the placebo arm by providing increased surveillance and early detection and treatment of UTIs, increased frequency of monitoring for renal scarring, and strict and conservative protocol exit and stopping rules. The study will exclude children with grade V VUR, who are at the greatest risk for developing renal scarring.

VI.C.6.a.ii. Antimicrobial prophylaxis arm

The risk that a patient will develop a UTI with a drug-resistant organism is unknown. If it occurs, several other antimicrobials can be used for prophylaxis and treatment.

Families will be queried about a subject's history of allergies to TMP/SMZ and other sulfa medications. Families will be provided with literature on adverse reactions to TMP/SMZ and instructions to call or visit if any evidence of such a reaction occurs.

VI.C.6.a.iii. VCUG

The VCUG will be performed following a standard protocol by healthcare provider's expert in the care of children, thus minimizing the risk of physical or psychological harm. VCUG procedures will be conducted and supervised by qualified radiologists and X-ray equipment will be frequently evaluated by qualified medical physicists and technologists.

VI.C.6.a.iv. DMSA

The DMSA scan will be performed following a standard protocol by healthcare providers expert in the care of children, thus minimizing the risk of physical harm. All DMSA scans will be conducted under the supervision of an authorized Nuclear Medicine physician. Dose calibration equipment and Gamma cameras will be calibrated frequently by qualified individuals.

VI.C.6.a.v. Blood draws

Blood draws will be performed by qualified nurses, physicians and phlebotomists according to standard phlebotomy techniques.

VI.C.6.a.vi. Potential loss of confidentiality

No personal information, such as names, contact information, social security numbers, etc. will be stored in the DCC database. Information such as dates of birth and dates of events will be stored in the DCC database by study ID number. Physical files linking study ID numbers to personal information will reside in locked files in the office of the principal investigator or the clinical coordinator at the clinical site where the patient is enrolled into the study.

VI.C.6.b. Protection against Risks to Study Personnel

The major hazard to personnel is exposure to blood and urine during collection and processing of samples. All personnel that may be exposed will be trained in universal blood and body fluid precautions. Personnel who ship samples will be trained according to the International Air Transport Association (IATA) requirements.

VII. CENTRAL LABORATORIES AND IMAGE READING COMMITTEES

VII.A. Central Laboratories

Rectal swabs, and blood specimens for serum creatinine and cystatin–C, will be sent to separate laboratories for storage and eventual analysis.

VII.B. Central Biospecimen Repository

Urine and blood specimens from participants for whom appropriate consent has been obtained will be collected, processed, and submitted to the NIDDK specimen repository. Specimens for the NIDDK specimen repository will be collected at baseline and during the 24-month visit at a lower priority than specimens with pre-specified study use and specimens for the genetics repository.

VII.C. Central Genetics Repository

Genetic specimens from participants for whom appropriate consent has been obtained will be collected, processed, and submitted to the NIDDK genetics repository. Genetic specimens will be collected at baseline and during the 24-month visit at a lower priority than specimens with pre-specified study use.

VII.D. Imaging Studies Reading and Classification Committee

DMSA scans, renal ultrasound scans, and contrast VCUG images will be obtained and stored locally. DMSA, ultrasound scans, and digital VCUG scans will be copied to an appropriate format and sent to the reference radiologists. Ultrasound scans and VCUG images obtained and stored on regular film will be copied and mailed to the reference radiologists. All studies will be read by at least two reference radiologists, each entering their reading results into the RIVUR web-based data management system. The results will be compared and discrepancies will be adjudicated by the reference radiologists. The adjudicated result will serve as the principal analysis data. This central evaluation, with the subject's identity and intervention group assignment blinded, will help insure unbiased classification of reported events and reduce problems of variable interpretation of event definitions. To ensure uniformity in reading and technique of ultrasound, VCUG and DMSA scans, a pilot study of 10 ultrasound, 10 VCUG and 10 DMSA scans from each of the five Clinical Treatment Centers (CTCs), in addition to 2 ultrasound, 2 VCUG and 2 DMSA scans from each of the satellite sites, will be conducted prior to the initiation of randomization.

VII.E. UTI Classification Committee

This Committee has responsibility for the review of possible recurrent UTI events for determining if study endpoint criteria are met. This committee will determine (1) whether recurrent $_{F/S}$UTI occurred, (2) the date of the recurrent UTI, (3) whether the study's criteria for treatment failure have been met, and (4) the date of treatment failure. The role of this committee is ongoing throughout the entire study period. Each potential event referred to the committee will be reviewed by at least two members. Review and classification results will be entered by the committee member into the RIVUR web-based data management system. The DCC will compare results and discrepancies will be adjudicated by the committee. The adjudicated result will serve as the principal analysis data. This central evaluation, with the subject's identity and intervention group assignment blinded, will help insure unbiased classification of reported events and reduce problems of variable interpretation of event definitions.

VIII. INTERVENTION

VIII.A. Active and Placebo Interventions

Antimicrobial prophylaxis will consist of trimethoprim/sulfamethoxazole, 3 mg/kg based on TMP concentration, administered once daily. The placebo will be nearly identical in color, taste, and consistency to TMP/SMZ. Both TMP/SMZ and placebo will be labeled with a code that masks whether the content is active or placebo. Patients who are allergic or develop allergies to TMP/SMZ or placebo will be discontinued from study medication.

VIII.B. Intervention Procurement

TMP/SMZ suspension will be purchased (Sulfatrim® Pediatric Suspension from Actavis, Inc., Cranford, NJ – See Appendix A) and rebottled by UPM Pharmaceuticals (Baltimore, MD). The active and placebo interventions will be similarly labeled with a code number that masks site investigators, site staff, parents and children to the formulation. Study medication will be distristibuted to clinical sites by the RIVUR drug distribution Center (HHS Supply Services Center, Perry Point, MD) upon request by the DCC.

Parents will be sent/or pick up their child's medication at the treatment center where they were enrolled. Study medication will be dispensed by the Study Coordinator or other authorized entity (e.g., research pharmacist) who will also keep track of the medication inventory and records of study medications dispensed. Study medication supply will be documented by each study center as well as by the DCC.

VIII.C. Compliance

Parents will be reminded about the importance of daily administration of study medication at each scheduled telephone contact. Study medication usage data based on bottles returned at scheduled follow-up visits and self-report through patient diaries and interviews will be used to determine compliance with administration of study medication.

VIII.D. Side Effect Management, Discontinuation and Re-challenge

Serious side effects:

Patients who develop Stevens-Johnson Syndrome, anaphylaxis, toxic epidermal necrolysis or blood dyscrasias will be taken off study medication and offered an alternative long-term antimicrobial prophylaxis as part of routine clinical care.

Common Side Effects

Patients who develop common side effects will have the study medication discontinued temporarily. They will be restarted on the study medication 24-48 hours after the side effects resolve. If the same side effect recurs within 24-72 hours of restarting the medication and is unacceptable to the treating physician, patient, or parents, study medication will be discontinued. Common side effects include nausea, vomiting, or diarrhea, mild allergic rash and/or urticaria, and headache.

All patients will be advised that the study medication may increase photosensitivity and will be advised to use sunscreens.

IX. ADVERSE EVENTS

This protocol involves the study of children with congenital VUR in two arms: continuous low dose antimicrobial prophylaxis (TMP/SMZ) and no prophylaxis (placebo). TMP/SMZ has been employed for this purpose in children for decades, have established safety records for pediatric use, and have well described side effect profiles. During telephone contacts and follow up visits, study participants will be asked to report on any hospital or doctor visits since their last study contact, and on any possible adverse reactions. All potential serious adverse events or reported side effects will be recorded as study data.

IX.A. Definition of Serious Adverse Events

An adverse event is any unexpected or dangerous reaction to a study intervention, either active or placebo.

Serious adverse events have been defined to include any of the following adverse drug experiences:

- Death
- A life threatening adverse experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent disability or incapacity
- A medical event that may not be life threatening or require immediate hospitalization but that may require medical or surgical intervention to prevent a serious adverse event.

Non-serious adverse events are all adverse events that do not meet the above criteria for "serious."

IX.B. Reporting of Serious and Other Adverse Events

All serious adverse events will be reported to the DCC using procedures outlined in the Manual of Procedures. Clinical sites are responsible for reporting adverse events (serious or non serious) to their local IRB in accordance with the local IRB requirements. The medical director at the site will determine the proper response per the research protocol—i.e.: changing therapy, initiating new therapy, or having the subject discontinue study medication.

The DCC will report serious adverse events to the independent Data Safety Monitoring Board (DSMB) according to the guidelines and schedule established by that group. All adverse events and safety data will be reported to the DSMB through regularly scheduled reports.

X. DATA MANAGEMENT

X.A. Data Management System

A web-based data management system (DMS) will be used for this study. The data management system will provide all of the capabilities required for research data management, including: data transfer, data entry, data validation, database updating, database closure, data retrieval, data inventory, security and confidentiality, and archiving, and in addition will support randomization.

Each clinical site will be responsible for entering the data it collects. The clinical site staff will use the DMS to enter screening data and eligibility data, run an algorithm to determine eligibility, and for each eligible patient, the DMS will issue a random treatment assignment. Follow-up data will also be entered at the clinical sites into the DMS.

The server and main database reside at the DCC at the Collaborative Studies Coordinating Center (CSCC) at the University of North Carolina at Chapel Hill.

X.B. Data Entry, Editing and Reporting

Direct data entry, where data initially are entered on the screen without having completed a paper form first, will be available at each center. Direct data entry eliminates the time-consuming and error prone process of keying from paper forms. Paper versions of each data collection instrument will be available as backup in situations in which the computer systems are inaccessible for any reason. In addition, if there are forms that are routinely collected on paper for convenience or another reason, then the data on these forms will subsequently be keyed at the clinical sites using the web-based data entry system. The data entry system will display data entry screens that closely resemble the paper data collection forms. The system will be menu driven, with context-sensitive help available at any time. Each data field will be edited during entry.

The DMS will include the ability for each center to generate locally a variety of summary reports concerning the data completeness, outstanding questionable values, etc. This capability is valuable in permitting study coordinators to monitor the quality of their center's performance. This facilitates timely identification and resolution of problems in data collection and processing.

X.C. Central Laboratory Data Management

The central laboratories will prepare data files from their local data management systems in a standardized format and transfer these to the DCC on a regular schedule. Upon receipt at the DCC, these data files will be processed for incorporation into the study's consolidated database. Alternatively, central laboratories may enter data into the study's web-based data management system.

X.D. Data Security

The DMS will require entry of a valid user ID and password for use. Sensitive files will be encrypted. Regular back-ups that are stored apart from the DMS server and database will be required.

All data transferred to the DCC will be stored, processed and analyzed within the CSCC office suite or its secure back-up location. At the CSCC, all access to office space containing data is controlled through locked doors. Visitors are screened by CSCC staff and cannot move about without a CSCC escort. All office space is locked after working hours. Access to computer data is controlled by passwords released only to those CSCC personnel who use the files. In addition, critical data files are encrypted.

X.E. Data Reporting

On a monthly basis, the DCC will prepare a study data report that provides clinic-specific and overall summaries of patients screened and randomized by month. Timeliness and completeness of follow-up contacts will also be reported. In addition, the DCC will routinely generate reports for the clinical sites and laboratories concerning data quality (missing or overdue forms, outstanding data queries, etc.), and facilitate the timely review, correction and resolution of data quality issues at the clinical sites.

X.F. Study Communications and Monitoring.

The DCC will maintain current contact information on the study web page for all study staff from the clinical sites, central laboratories, central reading centers or committees, and DCC. Methods of study communications will include e-mail, web-postings, telephone, fax, regular mail, and express delivery services.

X.G. Technical Support

The clinics will have a liaison at the DCC who can be called for an immediate answer to an operational or data management question or for help in obtaining clarification of a particular situation. For each clinic, a primary study coordinator is identified, and a principal pediatric nephrologist or urologist investigator is identified who has the overall responsibility for the recruitment of patients and management of the study at the center.

XI. QUALITY ASSURANCE

XI.A. Training and Certification

All staff involved with data collection will be required to have appropriate training and certifications. Each clinical site will have a study coordinator or project manager who has received formal training from the DCC about the RIVUR protocol and procedures. This individual can then train other local staff in study procedures, but the site must have at least one DCC-trained individual throughout the study.

XI.B. Imaging Evaluation Pilot Study

In order to ensure uniformity in technique and reading of renal ultrasound, VCUG and DMSA scans, an imaging evaluation pilot study will be conducted prior to the initiation of randomization. The study will include 10 ultrasound, 10 VCUG and 10 DMSA scans from each of the five Clinical Treatment Centers in addition to 2 ultrasound, 2 VCUG and 2 DMSA scans from each of the satellite sites. Site personnel will be asked to de-identify each scan and submit them to two central readers. Inter-reader agreement will be assessed for all quantitative data fields to be evaluated in RIVUR. Discrepant fields will be adjudicated and, through this process, the reading procedures fine-tuned.

XI.C. Data Reporting for Quality Assurance

Monthly data reports of study status and data quality are prepared by the DCC and posted on the secure study website. Data will be summarized overall and by site. These reports include information such as the number of patients screened, number of participants randomized, percent of follow-up contacts completed, and the number and percent of missing forms. In addition, the DCC will generate site-specific reports for data quality, such as missing and overdue forms, missing or suspicious data items, outstanding data queries, etc., and facilitate the timely review and resolution of data quality issues within the study.

XI.D. Site Monitoring Visits

The DCC will conduct periodic monitoring visits to each participating clinical site, central reading center, and central laboratory. In addition to evaluating the quality with which the trial is being conducted at individual sites, monitors will assess specific implementation methods, compare implementation strategies across sites, and make as well as receive suggestions for improving trial performance. Monitors will review research and medical records of trial participants for accuracy of case report forms. In addition, if recruitment falls below a certain level or other problems with study conduct arise, a more diverse site visit team may be initiated. This larger site visit team would include personnel designated by the Principal Investigators Committee, such as a team consisting of a clinician from a highly productive center, and representatives from the Project Office and DCC.

XI.E. Replicate Measures Program

Some procedures or data collection may be repeated for quality assurance purposes. When this involves additional participant burden, informed consent will be obtained. A sample of participants will provide an additional specimen (blood, urine, and/or swab material) for blinded laboratory analysis and quality assurance comparison with the study values. A sample of imaging scans will be re-read at a later time to determine estimates of intra-observer agreement.

XI.F. Participant Retention and Drop-out Recovery

The RIVUR protocol has been developed to minimize the number of participants lost to follow-up and reduce barriers to participation. The schedule of contacts is designed to facilitate participant retention through regular contacts. Parents will be asked to provide contact information for individuals (relatives, friends, co-workers) who would likely know their location in the event the child becomes lost to follow-up. This contact information will be stored locally in a secure location. Established methods for the recovery of dropouts will be implemented to re-engage participants who become inactive with trial [42].

XII. STATISTICAL ANALYSIS

XII.A. Primary Endpoint

The primary study endpoint is recurrent $_{F/S}$UTI. The proportion of participants who have at least one recurrence of $_{F/S}$UTI will serve as the primary analysis variable. The primary analysis will test the null hypothesis of no difference in the proportion of patients with recurrent $_{F/S}$UTI, in the two treatment groups, using a chi-square test, stratified by recruitment site. A two-sided test at a significance level of .05 will be employed (with adjustment for multiple looks, as described in section XIII.B.). All analyses will be based on the principal of intention to treat (i.e., by the treatment assignment of patients at randomization, regardless of subsequent compliance to the assigned treatment). We will also perform "sensitivity analyses" making assumptions about patients lost to follow-up that are biased towards the null hypothesis (e.g., assuming the event rate for incomplete patients in each group is equal to that of observed patients in the opposite treatment).

Supplemental analyses will use logistic regression techniques to adjust the estimated treatment effects for baseline covariates measuring severity of the VUR, and other prognostic variables [43, 44]. We will also use survival analysis models with time-dependent covariates to adjust for effects such as concomitant use of other antibiotics and compliance with the study medication.

XII.B. Other Endpoints

Efficacy with respect to UTI will also be assessed based on analysis of time to recurrent $_{F/S}$UTI and proportion of participants declared treatment failures.

Categorical variables such as non-E. coli UTI, TMP/SMZ-resistant UTI, and rates of antimicrobial resistance will be compared using chi-square analysis. Other models will compare the number of specimens that are positive for resistance for each patient.

Renal scarring is a secondary outcome measure. The proportion of participants who have any renal scars assessed on the outcome DMSA scan will serve as the principal analysis variable for scarring. The proportion with *severe* scarring will also be evaluated.

The development of antimicrobial resistance in the stool will also be measured as a secondary outcome.

The relationship between treatment and the secondary endpoints will be explored using a variety of methods. Endpoints that are dichotomous will be analyzed using chi-square or exact tests, as appropriate. Endpoints that are time to event variables will be analyzed using survival-time regression techniques. Secondary endpoints that are continuous (or approximately so); these will be analyzed using conventional linear models and rank statistics.

XII.C. Sub-Population Comparisons

Treatment effects for the primary endpoint will be estimated and compared for subpopulations defined by gender and severity of VUR using logistic regression models. Models will be fit including treatment by sub-population interactions. Sub-population differences in treatment effects will only be reported if the interactions are significant (at the .05 level). An analogous approach will be used for the various secondary endpoints.

The power of these comparisons is low for the primary endpoint and other dichotomous or time-to-event endpoints. The study is only likely to detect marked differences in treatment efficacy for these outcomes. The trial will have much better power to detect differences among sub-populations for continuous outcome variables.

XII.D. Study Power

Power calculations were based on a simple comparison of the difference in proportion of events between treatment groups. The table below presents estimates of the study power for a range of plausible event rates and treatment effects. The calculations below assume that the event rate in the placebo group will be either 20% or 25%. The event rate in complying patients in the active treatment group is assumed to be 10%. All calculations assume a type I error rate of $\alpha = .05$, two-sided.

In estimating the effect of non-compliance / drop-out, we have assumed that patients in the treated group who drop-out or are non-compliant have the same rate of $_{F/S}$UTIs as those in the placebo group (i.e., no treatment effect). Since many of those patients will receive some active therapy for some period of time, this is a somewhat conservative assumption. In order to adjust for these effects, the observed event rate in the treated group will be estimated as a blend of the unadjusted event rates for the two groups. Thus, for example, if the event rate in the placebo group is 20%, the non-adjusted event rate in the treated group is 10%, and Non-compliance / attrition is 15%, the adjusted event rate in the treated group will be:
$(.10 \times .85) + (.20 \times .15) = .115$.

Table 5. Event Rate in Treated Group, Adjusted for Non-Compliance / Attrition

Placebo Event Rate	Non-compliance / Attrition		
	5%	10%	15%
20%	.105	.11 .115	
25%	.108	.115 .122	

Given these assumptions and adjustments, the estimated study power for the primary hypothesis is:

Table 6. Estimated Power

Placebo Event Rate	Non-compliance / Attrition		
	5%	10%	15%
20%	.87	.83 .78	
25%	.99	.98 .97	

XIII. DATA AND SAFETY MONITORING PLAN

XIII.A. Data and Safety Monitoring Board

The Data Safety Monitoring Board reports will be prepared two times a year (or as specified by the DSMB). Although the DSMB will determine the format of the report, we anticipate that each report will consist of six sections: 1) recruitment, 2) treatment efficacy, 3) adverse effects of the study medication, 4) patient adherence, 5) data quality, and 6) sub-studies. The recruitment section will present overall recruitment, as well as recruitment by grade of VUR, and for other subgroups of interest (e.g., by gender). The treatment efficacy section will contain a comparison of recurrent $_{F/S}$UTIs in the active prophylaxis and placebo groups. The section on adverse effects of the treatments will report any adverse outcomes associated with the intervention, and it will summarize the use of drugs to treat break-through UTIs. Patient adherence data will compare the distribution of consumption of study medication between the prophylaxis and placebo groups. The quality control sections will include summaries of the quality control data collected by the DCC to monitor and correct operational data collection. Sub-studies will be monitored to ensure that they do not adversely effect recruitment or adherence.

Approximately 6 weeks prior to the scheduled meeting of the DSMB, an edited data file will be created by the DCC. A random sample of the records on the file will be compared to the original data sources to check that patient records have not been altered or processing errors have occurred.

Key data fields will be checked to ensure that invalid values have not been entered. A report based on the final edited data file will be sent to members of the DSMB one-to-two weeks prior to the meeting. Steps taken to insure security and confidentiality include distribution by an express delivery service and enactment of a return policy of all reports. Tables comparing the primary endpoint and other major outcomes will be updated the week before the DSMB meeting to provide the committee with the most up-to-date data.

XIII.B. Analysis Plan

The DCC will provide analyses to assist judgments about whether the study should be terminated early because of proven efficacy or unanticipated harmful effects of the treatment. A number of methods for the repeated analysis of accumulating data have been proposed [45, 46]. When considering the stopping of a trial in which efficacy of the experimental treatment is claimed, the method used for monitoring the trial should be conservative in the sense that the trial should be stopped before its planned end only if the treatment is clearly superior. The methods referenced here provide such a conservative approach. The Cochran-Mantel-Haenzel test will be the primary statistic evaluated by the interim stopping methods. The O'Brien-Fleming boundary [46] is a conservative approach that is frequently used in the interim monitoring of trials. However, when the number and timing of interim analyses cannot be specified a priori, a Lan-DeMets type spending function[45] that approximates the O-Brien-Fleming boundary is more flexible. We plan to perform two interim evaluations after approximately 1/3 and 2/3 of the expected number of events have occurred and a final analysis at the scheduled end of trial using a two-sided O'Brien-Fleming type boundary with overall type I error=.05 computed using a Lan-DeMets spending function approach.

The method proposed by Halperin, et al., 1982, will also be reported to guide judgments by the DSMB about whether interim data is sufficient to determine that the treatment effect is likely to be 1) too small to be of practical importance or 2) so small that it cannot be demonstrated with a trial of the currently planned size [47].

Although we have proposed methods for monitoring the progress of the trial and we will provide data management and statistical computing to support the monitoring, the actual recommendation concerning the continuation or cessation of the trial will be made by the DSMB to the NIDDK.

XIV. TRIAL AND COMMITTEE ORGANIZATION

XIV.A. Participating Sites

XIV.A.1. Clinical Treatment Centers

- Children's Hospital of Philadelphia — Ron Keren, MD
- Children's Hospital of Pittsburgh — Alejandro Hoberman, MD
- Johns Hopkins School of Medicine — Ranjiv Mathews, MD
- Wayne State University School of Medicine — Tej K. Mattoo, MD
- Women and Children's Hospital of Buffalo — Saul P. Greenfield, MD

Participating Sites: Listed below are names of the clinical centers willing to participate in the trial and their principal investigators.

Affiliated with Johns Hopkins School of Medicine (Ranjiv Mathews, MD)

- Children's Hospital of Akron, Akron, OH — Dan McMahon, MD
- Penn State Hershey Medical Center, Hershey, PH — Ross Decter, MD

Affiliated with Wayne State University School of Medicine (PI: Tej K. Mattoo, MD)

- Children's Hospital of Boston, Boston, MA — Caleb Nelson MD
- Children's Mercy Hospital, Kansas City, MO — Uri Alon, MD
- Texas Children's Hospital, Houston, TX — Eileen D. Brewer, MD
- University of Alabama, Birmingham, AL — Mark Benfield, MD
- Univ. of Wis. Children's Hospital, Madison, WI — Sharon Bartosh, MD
- Wake Forest Univ. Baptist Med. Ct., Winston Salem, NC — Gordon McLorie, MD

Affiliated with Women and Children's Hospital of Buffalo (Saul P. Greenfield, MD)

- Children's Memorial Hospital, Chicago, IL — Earl Cheng, MD
- Children's National Medical Center, Washington, DC — H. Gil Rushton, MD
- Cincinnati Children's Medical Center, Cincinnati, OH — William Robert DeFoor, MD
- Oregon Health & Science University, Portland, OR — Steven Skoog, MD
- University of Oklahoma, Oklahoma City, OK — Brad Kropp, MD

Affiliated with Children's Hospital of Philadelphia (Ron Keren, MD)

- Alfred I. DuPont Hospital for Children, DE — Amy Renwick, MD

Potential Backup Clinical Sites: Listed below are names of locations and investigators that will be initiated as clinical sites if the participating sites are unable to recruit 600 participants.

Affiliated with Wayne State University School of Medicine

- Cardinal Glennon Children's Hospital, St. Louis, MO — Ellen Wood, MD
- Cleveland Clinic- Children's Hospital, Cleveland, OH — Deepa Chand, MD; Jonathan Ross, MD
- Emory University, Atlanta, GA — Larry Greenbaum, MD
- Loma Linda University Medical Center, CA — Shobha Sahney, MD
- Hospital for Sick children, Toronto, Canada — Denis Geary, MD

• Medical College of Ohio, Toledo, Ohio	Martin DeBeukalaer, MD Kenneth Kropp, MD
• Medical College of Wisconsin, Milwaukee, WI	Hrair Mesrobian, MD
• MSU-Kalamazoo Ctr. Med. Stud., Kalamazoo, MI	Alfonso Torres, MD
• Nationwide Children's Hospital, Columbus, OH	Mark Menster, MD
• Children's Hospital, New Orleans, LA	Dough Silverstein, MD
• St. Barnabas Medical Center, NJ	Isabel Roberti, MD
• Stanford University Medical Center, Palo Alto, CA	Steven Alexander, MD
• State Univ. of NY, Stony Brook, NY	Dilys Whyte, MD
• Stollery Children's Hospital, Edmonton, Canada	Manjula Gowrishankar, MD
• University of Virginia, Charlottesville, VA	John Barcia, MD Jonathan Roth, MD
• University of Arkansas, AK	Richard Blaszak, MD
• University of Florida, FL	Eduardo Garin, MD
• University of Michigan, Ann Arbor, MI	Jen-Jar Lin, MD
• University of South Florida, Tampa, FL	Alfonso Campos, MD
• University of Texas, San Antonio, TX	Arar Mazen, MD Denis Peppas, MD
• West Virginia University, Charleston, WV	Myra Chiang, MD

Affiliated with Women and Children's Hospital of Buffalo

• Children's Hospital of Atlanta, Atlanta, GA	Andrew Kirsch, MD
• University of Michigan, Ann Arbor, MI	Julian Wan, MD
• Denver Children's Hospital, Denver, CO	Martin Koyle, MD
• Vanderbilt University, Nashville, TN	Mark Adams, MD
• Kaiser Permanente, Los Angeles, CA	Richard Hurwitz, MD

XIV.A.2. Data and Statistical Coordinating Center

• Collaborative Studies Coordinating Center, University of North Carolina, Chapel Hill, NC	Myra A. Carpenter, PhD

XIV.A.3. Central Laboratories

Blood Serum Creatinine and Cystatin C analysis

• University of Rochester Medical Center, Rochester, NY	George Schwartz, MD

Rectal swab analysis

• Infectious Disease Laboratory, Childrens Hospital of Pittsburgh, Pittsburgh, PA	Karen Barbadora

XIV.A.4 Central Repositories

Storage of Blood and Urine specimens

- NIDDK Specimen Repository, Fisher BioServices, Inc., Rockville, MD

Storage of Genetic specimens

- NIDDK Genetics Repository, Rutgers, The State University of New Jersey, Piscataway, NJ

XIV.A.5. National Institutes of Health

- NIDDK (Marva Moxey-Mims, MD)

XIV.B. Committees

XIV.B.1. Steering Committee

This committee consists of Principal Investigators and Co-Investigators of the Clinical Treatment Centers and Data Coordinating Center, and representatives from NIDDK. The committee is chaired by an outside consultant, Dr. Russell Chesney, not affiliated with any study Clinical site. Each of the five participating clinical centers, including the DCC and NIDDK has one vote on the Committee.

The Steering Committee will oversee all aspects of the design, execution, and publication of the study. The Steering Committee will meet as necessary, and at least once a year, and convene by conference calls throughout the study, including the period for final analysis and writing activities that follow the conclusion of patient follow-up. These meetings bring together investigators and clinical coordinators from the various participating centers for discussion regarding development of the protocol, study logistics, progress of the trial, possible changes in the protocol or methodology, new developments in the field, revitalization of interest, and other matters of concern to participants in the study. These meetings also provide an opportunity for staff training and education. The Steering Committee will establish subcommittees to develop and monitor all aspects of the study, reporting recommendations to the Steering Committee for approval.

XIV.B.2. Executive Committee

The Executive committee provides clinical and scientific direction for the study at the operational level. The committee is comprised of the Steering Committee Chair, the PI and Co-PI from the Data Statistical Coordinating Center, and the NIDDK Project Officers.

The major responsibilities of the Executive Committee are reviewing overall progress of the study with particular emphasis on programmatic issues, including operational, budgetary, safety, compliance, and quality issues. In addition to formulating the Steering Committee agendas, this Committee will provide planning and organization for DSMB meetings, including review of preliminary, non-confidential data in preparation for these meetings.

XIV.B.3. Principal Investigators Committee

This committee consists of the five clinical center PIs, the DCC PI, NIDDK Project Officers, and the Steering Committee Chair.

The major responsibilities of the Principal Investigators Committee include:

- Facilitate Steering Committee meetings though submission of agenda items, preparation of materials for Steering Committee review and approval, etc.
- Review and approve any proposed revisions to the protocol

- Review of reports from the Data Coordinating Center on performance of each participating institution specifically recruitment, data quality, and adherence to protocol. This committee will also identify and implement solutions to problems which arise, including giving consideration to on-site visits to those institutions with deficiencies and consideration of additional institutions if one drops out or is dropped
- overseeing subcommittees listed below

XIV.B.4. Ancillary Studies Committee

It is anticipated that both intramural and extramural investigators will wish to capitalize on the potential for collaborative ancillary investigations afforded by the implementation of the main study. The Ancillary Studies Committee will formally review and recommend approval or disapproval of all proposed ancillary studies, considering both their impact on the conduct of the main study, and their scientific merit.

XIV.B.5. Publications Committee

This committee will formulate publication policy for this collaborative research and review all abstracts, papers and scientific presentations which utilize study data. The Publications Committee will be responsible for identifying topics for publication as well as making writing group assignments. The committee will review and recommend approval or disapproval of all scientific abstracts and papers or presentations using unpublished study data, as well as every paper using published data that purports to represent official study views or policy. Another major responsibility of the Publications Committee is in the development of plans for the dissemination of trial findings and incorporation of the findings into medical care policy. This will involve not only reports in medical journals but consideration of continuing education courses, conferences and seminars and special efforts such as press conferences, editorials, physician newsletters and presentations at local medical association meetings.

XIV.B.6. Quality Control Committee

This committee will be responsible for assuring high quality data by monitoring clinic, laboratory, and classification committee performance and initiating corrective action when needed. Internal quality control reports provided by the DCC will be reviewed. A system for sending blinded replicate samples to the central lab will be developed by this committee and implemented by the DCC with the results monitored by this committee.

XIV.B.7. Recruitment Committee

The responsibilities of this committee are to develop materials and presentations to assist investigators in recruitment of participants, and materials to encourage patient and physician interest and participation in the study. Throughout the study recruitment period, this committee advises the Principal Investigators Committee on suggested strategies to decrease deficiencies in patient accrual and where necessary, and works with specific clinical sites with particular problems.

XIV.B.8. Study Operations Committee

The Operations Committee is concerned with the day-to-day operations of the study. Membership may include Study Coordinators, Principal and Co-Investigators, and other individuals affiliated with the study. This committee proposes modifications to the Manual of Procedures, serves as a liaison with the Quality Control Committee to resolve identified problems, and considers comparability issues of trial conduct across clinical sites.

XIV.C. Data and Safety Monitoring Board (DSMB)

Established by NIDDK, this committee is comprised of independent scientists who monitor the study results for evidence of adverse or beneficial treatment effects throughout the study period. The DSMB will remain "blinded" to outcome characteristics of the study for as long as possible. While the Board may have access to any information that is deemed necessary to make an appropriate determination, highly sensitive information in relation to the outcome of the study will be requested on a "need to know" basis as it may arise during the course of the Board's deliberations. DSMB attention will be directed to patient accrual, appropriate follow-up, compliance, data acquisition, undue complications, and whether the study as it is currently being conducted will be able to answer the hypotheses it addresses.
The membership and frequency of meeting are at the discretion of NIDDK but will presumably consist of at least 5 members including a biostatistician, 3 clinical investigators, and an NIDDK representative. It is expected that this Board will meet 1 to 2 times per year and will report to NIDDK on scientific and administrative issues. For example, the Board has the responsibility for recommending early termination in case of unanticipated toxicity or greater than expected benefit. The responsibility for subject safety is particularly important, and the Board will review all adverse events by blinded (or unblinded, when appropriate) treatment group assignment.

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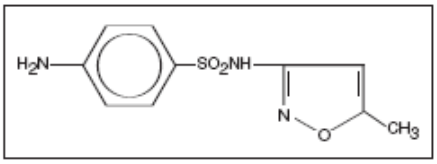
Appendix A

Sulfamethoxazole and Trimethoprim Oral Suspension

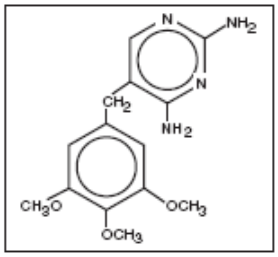
SULFAMETHOXAZOLE AND TRIMETHOPRIM ORAL SUSPENSION

DESCRIPTION: Sulfamethoxazole and Trimethoprim Oral Suspension is a synthetic antibacterial combination product. Each teaspoonful (5 mL) for oral administration, contains 200 mg sulfamethoxazole and 40 mg trimethoprim in a vehicle containing alcohol 0.26%, methylparaben 0.1% and sodium benzoate 0.1% (added as preservatives), carboxymethylcellulose sodium, citric acid (anhydrous), glycerin, microcrystalline cellulose, polysorbate 80, purified water, saccharin sodium, and sorbitol. The light purple, grape flavored suspension contains the following additional inactive ingredients: FD&C Red No. 40, FD&C Blue No. 1 and natural and artificial grape flavor. The pink, cherry flavored suspension contains the following additional inactive ingredients: FD&C Red No. 40, FD&C Yellow No. 6 and artificial cherry flavor.

Sulfamethoxazole is N^1-(5-methyl-3-isoxazolyl) sulfanilamide. It is an almost white, odorless, tasteless compound with a molecular weight of 253.28, and the molecular formula $C_{10}H_{11}N_3O_3S$. The structural formula is:



Trimethoprim is 2,4-diamino-5-(3,4,5-trimethoxybenzyl) pyrimidine. It is a white to light yellow, odorless, bitter compound with a molecular weight of 290.32, and the molecular formula $C_{14}H_{18}N_4O_3$. The structural formula is:



CLINICAL PHARMACOLOGY: Sulfamethoxazole and trimethoprim oral suspension is rapidly absorbed by following oral administration. Both sulfamethoxazole and trimethoprim exist in the blood as unbound, protein-bound, and metabolized forms; sulfamethoxazole also exists as the conjugated form. The metabolism of sulfamethoxazole occurs predominantly by N_4-acetylation, although the glucuronide conjugate has been identified. The principal metabolites of trimethoprim are the 1- and 3-oxides and the 3'- and 4'-hydroxy derivatives. The free forms of sulfamethoxazole and trimethoprim are considered to be the therapeutically active forms. Approximately 44% of trimethoprim and 70% of sulfamethoxazole are bound to plasma proteins. The presence of 10 mg percent sulfamethoxazole in plasma decreases the protein binding of trimethoprim by an insignificant degree; trimethoprim does not influence the protein binding of sulfamethoxazole.

Peak blood levels for the individual components occur 1 to 4 hours after oral administration. The mean serum half-lives of sulfamethoxazole and trimethoprim are 10 and 8 to 10 hours, respectively. However, patients with severely impaired renal function exhibit an increase in the half-lives of both components, requiring dosage regimen adjustment (see **DOSAGE AND ADMINISTRATION**). Detectable amounts of trimethoprim and sulfamethoxazole are present in the blood 24 hours after drug administration. During administration of 160 mg trimethoprim and 800 mg sulfamethoxazole b.i.d., the mean steady-state plasma concentration of trimethoprim was 1.72 mcg/mL. The steady-state minimal plasma levels of free and total sulfamethoxazole were 57.4 mcg/mL and 68.0 mcg/mL, respectively. These steady-state levels were achieved after 3 days of drug administration.[1]

Excretion of sulfamethoxazole and trimethoprim is primarily by the kidneys through both glomerular filtration and tubular secretion. Urine concentrations of both sulfamethoxazole and trimethoprim are considerably higher than are the concentrations in the blood. The average percentage of the dose recovered in urine from 0 to 72 hours after a single oral dose is 84.5% for total sulfonamide and 66.8% for free trimethoprim. Thirty percent of the total sulfonamide is excreted as free sulfamethoxazole, with the remaining as N_4-acetylated metabolite.[2] When administered together, neither sulfamethoxazole nor trimethoprim affects the urinary excretion pattern of the other.

Both sulfamethoxazole and trimethoprim distribute to sputum, vaginal fluid, and middle ear fluid; trimethoprim also distributes to bronchial secretions, and both pass the placental barrier and are excreted in human milk.

Geriatric Pharmacokinetics: The pharmacokinetics of sulfamethoxazole 800 mg and trimethoprim 160 mg were studied in 6 geriatric subjects (mean age: 78.6 years) and 6 young healthy subjects (mean age: 29.3 years) using a non-U.S. approved formulation. Pharmacokinetic values for sulfamethoxazole in geriatric subjects were similar to these observed in young adult subjects. The mean renal clearance of trimethoprim was significantly lower in geriatric subjects compared with young adult subjects (19 mL/h/kg vs. 55 mL/h/kg). However, after normalizing by body weight, the apparent total body clearance of trimethoprim was an average 19% lower in geriatric subjects compared with young adult subjects.[3]

Microbiology: Sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid by competing with *para*-aminobenzoic acid (PABA). Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. Thus, this combination blocks two consecutive steps in the biosynthesis of nucleic acids and proteins essential to many bacteria.

In vitro studies have shown that bacterial resistance develops more slowly with this combination than with either trimethoprim or sulfamethoxazole alone.

In vitro serial dilution tests have shown that the spectrum of antibacterial activity of sulfamethoxazole and trimethoprim includes the common urinary tract pathogens with the exception of *Pseudomonas aeruginosa*. The following organisms are usually susceptible: *Escherichia coli, Klebsiella* species, *Enterobacter* species, *Morganella morganii, Proteus mirabilis* and indole-positive *Proteus* species including *Proteus vulgaris*.

The usual spectrum of antimicrobial activity of sulfamethoxazole and trimethoprim includes bacterial pathogens isolated from middle ear exudate and from bronchial secretions (*Haemophilus influenzae*, including ampicillin-resistant strains, and *Streptococcuspneumoniae*), enterotoxigenic strains of *Escherichia coli (ETEC)* causing bacterial gastroenteritis. *Shigella flexneri* and *Shigella sonnei* are also usually susceptible.

Susceptibility Testing:

Dilution techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method [5,7] (broth or agar) or equivalent with standardized incoulum concentrations and standardized concentrations of sulfamethoxazole/trimethoprim powder. The MIC values should be interpreted according to the following criteria:

For testing *Enterobacteriaceae, Acinetobacter* spp., *Staphylococcus* spp., *Burkholderia cepacia, Stenotrophomonas maltophilia,* and *Vibrio cholerae:*

MIC (mcg/mL)	Interpretation
≤ 2/38	Susceptible (S)
≥ 4/76	Resistant (R)

For testing *Haemophilus influenzae and Haemophilus parainfluenzae:*

MIC (mcg/mL)	Interpretation
≤ 0.5/9.5	Susceptible (S)
1/19 to 2/38	Intermediate (I)
≥ 4/76	Resistant (R)

These interpretative standards are applicable only to broth microdilution susceptibility testing using *Haemophilus* Test Medium[5].

For testing *Streptococcus pneumoniae:*

MIC (mcg/mL)	Interpretation
≤ 0.5/9.5	Susceptible (S)
1/19 to 2/38	Intermediate (I)
≥ 4/76	Resistant (R)

These interpretive standards are applicable only to broth microdilution susceptibility testing using cation-adjusted Mueller-Hinton broth with 2.5 to 5% lysed horse blood[5].

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control: Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard sulfamethoxazole/trimethoprim powder should provide the following MIC values:

Microorganism	MIC Range (mcg/mL)
Escherichia coli ATCC 25922	≤ 0.5/9.5
Staphylococcus aureus ATCC 29213	≤ 0.5/9.5
Pseudomonas aeruginosa ATCC 27853	8/152 to 32/608
Haemophilus influenzae ATCC 49247	0.03/0.59 to 0.25/4.75
Streptococcus pneumoniae ATCC 49619	0.12/2.4 to 1/19

Diffusion techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure [6,7] requires the use of standard incoculum concentrations. This procedure uses paper disks impregnated with 1.25 mcg/23.75 mcg sulfamethoxazole/trimethoprim to test the susceptibility of microorganism to sulfamethoxazole/trimethoprim.

Reports from the laboratory providing results of the standard disk susceptibility test with a 1.25 mcg/23.75 mcg sulfamethoxazole/trimethoprim disk should be interpreted according to the following criteria:

For testing *Enterobacteriaceae, Acinetobacter* spp., *Staphylococcus* spp., *Burkholderia cepacia, Stenotrophomonas maltophilia,* and *Vibrio cholerae:*

Zone Diameter (mm)	Interpretation	MIC (mcg/mL)
≥16	Susceptible (S)	≤ 2/38
11 to 15	Intermediate (I)	-
≤10	Resistant (R)	≥ 8/152

For testing *Haemophilus influenzae and Haemophilus parainfluenzae:*

Zone Diameter (mm)	Interpretation	MIC (mcg/mL)
≥16	Susceptible (S)	≤ 0.5/9.5
11 to 15	Intermediate (I)	-
≤10	Resistant (R)	≥ 4/76

These zone diameter standards are applicable only to susceptibility testing with *Haemophilus* species using *Haemophilus* Test Medium[6].

For testing *Streptococcus pneumoniae:*

Zone Diameter (mm)	Interpretation	MIC (mcg/mL)
≥19	Susceptible (S)	≤ 0.5/9.5
16 to 18	Intermediate (I)	-
≤15	Resistant (R)	≥ 4/76

These interpretative standards are applicable only to disk diffusion testing using Mueller-Hinton agar adjusted with 5% sheep blood[6].

Quality Control: As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 1.25 mg/23.75 mcg sulfamethoxazole/trimethoprim disk* should provide the following zone diameters in these laboratory test quality control strains:

Microorganism	MIC Range(mcg/mL)
Escherichia coli ATCC 25922	23 to 29
Staphylococcus aureus ATCC 25923	24 to 32
Haemophilus influenzae ATCC 49247	24 to 32
Streptococcus pneumoniae ATCC 49619	20 to 28

*Mueller-Hinton agar should be checked for excessive levels of thymidine. To determine whether Mueller-Hinton medium has sufficiently low levels of thymidine and thymine, an *Enterococcus faecalis* (ATCC 29212 or ATCC 33186) may be tested with trimethoprim/sulfamethoxazole disks. A zone of inhibition ≥20 mm that is essentially free of fine colonies indicates a sufficiently low level of thymidine and thymine.

INDICATIONS AND USAGE To reduce the development of drug-resistant bacteria and maintain the effectiveness of sulfamethoxazole and trimethoprim oral suspension and other antibacterial drugs, sulfamethoxazole and trimethoprim oral suspension should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

URINARY TRACT INFECTIONS: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella* species, *Enterobacter* species, *Morganella morganii, Proteus mirabilis,* and *Proteus vulgaris*. It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.

ACUTE OTITIS MEDIA: For the treatment of acute otitis media in pediatric patients due to susceptible strains of *Streptococcus pneumoniae* or *Haemophilus influenzae* when, in the judgment of the physician, sulfamethoxazole and trimethoprim oral suspension offers some advantage over the use of other antimicrobial agents. To date, there are limited data on the safety of repeated use of sulfamethoxazole and trimethoprim in pediatric patients under two years of age. This product is not indicated for prophylactic or prolonged administration in otitis media at any age.

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS: For the treatment of acute exacerbations of chronic bronchitis due to susceptible strains of *Streptococcus pneumoniae* or *Haemophilus influenzae* when, in the judgment of the physician, sulfamethoxazole and trimethoprim oral suspension offers some advantage over the use of a single antimicrobial agent.

TRAVELERS' DIARRHEA IN ADULTS: For the treatment of travelers' diarrhea due to susceptible strains of enterotoxigenic *E. coli.*

SHIGELLOSIS: For the treatment of enteritis caused by susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

PNEUMOCYSTIS CARINII PNEUMONIA: For the treatment of documented *Pneumocystis carinii* pneumonia. For prophylaxis against *Pneumocystis carinii* pneumonia in individuals who are immunosuppressed and considered to be at an increased risk of developing *Pneumocystis carinii* pneumonia.

CONTRAINDICATIONS Sulfamethoxazole and trimethoprim oral suspension is contraindicated in patients with a known hypersensitivity to trimethoprim or sulfonamides and in patients with documented megaloblastic anemia due to folate deficiency. Sulfamethoxazole and trimethoprim oral suspension is also contraindicated in pregnant patients at term and in nursing mothers, because sulfonamides pass the placenta and are excreted in the milk and may cause kernicterus. Sulfamethoxazole and trimethoprim oral suspension is also contraindicated in pediatric patients less than two months of age.

WARNINGS: FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA, AND OTHER BLOOD DYSCRASIAS.

SULFONAMIDES, INCLUDING SULFONAMIDE-CONTAINING PRODUCTS SUCH AS SULFAMETHOXAZOLE/TRIMETHOPRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. In rare instances, a skin rash may be followed by a more severe reaction such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis and serious blood disorder (see **PRECAUTIONS**).

Clinical signs, such as rash, sore throat, fever, arthralgia, pallor, purpura, or jaundice may be early indications of serious reactions.

Cough, shortness of breath, and pulmonary infiltrates are hypersensitivity reactions of the respiratory tract that have been reported in association with sulfonamide treatment.

The sulfonamides should not be used for the treatment of group A beta-hemolytic streptococcal infections. In an established infection, they will not eradicate the streptococcus and, therefore, will not prevent sequelae such as rheumatic fever.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including sulfamethoxazole and trimethoprim oral suspension, USP, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile.*

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antiobiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS: **General:** Prescribing sulfamethoxazole and trimethoprim oral suspension in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. Sulfamethoxazole and trimethoprim oral suspension should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency (e.g., the elderly, chronic alcoholics, patients receiving anticonvulsant therapy, patients with malabsorption syndrome, and patients in malnutrition states), and to those with severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur. This reaction is frequently dose-related (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

Use in the Elderly: There may be an increased risk of severe adverse reactions in elderly patients, particularly when complicating conditions exist, e.g., impaired kidney and/or liver function, or concomitant use of other drugs. Severe skin reactions, generalized bone marrow suppression (see **WARNINGS** and **ADVERSE REACTIONS**), or a specific decrease in platelets (with or without purpura) are the most frequently reported severe adverse reactions in elderly patients. In those concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Appropriate dosage adjustments should be made for patients with impaired kidney function (see **DOSAGE AND ADMINISTRATION**).

Use in the Treatment of and Prophylaxis for *Pneumocystis carinii* Pneumonia in Patients with Acquired Immunodeficiency Syndrome (AIDS): The incidence of side effects, particularly rash, fever, leukopenia, and elevated aminotransferase (transaminase) values in AIDS patients who are being treated with sulfamethoxazole and trimethoprim therapy for *Pneumocystis carinii* pneumonia has been reported to be greatly increased compared with the incidence normally associated with the use of sulfamethoxazole and trimethoprim in non-AIDS patients. The incidence of hyperkalemia and hyponatremia appears to be increased in AIDS patients receiving sulfamethoxazole and trimethoprim. Adverse effects are generally less severe in patients receiving sulfamethoxazole and trimethoprim for prophylaxis. A history of mild intolerance to sulfamethoxazole and trimethoprim in AIDS patients does not appear to predict intolerance of subsequent secondary prophylaxis. However, if a patient develops skin rash or any sign of adverse reaction, therapy with sulfamethoxazole and trimethoprim should be re-evaluated (see **WARNINGS**).

The concomitant use of leucovorin with sulfamethoxazole/trimethoprim for the acute treatment of *Pneumocystis carinii* pneumonia in patients with HIV infection was associated with increased rates of treatment failure and morbidity in a placebo-controlled study.

Information for Patients: Patients should be counseled that antibacterial drugs including sulfamethoxazole and trimethoprim oral suspension should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When sulfamethoxazole and trimethoprim oral suspension is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of the therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by sulfamethoxazole and trimethoprim oral suspension or other antibaceterial drugs in the future.

Patients should be instructed to maintain an adequate fluid intake in order to prevent crystalluria and stone formation.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with and without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible."

Laboratory Tests: Complete blood counts should be done frequently in patients receiving sulfamethoxazole and trimethoprim; if a significant reduction in the count of any formed blood element is noted, sulfamethoxazole and trimethoprim oral suspension should be discontinued. Urinalyses with careful microscopic examination and renal function tests should be performed during therapy, particularly for those patients with impaired renal function.

Drug Interactions: In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. In the literature, two cases of hyperkalemia in elderly patients have been reported after concomitant intake of sulfamethoxazole/trimethoprim and

an angiotensin converting enzyme inhibitor.

It has been reported that sulfamethoxazole and trimethoprim may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin. This interaction should be kept in mind when sulfamethoxazole and trimethoprim is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

Sulfamethoxazole and trimethoprim may inhibit the hepatic metabolism of phenytoin. Sulfamethoxazole and trimethoprim, given at a common clinical dosage, increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 27%. When administering these drugs concurrently, one should be alert for possible excessive phenytoin effect.

Sulfonamides can also displace methotrexate from plasma protein binding sites,thus increasing free methotrexate concentrations.

Drug/Laboratory Test Interactions: This combination product, specifically the trimethoprim component, can interfere with a serum methotrexate assay as determined by the competitive binding protein technique (CBPA) when a bacterial dihydrofolate reductase is used as the binding protein. No interference occurs, however, if methotrexate is measured by a radioimmunoassay (RIA).

The presence of trimethoprim and sulfamethoxazole may also interfere with the Jaffé alkaline picrate reaction assay for creatinine, resulting in overestimations of about 10% in the range of normal values.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: Long-term studies in animals to evaluate carcinogenic potential have not been conducted with sulfamethoxazole and trimethoprim.

Mutagenesis: Bacterial mutagenic studies have not been performed with sulfamethoxazole and trimethoprim in combination. Trimethoprim was demonstrated to be non-mutagenic in the Ames assay. In studies at two laboratories, no chromosomal damage was detected in cultured Chinese hamster ovary cells at concentrations approximately 500 times human plasma levels; at concentrations approximately 1,000 times human plasma levels in these same cells, a low level of chromosomal damage was induced in one of these laboratories. No chromosomal abnormalities were observed in cultured human leukocytes at concentrations of trimethoprim up to 20 times human steady-state plasma levels. No chromosomal effects were detected in peripheral lymphocytes of human subjects receiving 320 mg of trimethoprim in combination with up to 1,600 mg of sulfamethoxazole per day for as long as 112 weeks.

Impairment Of Fertility: No adverse effects on fertility or general reproductive performance were observed in rats given oral dosages as high as 70 mg/kg/day trimethoprim plus 350 mg/kg/day sulfamethoxazole.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. In rats, oral doses of 533 mg/kg sulfamethoxazole or 200 mg/kg trimethoprim produced teratologic effects manifested mainly as cleft palates.The highest dose which did not cause cleft palates in rats was 512 mg/kg sulfamethoxazole or 192 mg/kg trimethoprim when administered separately. In two studies in rats, no teratogenicity was observed when 512 mg/kg of sulfamethoxazole was used in combination with 128 mg/kg of trimethoprim. In one study, however, cleft palates were observed in one litter out of 9 when 355 mg/kg of sulfamethoxazole was used in combination with 88 mg/kg of trimethoprim.

In some rabbit studies, an overall increase in fetal loss (dead and resorbed and malformed conceptuses) was associated with doses of trimethoprim six times the human therapeutic dose.

While there are no large, well-controlled studies in the use of trimethoprim and sulfamethoxazole in pregnant women, Brumfitt and Pursell,[4] in a retrospective study, reported the outcome of 186 pregnancies during which the mother received either placebo or trimethoprim and sulfamethoxazole. The incidence of congenital abnormalities was 4.5% (3 of 66) in those who received placebo and 3.3% (4 of 120) in those receiving trimethoprim and sulfamethoxazole. There were no abnormalities in the 10 children whose mothers received the drug during the first trimester. In a separate survey, Brumfitt and Pursell also found no congenital abnormalities in 35 children whose mothers had received oral trimethoprim and sulfamethoxazole at the time of conception or shortly thereafter.

Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, sulfamethoxazole and trimethoprim oral suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: See **CONTRAINDICATIONS** section.

Nursing Mothers: See **CONTRAINDICATIONS** section.

Pediatric Use: Sulfamethoxazole and trimethoprim oral suspension is not recommended for pediatric patients younger than 2 months of age (see **INDICATIONS AND USAGE** and **CONTRAINDICATIONS**).

Geriatric Use: Clinical studies of sulfamethoxazole and trimethoprim oral suspension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

There may be an increased risk of severe adverse reactions in elderly patients, particularly when complicating conditions exist, e.g., impaired kidney and/or liver function, possible folate deficiency, or concomitant use of other drugs. Severe skin reactions, generalized bone marrow suppression (see **WARNINGS** and **ADVERSE REACTIONS**), a specific decrease in platelets (with or without purpura), and hyperkalemia are the most frequently reported severe adverse reaction in elderly patients. In those concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Increased digoxin blood levels can occur with concomitant sulfamethoxazole and trimethoprim therapy, especially in elderly patients. Serum digoxin levels should be monitored. Hematological changes indicative of folic acid deficiency may occur in elderly patients. These effects are reversible by folinic acid therapy. Appropriate dosage adjustments should be made for patients with impaired kidney function and duration of use should be as short as possible to minimize risks of undesired reactions (see **DOSAGE AND ADMINISTRATION**). The trimethoprim component of this product may cause hyperkalemia when administered to patients with underlying disorders of potassium metabolism, with renal insufficiency, or when given concomitantly with drugs known to induce hyperkalemia, such as angiotensin converting enzyme inhibitors. Close monitoring of serum potassium is warranted in these patients. Discontinuation of sulfamethoxazole and trimethoprim treatment is recommended to help lower potassium serum levels.

Pharmacokinetics parameters for sulfamethoxazole were similar for geriatric subjects and younger adult subjects. The mean maximum serum trimethoprim concentration was higher and mean renal clearance of trimethoprim was lower in geriatric subjects compared with younger subjects (see **CLINICAL PHARMACOLOGY**, **Geriatric Pharmacokinetics**).

ADVERSE REACTIONS: To report SUSPECTED ADVERSE REACTIONS, contact Hi-Tech Pharmacal, Co., Inc. at 1-800-262-9010 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. The most common adverse effects are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria). **FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA, OTHER BLOOD DYSCRASIAS, AND HYPERSENSITIVITY OF THE RESPIRATORY TRACT (SEE WARNINGS).**

Hematologic: Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia.

Allergic: Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills, Henoch-Schönlein purpura, serum sickness-like syndrome, generalized allergic reactions, generalized skin eruptions, photosensitivity, conjunctival and scleral injection, pruritus, urticaria and rash. In addition, periarteritis nodosa and systemic lupus erythematosus have been reported.

Gastrointestinal: Hepatitis, including cholestatic jaundice and hepatic necrosis, elevation of serum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, anorexia.

Genitourinary: Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, and crystalluria.

Metabolic: Hyperkalemia, hyponatremia.

Neurologic: Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache.

Psychiatric: Hallucinations, depression, apathy, nervousness.

Endocrine: The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides), and oral hypoglycemic agents. Cross-sensitivity may exist with these agents. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides.

Musculoskeletal: Arthralgia and myalgia.

Respiratory System: Cough, shortness of breath, and pulmonary infiltrates (see **WARNINGS).**

Miscellaneous: Weakness, fatigue, insomnia.

OVERDOSAGE:

Acute: The amount of a single dose of sulfamethoxazole and trimethoprim that is either associated with symptoms of overdosage or is likely to be life-threatening has not been reported. Signs and symptoms of overdosage reported with sulfonamides include anorexia, colic, nausea, vomiting, dizziness, headache, drowsiness and unconsciousness. Pyrexia, hematuria and crystalluria may be noted. Blood dyscrasias and jaundice are potential late manifestations of overdosage. Signs of acute overdosage with trimethoprim include nausea, vomiting, dizziness, headache, mental depression, confusion and bone marrow depression. General principles of treatment include the institution of gastric lavage or emesis; forcing oral fluids; and the administration of intravenous fluids if urine output is low and renal function is normal. Acidification of the urine will increase renal elimination of trimethoprim. The patient should be monitored with blood counts and appropriate blood chemistries, including electrolytes. If a significant blood dyscrasia or jaundice occurs, specific therapy should be instituted for these complications. Peritoneal dialysis is not effective and hemodialysis is only moderately effective in eliminating trimethoprim and sulfamethoxazole.

Chronic: Use of sulfamethoxazole and trimethoprim at high doses and/or for extended periods of time may cause bone marrow depression manifested as thrombocytopenia, leukopenia and/or megaloblastic anemia. If signs of bone marrow depression occur, the patient should be given leucovorin; 5 to 15 mg leucovorin daily has been recommended by some investigators.

DOSAGE AND ADMINISTRATION: Contraindicated in pediatric patients less than two months of age.

Urinary Tract Infections and Shigellosis in Adults and Pediatric Patients and Acute Otitis Media in Pediatric Patients:

Adults: The usual adult dosage in the treatment of urinary tract infections is four teaspoonfuls (20mL) Sulfamethoxazole and Trimethoprim Oral Suspension every 12 hours for 10 to 14 days. An identical daily dosage is used for 5 days in treatment of Shigellosis.

Pediatric Patients: The recommended dose for pediatric patients with urinary tract infections or acute otitis media is 40 mg/kg sulfamethoxazole and 8 mg/kg trimethoprim per 24 hours, given in two divided doses every 12 hours for 10 days. An identical daily dosage is used for 5 days in the treatment of shigellosis. The following table is a guideline for the attainment of this dosage:

Pediatric Patients Two months of age or older:

Weight		Dose — Every 12 hours	
lb	kg	Teaspoonfuls	
22	10	1	(5 mL)
44	20	2	(10 mL)
66	30	3	(15 mL)
88	40	4	(20 mL)

For Patients with Impaired Renal Function: When renal function is impaired, a reduced dosage should be employed using the following table:

Creatinine Clearance (mL/min)	Recommended Dosage Regimen
Above 30	Usual Standard Regimen
15-30	1/2 the Usual Regimen
Below 15	Use Not Recommended

Acute Exacerbations of Chronic Bronchitis in Adults:

The usual adult dosage in the treatment of acute exacerbations of chronic bronchitis is four teaspoonfuls (20 mL) Sulfamethoxazole and Trimethoprim Oral Suspension every 12 hours for 14 days.

Travelers' Diarrhea in Adults:

For the treatment of travelers' diarrhea, the usual adult dosage is four teaspoonfuls (20mL) of sulfamethoxazole and trimethoprim oral suspension every 12 hours for 5 days.

***Pneumocystis Carinii* Pneumonia:**

Treatment: Adults and Pediatric Patients: The recommended dosage for treatment of patients with documented *Pneumocystis carinii* pneumonia is 75 to 100 mg/kg sulfamethoxazole and 15 to 20 mg/kg trimethoprim per 24 hours given in equally divided doses every 6 hours for 14 to 21 days. The following table is a guideline for the upper limit of this dosage:

Weight		Dose — Every 6 Hours	
lb	kg	Teaspoonfuls	
18	8	1	(5 mL)
35	16	2	(10 mL)
53	24	3	(15 mL)
70	32	4	(20 mL)
88	40	5	(25 mL)
106	48	6	(30 mL)
141	64	8	(40 mL)
176	80	10	(50 mL)

For the lower limit dose (75 mg/kg sulfamethoxazole and 15 mg/kg trimethoprim per 24 hours) administer 75% of the dose in the above table.

Prophylaxis:

Adults: The recommended dosage for prophylaxis in adults is four teaspoonfuls (20 mL) of the suspension daily.

Pediatric Patients: For pediatric patients, the recommended dose is 750 mg/m^2/day sulfamethoxazole with 150 mg/m^2/day trimethoprim given orally in equally divided doses twice a day, on 3 consecutive days per week. The total daily dose should not exceed 1,600 mg sulfamethoxazole and 320 mg trimethoprim. The following table is a guideline for the attainment of this dosage in pediatric patients:

Body Surface Area	Dose — Every 12 Hours	
(m^2)	Teaspoonfuls	
0.26	1/2	(2.5 mL)
0.53	1	(5 mL)
1.06	2	(10 mL)

HOW SUPPLIED

Sulfamethoxazole and Trimethoprim Oral Suspension is supplied in a purple grape-flavored suspension and in a pink cherry-flavored suspension containing 40 mg trimethoprim and 200 mg sulfamethoxazole per 5 mL (teaspoonful) both packaged in 1 pint (473 mL) bottles.

Store at room temperature 15°-30°C (59°-86°) and protect from light.

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Rx only

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Amityville, New York 11701

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Appendix B

Clinical Sedation Policies

Clinical Site Sedation Policies				
Site Name	Location	Investigator	VCUG	DMSA
			Sedation (y/n)	Sedation (y/n)
Women and Children's Hospital of Buffalo	Buffalo, NY	Saul Greenfield, MD	N	N
Children's National Medical Center	Washington, DC	Gil Rushton, MD	N*	Y
Oregon Health & Science University	Portland, OR	Steven Skoog, MD	Y	Y
University of Oklahoma	Oklahoma City, OK	Brad Kropp, MD	N	N
Johns Hopkins School of Medicine	Baltimore, MD	Ranjiv Mathews, MD	Y	Y
Children's Hospital of Philadelphia	Philadelphia, PA	Ron Keren, MD	N*	N*
Children's Hospital of Pittsburgh	Pittsburgh, PA	Alejandro Hoberman, MD	N	N
Children's Hospital of Michigan (Official Affiliation: Wayne State University School of Medicine)	Detroit, MI	Tej Mattoo, MD	N	Y
Children's Hospital of Boston	Boston, MA	Caleb Nelson, MD Ghalib Daouk, MD	N	N
Nationwide Children's Hospital	Columbus, OH	Mark Mentser, MD	N*	N*
Children's Mercy Hospital of Kansas City	Kansas City, MO	Uri Alon, MD	N	Y
Emory University School oF Medicine	Atlanta, GA	Larry Greenbaum, MD	N	N
Hospital for Sick Children	Toronto, Canada	Dennis Geary, MD	N	Y
Texas Children's Hospital	Houston, TX	Stuart Goldstein, MD	N	N
University of Alabama - Birmingham	Birmingham, AL	Mark Benfield, MD	N	N

* Unless requested by parent or physician

Women
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Hospital of Buffalo

KALEIDA
HEALTH

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Saul P. Greenfield, M.D.
Director

Pierre E. Williot, M.D.

September 25, 2006

Myra A. Carpenter, Ph. D.
Research Assistant Professor, Epidemiology
Collaborative Studies Coordinating Center
Department of Biostatistics
137 East Franklin Street, Suite 203, CB # 8030
University of North Carolina
Chapel Hill, NC 27514-4145

Dear Myra,

As you requested, I am writing to confirm that no sedation is used for either VCUG's or DMSA renal scans at 2 of our sites: Women & Children's Hospital of Buffalo and the University of Oklahoma. Both Rainbow Babies Hospital in Cleveland and Children's National Medical Center in Washington DC do occasionally use sedation and their policies are outlined below:

Rainbow Babies Hospital:

At Rainbow Babies & Children's children are considered for VCUG sedation if they are >18 months and weigh <70 lb. They are kept NPO for 3 hours before the study and are given nasal midazolam 0.2 mg/kg. If they have an upper respiratory infection, they are rescheduled. Vital signs are obtained before the study and after the study, but not after the medication is administered. An RN monitors the patient.

Children's National Medical Center:

We do not use sedation routinely for VCUG. When requested by parents, we use Versed 0.5 mg/kg.

For DMSA Scans, we use sedation in about 10%, usually infants between 1-3 years. Majd uses chloral hydrate 75-100 mg/kg.

Sincerely,

Saul P. Greenfield, M.D.
Director, Division of Pediatric Urology
Department of Pediatric Surgical Services
Women & Children's Hospital of Buffalo
Clinical Professor of Urology
State University of New York at Buffalo School of Medicine

Women
& Children's
Hospital of Buffalo

KALEIDA
HEALTH

March 15, 2007

Myra A. Carpenter, Ph. D.
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Saul P. Greenfield, M.D.
Director

Pierre E. Williot, M.D.

Dear Myra,

I am writing to update the sedation policies being used at the clinical sites associated with Women's & Children's Hospital of Buffalo. As you know, Rainbow Babies Hospital in Cleveland is no longer participating in this project. They are being replaced by the Oregon Health & Science University/Doernbecher Children's Hospital. The sedation regimens in Oregon for both VCUG's and DMSA renal scans are as follows:

Children are sedated for VCUG's on an as needed basis. Children are sedated with midazolam at 0.05 to 0.1 mg/kg over the first 2-3 minutes; then in small increments after 2-3 minutes for a total dose up to 0.6mg/kg, not to exceed 6 mg for children 6 months to 5 years of age. They are kept NPO for 3-4 hours before the procedure. Vital signs are monitored during the procedure by an RN, with a physician present.

All children undergoing a DMSA scan are sedated. Infants and children are sedated with Versed and Propofol. An anesthesiologist and RN are present to monitor and recover the patient pre and post procedure. The dosages are: Versed 0.1-0.2 mg/kg and/or Propofol 125 to 300 mcg/minute (max 7.5 to 18 mg/kg/hour).

Sincerely,

Saul P. Greenfield
Director, Division of Pediatric Urology
Department of Pediatric Surgical Services
Women and Children's Hospital of Buffalo
Clinical Professor of Urology
State University of New York at Buffalo School of Medicine

OHSU HEALTH CARE SYSTEM
CLINICAL POLICY MANUAL
Chapter Five: Medication & Parenteral Infusions

Procedure Sedation and Analgesia, Clin 05.24

Last Reviewed Date: October 29, 2005

POLICY

A. INTRODUCTION

Procedure Sedation is a technique of administering sedatives or dissociative agents with or without analgesics to induce a state that allows the patient to tolerate unpleasant procedures while maintaining cardio-respiratory function.

The standards for sedation and anesthesia care apply when patients receive moderate or deep sedation (Procedure Sedation) in any setting or by any route.

B. PURPOSE

The purpose of these standards is to allow clinicians to provide their patients with the benefits of sedation/analgesia while minimizing the associated risks. Excessive sedation/analgesia may result in cardiac or respiratory depression that must be rapidly recognized and appropriately managed to avoid the risk of hypoxic brain damage, cardiac arrest, or death. Conversely, inadequate sedation/analgesia may result in undue patient discomfort or patient injury because of lack of cooperation or adverse physiologic response to stress.

C. FOCUS

This policy is designed to:

- Standardize the management of patients receiving sedative agents regardless of the setting at OHSU Hospitals and Clinics.
- Establish requirements for credentialing practitioners who perform sedation and competency for personnel administering medications or monitoring patients undergoing sedation. This policy specifically excludes the following:
    1. Patients receiving single analgesic/sedative medications for pain reduction, insomnia, or anxiolysis alone.
    2. Healthy patients receiving peripheral nerve blocks, local or topical anesthesia, and/or no more than 50% N2O with oxygen and no other sedative or analgesic agents administered by any route.
    3. Patients undergoing general anesthesia or major conduction anesthesia (spinal or epidural/caudal blockade).
    4. Use of sedatives on ventilator supported patients in the intensive care area for facilitating elective diagnostic or therapeutic procedures and the intent is to change no more than one level of sedation.
    5. Sedative drugs to facilitate emergency and life saving procedures.

D. DEFINITIONS OF CONTINUUM

1. **Minimal sedation (anxiolysis)**: A drug-induced state during which patients respond normally to verbal commands. Although cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are unaffected. For very young or handicapped patients incapable of verbal response or understanding of verbal commands this state would be defined as a minimally depressed level of consciousness where the patient remains awake and is responsive to interaction or stimulus as prior to medication.
2. **Moderate sedation/analgesia**: A drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained. For very young or handicapped patients incapable of verbal response or understanding of verbal commands this state would be defined as one where the patient responds appropriately to touch or painful stimuli. The patient's eyes may be closed and a light level of sleep may be present.
3. **Deep sedation/analgesia**: A drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully following repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining airway patency and ventilatory effort. Cardiovascular function is usually maintained. Note that patients whose only response is reflex withdrawal from a painful stimulus are sedated to a greater degree than encompassed by "deep sedation/analgesia". With the specific exceptions of the use of pre-printed Ketamine analgesia orders for bolus and infusion, the pre-printed Ketamine infusion orders for intubated PICU patients, and the use of Ketamine in palliative care when death is imminent, administration of the following drugs in any dose constitutes Deep Sedation:
    - Propofol,
    - Ketamine,
    - Etomidate,
    - Methohexital, and
    - Thiopental
4. **Anesthesia**: Consists of general anesthesia and spinal or major regional anesthesia. It does not include local anesthesia. General anesthesia is a drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.

Because sedation-to-anesthesia is a continuum, it is not always possible to predict how an individual patient receiving moderate or deep sedation will respond. It is therefore required that practitioners administering sedation are qualified to administer pharmacological agents to predictably achieve desired levels of sedation and to monitor patients carefully in order to maintain them at the desired level of sedation.

E. EXPECTATIONS/CREDENTIALING FOR PERFORMING/MONITORING SEDATION

Practitioners administering moderate or deep sedation shall be qualified and have the appropriate credentials to manage patients at whatever level of sedation or anesthesia is achieved either intentionally or unintentionally. The following minimum requirements must be met by those responsible for administering and monitoring sedation/analgesia:

Licensed Independent Practitioner (LIP) Responsible for Administering Moderate and Deep Sedation/Analgesia as developed by the OHSU Sedation Oversight Committee and approved by the OHSU Credentialing Committee and Medical Board are outlined below:

- Moderate and Deep Sedation will be two separate and distinct privileges.

- Adult and pediatric (< 13 years old) sedation will also be separate privileges

The basic tenet underlying sedation privileging is airway protection. LIPs administering moderate or deep sedation are qualified and have the appropriate credentials to manage patients at whatever level of sedation or anesthesia is achieved, either intentionally or unintentionally.

- Practitioners with appropriate credentials permitted to administer moderate sedation are qualified to rescue from deep sedation and are competent to manage a compromised airway and to provide adequate oxygenation and ventilation.
- Practitioners with appropriate credentials permitted to administer deep sedation are qualified to rescue patients from general anesthesia and are competent to manage an unstable cardiovascular system as well as a compromised airway and inadequate oxygenation and ventilation.

Training & Current Competence

1. The grid lists the qualifications required to perform Moderate and/or Deep Sedation Privileges.
2. The practitioner requesting sedation privileges submits the required documentation supporting training, experience, and effectiveness.
3. Privilege requests with missing documentation will be withdrawn from consideration.
4. The Credentialing Committee recommends approval of sedation privileges based upon meeting the qualifications or being proctored in sedation.

Qualification Evidence	**Moderate Sedation**	**Deep Sedation**
Residency Core Curriculum (or equivalent graduate or postgraduate training):	Addressing airway support (i.e. opening airway, bag valve mask support), pharmacology including reversal agents, assessing sedation risks and alternatives.	Major focus on airway management (i.e., ability to intubate) and cardiovascular support, pharmacology of specific deep sedation medications
Board Prepared/Certified Specialty of LIP	None specified as long as meeting all minimum requirements The 5 specialties approved for deep can perform moderate.	1. Anesthesiology (including CRNA) 2. Critical Care (Adult & Pediatric, Neonatology), 3. Emergency Medicine 4. Oral & Maxillofacial Surgery 5. Pulmonary The above five specialties are NOT required to have ACLS & other cardiopulmonary support certification. Others qualified by training (hands-on) and mentored sedations & approval by the Credentialing Committee & Medical Board.
Cardiopulmonary Support	BLS (pediatric BLS or PALS for pediatric sedations) or equivalent	If not in the above five specialties, required training in ACLS, (PALS, APLS, for those doing pediatric sedations) training or equivalent training.

Experience - Evidence of Proficiency	10 supervised moderate sedations either in training or through mentorship or performed at least 10 over the past 2 years. Verified by Residency Director or Department Chair.	20 supervised deep sedations either during training or mentorship or performed at least 20 over the past two years. Verified by Residency Director or Department Chair attestation
Evaluation of knowledge of regulatory & OHSU issues	Complete OHSU Moderate Sedation didactic core curriculum and test, Review OHSU Sedation Policy.	Complete OHSU Moderate Sedation didactic core curriculum and test, Review OHSU Sedation Policy.

- **Residency Core Curriculum**: Residency Director will need to attest to competence in Moderate and/or Deep Sedation including documenting core didactics & minimum supervised sedations.
- **Residents** are not included in OHSU Medical Staff Privileging. The Attending Physician or Residency Director decides when a resident can manage moderate sedation. The attending has ultimate responsibility for the sedation. Residents should be held to the same minimum standards for didactics, life support training, regulatory test and supervised sedations. Deep sedation can only be performed under the direct supervision of an Attending Physician credentialed for deep sedation.
- **Medical Students** are not allowed to write orders for or perform sedation independently.

The grid lists examples of the qualifications the Credentialing Committee will be looking for when reviewing recredentialling of a faculty's Moderate and/or Deep Sedation Privileges. The Medical Staff Office personnel will identify and tag any privilege requests that lack evidence of meeting the qualifications for sedation for the Department Chair and Credentialing Committee.

Qualification Evidence	**Moderate Sedation**	**Deep Sedation**
Continuing medical education focused on sedation including airway management	2 hours of didactics and/or hands-on training over 2 years including updates on new sedatives or techniques appropriate for moderate sedation Following Specialties are exempt from continued education requirements: 1. Anesthesiology (including CRNA) 2. Critical Care (Adult & Pediatric, Neonatology), 3. Emergency Medicine 4. Oral & Axiological Surgery 5. Pulmonary	4 hours of didactics and/or hands-on training over 2 years including updates on new sedatives or techniques appropriate for deep sedation Following Specialties are exempt from continued education requirements: 1. Anesthesiology (including CRNA) 2. Critical Care (Adult & Pediatric, Neonatology), 3. Emergency Medicine 4. Oral & Maxillofacial Surgery 5. Pulmonary
Experience/Evidence of Proficiency	10 moderate sedations over two years and Department Chair attestation	20 deep sedations over two years and Department Chair attestation

Competency Requirements for Non-Credentialed Staff Assisting with Sedation

Personnel Administering Medications

- Administration of sedative/analgesic agents is within the individual practitioner's licensure scope of practice.
- Non-credentialed staff who administer medications will be required to complete a competency program for sedation.
- The administration of sedative medications will be under the supervision of the responsible LIP.
- Staff administering Deep Sedation Medications must have completed the competency for Deep Sedation, be knowledgeable of the medications being administered, and competent to monitor the patient's response to the medications given.
- Annual competency is determined by participation in >5 sedations annually or completion of the OHSU Training Module.

Personnel Monitoring Patients

- Monitoring of sedated patients is included in the practitioner's licensure scope of practice.
- Successful completion of OHSU Training for Sedation Monitoring or Medical Director approved equivalent. Annual competency is determined by participation in >5 sedations annually or completion of the OHSU Training Module.
- In addition to completion of OHSU Training for Sedation Monitoring, personnel monitoring adult patients undergoing deep sedation must have current ACLS certification and for monitoring pediatric deep sedation, current certification in PALS or ENPC.

F. SEDATION PROCESS
Documentation of pre-sedation evaluation, informed consent, monitoring results, adverse reactions and outcomes will be documented as part of the medical record using either the Sedation Flow sheet, #8.1-9p/op-1935 (available online), Pediatric Sedation Record, #8.1-5p/OP-1906 (order through Oracle # 130213), or the Anesthesia Record, OP-1902 (order through Oracle #131939).

Pre-Procedure

1. **Risk Assessment.** Patients who are ASA Class I, II, III, and IV are considered appropriate candidates for moderate sedation/analgesia in a non-OR setting. Patients in Class III and IV present special problems for deep sedation/analgesia and require additional and individual considerations. The Department of Anesthesiology is available for consultation on high-risk patients (see ASA Classification). Children (age <12 years) represent a particularly high-risk group. The possibility that deep sedation/analgesia will be required to achieve the procedure should be considered in making preparations. All patients undergoing sedation as defined in this policy must have a documented pre-procedural evaluation. This assessment includes but is not limited to:
    - A focused history and physical examination to assess cardiopulmonary status, ASA physical status, and relevant past and current medical conditions.
    - A review of current medications and drug allergies
    - A review of previous adverse experiences with sedation/analgesia/anesthesia
    - A review of NPO status.
2. **Informed Consent**. Informed consent for the sedation, independent of the consent for the procedure, shall be given and documented prior to sedation on either a consent form or as a PARQ (Procedures, Alternatives, Risks, Questions) in a physician note. The procedure, anticipated sedation requirements, alternatives, and risks shall be clearly explained to the patient, parents, or other legal guardian and the opportunity provided to have questions

answered. Patients will be advised they will need an adult to assist them after the procedure and that they should not drive. If the patient does not have an adult to assist them, they will need to be fully recovered under the supervision of a practitioner at OHSU prior to release.

During The Procedure

1. **Supervision**. All moderate sedation/analgesia and deep sedation/analgesia will be ordered and supervised by a practitioner who has privileges for moderate or deep sedation/analgesia. There must be at least one appropriately trained practitioner, who is not involved in the procedure, attending to the patient and monitoring physiologic parameters. (See Training Requirements)
2. **Facilities and Equipment**. Emergency code cart equipment and defibrillator must be readily available. A positive pressure oxygen delivery system must be available. The equipment must be appropriate for the age and size of the patient. The sedation site must have the following additional equipment:
    - Airway resuscitation equipment including oral and nasal airways
    - Cardiac Monitor
    - Pulse Oximeter
    - Blood pressure monitor
3. **Reversal of Sedation and IV Access**. Patients undergoing moderate or deep sedation shall have IV access. When medications are used for which there is an antidote or reversal agent (e.g. naloxone or flumazanil), the reversal agent must be readily available at the sedation site.
4. **Monitoring Patients Receiving Sedation**. Monitoring must be of a degree to which one can be expected to detect the respiratory, cardiovascular, or neurological effects of the drugs being used.

Monitoring Moderate Sedation/Analgesia:

One appropriately trained person shall continuously monitor the patient's level of consciousness, breathing and oxygen saturation. Parameters need to be recorded within 5 minutes of medication administration and at least every 10 minutes until the patient returns to an easily arousable state and stable hemodynamic status are:

- Level of consciousness
- Respiratory rate
- Oxygen saturation
- Heart rate

Patient's level of pain shall be documented prior to and post-procedure.

A patient who unexpectedly becomes deeply sedated will have a qualified practitioner immediately available for resuscitation and airway management until the patient is easily arousable.

Monitoring Deep Sedation/Analgesia:

One appropriately trained person shall continuously monitor and record every 5 minutes the patient's level of consciousness, heart rate, breathing, airway patency and O2 saturation until the patient returns to an easily arousable state and stable hemodynamic status:

- Level of consciousness
- Respiratory rate

- Oxygen saturation
- Heart rate

Blood pressure shall be documented every 10 minutes as permitted by the procedure. In those settings where extended deep sedation/analgesia occurs, vital signs shall be recorded at regular intervals. Cardiac monitoring shall be used for patients with significant cardiovascular disease or when dysrhythmias are anticipated or detected. Documentation of these parameters will continue until the patient arouses to voice or gentle touch and is hemodynamically stable.

Patient's level of pain shall be documented prior to and post-procedure.

Post-Procedure Recovery and Discharge:

Patients shall be recovered in an area where personnel with the skill and qualifications to recover patients are in attendance. In the event a patient fulfills the discharge criteria listed for patients recovering from sedation, the patient may be discharged to regular hospital patient care management or home when appropriate. Patients with residual sedation must be discharged to the care of an adult and should be advised not to drive. Patients without such resources will be fully recovered prior to discharge.

Discharge criteria are as follows:

- Vital signs are stable.
- The patient can be easily aroused.
- The patient's airway is intact as demonstrated by coughing, deep breathing, and drinking.
- No untoward side effects exist (e.g. persistent vomiting, dizziness, agitation).
- The patient has returned to baseline if discharged home without accompaniment of a responsible adult. Verbal and written discharge post sedation instructions shall be provided to the responsible person or fully recovered patient.
- For patients receiving a reversal agent during the course of sedation, the MD/LIP will consider the duration of effect for both the sedation agent and the reversal agent in determining appropriate length of time for recovery.
- Pain management plan is effective in maintaining pain < 4 on 0-10 scale or level acceptable to patient.

G. QUALITY ASSURANCE MONITORING

Credentialing

It is the responsibility of the Professional Board, Chairs of Clinical Departments, Program Directors, and Nurse Managers to ensure that individuals involved in the administration of sedation/analgesia are appropriately authorized.

Sedation Sites

The Medical Director and Nurse Manager of each sedation location site are responsible for quality assurance monitoring of all sedation/analgesia cases, and are responsible for ensuring that departmental policies and procedures comply with the established criteria in this policy. Cases in which complications occur during sedation shall be fully reviewed in the department's quality assessment and improvement process and reported to Medical Affairs/Quality Management Department which will refer trends to the Sedation Oversight Committee.

Bibliography:

- Practice guidelines for sedation and analgesia by non-anesthesiologists. Anesthesiology 2002;96 (4):1004-17.
- American Academy of Pediatrics Committee on Drugs. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: addendum. Pediatrics 2002;110:836-838.
- "Standards and Intents for Sedation and Anesthesia Care", Revisions to Anesthesia Care Standards for CAMAC, effective Jan. 1, 2001, p. 1-6, TX.2-PE.1.8, www.jcaho.org/standard/anesamb.html

Related Forms and Procedures:

- Sedation Flow sheet, #8.1-9p/OP-1935; Adult and Pediatric and Nursing
- Pediatric Sedation, #8.1-5p/op 1906 (Oracle # 130213)
- Anesthesia Record, OP-1902 (Oracle # 131939) Order from Relizon Forms - Item #131939

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Originator/Author:

Credentialing Committee
Sedation Oversight Committee

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September 25, 2006

MEMO: Sedation Policies for VCUG and DMSA scans

Division of Pediatric Urology
Children's National Medical Center

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Upper Marlboro:	(301) 868-5777
Georgetown:	(202) 444-4914

FROM: H. Gil Rushton, MD
Children's National Medical Center, Washington, DC

Sedation is not routinely used at CNMC for VCUG studies.
When requested by parents, we use Versed at a dose of 0.5 mg/kg.

For DMSA scans, we use sedation in about 10% of patients, usually infants between 1-3 yrs of age. For DMSA scans, we use choral hydrate at a dose of 75-100 mg/kg.

H. Gil Rushton, M.D.
Chief

A. Barry Belman, M.D.
Chairman Emeritus

M. David Gibbons, M.D.
Director of Pediatric Urology
Georgetown University Hospital

Hans Pohl, M.D.
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Najda Kalloo, M.D.
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Mary Micker, R.N., M.S.N., CPNP
Nurse Practitioner

Department of Urology
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PATIENT CARE OBJECTIVES

- The principal objectives of this protocol are the:
  - Safe and effective administration of moderate sedation/analgesia (MSA) or deep sedation/analgesia (DSA) by non-anesthesiologists to achieve a desired level of sedation during procedures, and
  - Monitoring of patients to maintain the desired level of sedation throughout the procedure.
- In all locations where MSA or DSA is performed, patients can expect a comparable level of quality of care.
- Medical staff, nurse practitioners, and physician assistants performing MSA or DSA shall follow the Medical Staff Policy Statement relating to this protocol (See **PAGES 3 & 4**).
- When MSA or DSA is administered at sites other than the procedure site, all transportation requirements identified in PATIENT CARE MANAGEMENT section apply.

DEFINITIONS

MINIMAL SEDATION/ ANXIOLYSIS	Refers to a drug-induced state of consciousness during which: • patients respond normally to verbal commands, • cognitive function and coordination may be slightly impaired • ventilatory and cardiovascular functions are unaffected
MODERATE SEDATION/ ANALGESIA ("Conscious Sedation" or "MSA")	A drug-induced depression of consciousness during which sedatives or combinations of sedatives and analgesic medications are often used and may be titrated to effect. • patients respond purposefully (reflex withdrawal from a painful stimulus is not considered a purposeful response) to verbal commands alone or accompanied by light tactile stimulation. • no interventions other than positioning of the head are required to maintain a patent airway • spontaneous ventilation is adequate • cardiovascular function is usually maintained
DEEP SEDATION/ ANALGESIA ("DSA")	A drug-induced depression of consciousness during which sedatives or combinations of sedatives and analgesic medications and/or anesthetizing agents are employed. • patients cannot be easily aroused • the ability to independently maintain ventilatory function may be impaired. • patients may require assistance in maintaining a patent airway, • spontaneous ventilation may be inadequate • cardiovascular function is usually maintained • sedation/analgesia that includes the use of propofol, ketamine, brevitol, pentothal, and/or etomidate is considered deep sedation/analgesia
SEDATIVE	A sedative drug decreases activity, moderates excitement, and calms the recipient.

INDICATIONS FOR USE OF PROTOCOL

- Adult and pediatric patients receiving MSA or DSA by NON-ANESTHESIOLOGY staff for diagnostic, operative, or invasive procedures.

NOTES:

- Titration of repeated doses of sedatives or titration to effect for procedures is considered MSA and not anxiolysis.
- Administration of a combination of parenteral benzodiazepines and narcotic analgesic drugs for procedures is considered MSA (*even if PCA pump is "turned off" prior to the procedure*).
- Use of anesthetizing agents such as propofol and ketamine is considered DSA.
- Pediatric patients sedated with chloral hydrate or nembutal (alone or in combination with other agents) for diagnostic, operative, or invasive procedures shall be sedated in accordance with this protocol, or another Medical Staff approved protocol specific to a procedure area.

SITUATIONS IN WHICH THIS PROTOCOL DOES NOT APPLY

- Use of pure anxiolytics (e.g. buspirone), or sedative drugs in low doses given once and expected to have little sedative effect.
- Pre-operative medications
- Analgesic therapies used alone for procedures (without concomitant drugs with sedative properties) for control of pain or discomfort (See PAT025 Pain Assessment and Management)
- Local anesthesia without sedation
- Drug used as a restraint (See PAT022 Chemical Restraint for Emergency Behavior Management)
- Patients receiving intravenous sedating drugs under approved treatment protocols (e.g., in oncology patients: lorazepam 1 mg IV administered as an anti-emetic before some types of chemotherapy)
- Patients who are endotracheally intubated and mechanically ventilated
- Patients in the MICU/MPC4 on the Withdrawal of Life Support Protocol.

CARE OF THE CONTINUUM OF SEDATION

- **Note**: Competency and skill levels for all personnel differ for MSA and DSA.
- Since sedation occurs along a continuum, the level of sedation may become deeper than desired. Practitioners who have appropriate credentials and are permitted to perform MSA are competent to manage a compromised airway and inadequate oxygenation and ventilation. Practitioners who have appropriate credentials and are permitted to perform DSA are competent to manage an unstable cardiovascular system as well as a compromised airway and inadequate oxygenation and ventilation.

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MEDICAL STAFF POLICY STATEMENT FOR MODERATE SEDATION/ANALGESIA (MSA) AND DEEP SEDATION/ANALGESIA (DSA) FOR DIAGNOSTIC, OPERATIVE, OR INVASIVE PROCEDURES

1. This Medical Staff Policy Statement shall apply to the administration of MSA and DSA for diagnostic, operative and invasive procedures.

2. The term "sedation" in this Policy Statement is used in a generic sense that encompasses the following definitions:

   Minimal sedation/anxiolysis: to a drug-induced state of consciousness during which:
   - patients respond normally to verbal commands,
   - cognitive function and coordination may be slightly impaired
   - ventilatory and cardiovascular functions are unaffected

   Moderate sedation/analgesia (MSA): A drug-induced depression of consciousness during which sedatives or combinations of sedatives and analgesic medications are often used and may be titrated to effect.
   - Patients respond purposefully (reflex withdrawal from a painful stimulus is not considered a purposeful response) to verbal commands, either alone or accompanied by light tactile stimulation.
   - No interventions other than positioning of the head are required to maintain a patent airway
   - Spontaneous ventilation is adequate
   - Cardiovascular function is usually maintained

   Deep sedation/analgesia (DSA): A drug-induced depression of consciousness during which sedatives or combinations of sedatives and analgesic medications and/or anesthetizing agents are employed.
   - patients cannot be easily aroused
   - the ability to independently maintain ventilatory function may be impaired.
   - patients may require assistance in maintaining a patent airway,
   - spontaneous ventilation may be inadequate
   - cardiovascular function is usually maintained
   - sedation/analgesia that includes the use of propofol, ketamine, brevitol, pentothal, and/or etomidate is considered deep sedation/analgesia

3. The objective of this Policy Statement is that in all locations in which MSA and DSA for diagnostic, operative, and invasive procedures are administered, patients with the same health status can expect a comparable level of quality of care. Accordingly, interdisciplinary protocols for administration of sedation are endorsed by the Medical Staff as defining the way in which sedation is to be administered, by qualified personnel, to patients receiving care under the auspices of The Johns Hopkins Hospital. These protocols define responsibilities of the medical staff for performance and documentation of the discussion of risks, benefits, or alternatives to sedation; the immediate pre-procedure evaluation of the patient; the plan for sedation; presence of medical staff during sedation and procedure; the writing of orders for MSA and DSA, and post-sedation care.

MEDICAL STAFF POLICY STATEMENT FOR MODERATE SEDATION/ANALGESIA (MSA) AND DEEP SEDATION/ANALGESIA (DSA) FOR DIAGNOSTIC, OPERATIVE, OR INVASIVE PROCEDURES (CONT)

4. MSA and DSA shall be performed only by members of the Medical Staff and Affiliate Staff with delineated clinical privileges to do so.

   Since sedation occurs along a continuum, the level of sedation may become deeper than desired. Practitioners who have appropriate credentials and are permitted to perform MSA are competent to manage a compromised airway and inadequate oxygenation and ventilation. Practitioners who have appropriate credentials and are permitted to perform DSA are competent to manage an unstable cardiovascular system as well as a compromised airway and inadequate oxygenation and ventilation.

   Criteria for the delineated clinical privilege for performance of DSA shall include successful completion of the DSA education program and post-test approved by the Medical Staff Credentials Committee. In the case of individuals with experience and demonstrated competence in the care of patients during DSA, the criteria for delineation of the privilege for DSA shall include verification of experience and competence and successful completion of the post-test of the DSA education program.

5. Physicians-in-training (with the exception of a Senior Clinical Fellow with delineated sedation privileges) shall perform sedation only under supervision in accordance with their written job description.

6. Exceptions from the procedures outlined in the Interdisciplinary Protocol shall be only for compelling medical reasons which shall be documented by the medical staff in the patient's medical record.

7. In an emergency with potential threat to the patient's life, the routine pre-procedure evaluation may be reduced in accordance with the urgency of the provision of care. Documentation at a minimum (if possible) should list the diagnosis, proposed procedure and allergies to medications.

8. Medical staff shall provide a written order for all drugs administered for sedation of patients.

9. Outcomes of patients undergoing moderate and deep sedation shall be collected and analyzed in the aggregate in order to identify opportunities to improve care.

10. Information concerning this Medical Staff Policy Statement and the Interdisciplinary Protocol shall be provided to clinical departments and procedure areas and included in Hospital Risk Management Seminars and the general orientation program given for new residents and clinical fellows in the beginning of the academic year. This educational activity shall be ongoing.

11. The Medical Staff Risk Management Committee shall monitor the implementation of this Policy Statement and the Interdisciplinary Protocol.

RESPONSIBILITIES	
PHYSICIAN/ DENTIST	• A physician/dentist who performs or supervises performance of MSA or DSA shall have delineated clinical privileges to do so. A separate delineated clinical privilege is required for the performance or supervision of deep sedation. • All references in this protocol to "physician/dentist" means physicians or dentists who have delineated clinical privileges to perform MSA or DSA for diagnostic, operative, or invasive procedures. • The physician/dentist shall assure that there is a discussion with the patient or the person responsible for the patient of the risks, benefits, or alternatives to sedation. This discussion and patient consent shall be DOCUMENTED in the medical record (see "Physical Assessment" section of *Sedation Flowsheet*). • The physician/dentist is responsible for performing and documenting the immediate pre-procedure assessment to determine that the patient is an appropriate candidate for the planned sedation and procedure (see "Physical Assessment" section of *Sedation Flowsheet*). • During the procedure, a physician/dentist who is a staff member of the procedure unit shall be immediately available in the room unless his/her presence shall interfere with the test, or put him/her at risk, e.g., CT, MRI. In these instances, the physician/dentist shall be immediately available in the area where the procedure is being performed. • There shall be a written order or verbal order countersigned by a physician/dentist at the completion of the procedure for all drugs administered for MSA or DSA. A physician/dentist who is a staff member of the procedure unit is responsible for providing the sedation orders. • The decision to order oral contrast media shall be made by the physician/dentist responsible for performing MSA or DSA based on his or her clinical evaluation of the patient.
RESIDENT STAFF/ FELLOWS	Physicians-in-training (with the exception of Senior Clinical Fellows with delineated sedation clinical privileges) • Shall participate in this protocol under supervision and in accordance with their Hospital job description. • May <u>not</u> write orders for DSA, except in the immediate presence of a physician/ dentist with delineated clinical privileges for DSA.
PROCEDURE AREA STAFF	• If the physician from a procedure area chooses to perform MSA or DSA prior to the patient's arrival in the procedure area, personnel from the procedure area shall monitor the patient at baseline, during administration of the medication, and during transportation to the procedure area (See PATIENT CARE MANAGEMENT, STATEMENTS 25-27). • Deeply sedated patients shall be transported in the presence of a physician credentialed for deep sedation or an anesthesiology staff member and in accordance with usual anesthesiology transport support.
NURSE PRACTITIONERS & PHYSICIAN ASSISTANTS	• Nurse practitioners and physician assistants shall only perform MSA if they are permitted to do so in their written agreement. • Nurse practitioners and physician assistants who perform MSA shall have demonstrated and documented competence in ACLS/PALS or equivalent skills and knowledge. • Nurse practitioners and physician assistants may only write MSA orders under the immediate supervision of a physician/dentist with delineated clinical privileges for MSA. • Nurse practitioners and physician assistants shall <u>not</u> write orders for DSA. • If a nurse practitioner or physician assistant is designated to provide patient monitoring and surveillance during sedation, s/he may not have other duties or responsibilities during the procedure and recovery period that would interrupt or compromise his/her continuous observation and monitoring of the patient. S/he may not leave the patient unattended until discontinuation of the protocol.

RESPONSIBILITIES	
REGISTERED NURSE (RN)	• RN may administer medication in accordance with this protocol and monitor patients receiving MSA or DSA when: - The medication is ordered by a physician/dentist - The RN has demonstrated/documented competence related to the management of patients receiving MSA or DSA; this includes, but is not limited to: ▪ anatomy and physiology ▪ pharmacologic action of drugs administered, including action of antagonist agents ▪ determination of sedation level ▪ arrhythmia recognition ▪ recognition of airway obstruction ▪ complications and nursing interventions ▪ basic life support. • RNs who participate in the care of patients receiving MSA shall have demonstrated competence in management of a compromised airway and provision of adequate oxygenation and ventilation. • RNs who participate in the care of patients receiving DSA shall have demonstrated and documented competence in ACLS/PALS or equivalent knowledge and skills (competence in management of unstable cardiovascular system as well as compromised airway and inadequate oxygenation and ventilation). • RN competency validation and documentation are carried out as defined in the Skills Competency Model, *Nursing Practice and Organization Manual*, Volume I, 400. • The RN monitoring the patient may not have other duties or responsibilities during the procedure and recovery period that would interrupt or compromise his/her continuous observation and monitoring. The RN may not leave the patient unattended until discontinuation of the protocol.
ANESTHESIOLOGY STAFF	• Anesthesiology staff administering MSA or DSA shall meet applicable guidelines and standards of the Department of Anesthesiology and Critical Care Medicine (ACCM) to include performance and documentation of the discussion of risks, benefits, or alternatives to sedation; the immediate pre-procedure evaluation of the patient; the plan for sedation; appropriate monitoring of the patient; and arrangement for post-sedation care.

PATIENT CARE MANAGEMENT	
CONSULTATION	1. A consultation with an anesthesiologist is **recommended** if a patient: - Has known respiratory compromise or hemodynamic instability - Presents with significant co-morbid conditions - Current history of sleep apnea 2. A consultation with an anesthesiologist is **required** for: - A patient who falls within ASA physical status 4 and is unstable or who falls within ASA physical status 5. - Infants who are born prematurely (< 37 weeks gestation) who at the time of the procedure are < 60 weeks post conception and who are not residing in the NICU or PICU (Note: post conceptual age is the gestational age at birth plus the age since birth – so a baby born at 32 weeks who is 12 weeks old is 44 weeks post conception) - History of airway problems during sedation/analgesia or general anesthesia - History of adverse reaction to sedation/analgesia or general anesthesia - Children with neuromuscular disease affecting respiratory or brain stem function. - Failure of airway screening examination

PATIENT CARE MANAGEMENT	
BEFORE SEDATION ADMINISTRATION	3. On day of, or within 24 hours before procedure, physician/dentist/designee (nurse practitioner, physician assistant): • Shall identify and document factors that may increase risk of complications and/or may alter drug dosage requirements. • Shall perform and document on the Sedation Flowsheet or critical pathway: - Assessment of airway - Auscultation of heart and lungs - Examination specific to the procedure proposed - Assessment of patient's ASA (American Society of Anesthesiologists) classification - Explanation of risks, benefits, alternatives to sedation - Pregnancy status - Interpretation of cardiac rhythm if other than regular rate and rhythm - Review of appropriate diagnostic/laboratory data and determination of need for and availability of blood/blood products - Procedure/study to be performed - Type of sedation planned - Assessment of patient as appropriate candidate for sedation and procedure - Signature in the "Physical Assessment" section, noting any changes - Assurance of continuous intravenous access for <u>all</u> cases of DSA (unless there are documented clinical contraindications), whenever MSA is administered intravenously, and as indicated when MSA is administered by other than intravenous route. 4. The nurse/licensed clinician shall notify the physician/dentist and shall not administer sedation when: • A responsible adult is not present to accompany patient at discharge • There is a significant change in hemodynamic, neurologic, or pulmonary status • Fasting/feeding guidelines not met (APPENDIX B) - Last solid intake was < 8 hours prior to sedation - Last intake of breast milk was < 4 hours prior to sedation - Last clear liquid intake was < 2 hours prior to sedation 5. If a patient shall be sedated for a procedure before meeting the criteria in STATEMENT 4, the physician/dentist shall administer sedation and shall document in the medical record the rationale for proceeding with sedation. Strategies implemented to decrease risk of acid aspiration shall be documented, as appropriate (APPENDIX C) 6. Before procedure, RN (physician/dentist, nurse practitioner, physician assistant if RN is not participating) shall: • Assure presence and working condition of following equipment in procedure room and recovery location: - Pulse oximeter - Cardiac monitor - Oxygen source, tubing - Oral pharyngeal airways, bag for ventilation with face mask, appropriate size for patient - Blood pressure device, appropriate size for patient - Suction machine - Capnometer (recommended if continuous direct observation of adequacy of ventilation not possible) • Assure immediate accessibility of following emergency equipment in patient care unit or procedure area: - Defibrillator; recorder capability of defibrillator or EKG machine - Emergency cart - Emergency drug box

PATIENT CARE MANAGEMENT	
BEFORE SEDATION ADMINISTRATION	7. Prior to the procedure, the RN (or physician/dentist, nurse practitioner, physician assistant if the RN is not participating) shall: • Ascertain previous documentation of the following data elements and if not available, determine and document the missing information: - Past medication history, including previous adverse reactions to sedation - Present medication regimen, especially medication taken within the last 48 hours - Allergies - Pregnancy status, when applicable - Exposure to infectious disease and the need for isolation procedures. • Determine and document the following: - Last oral intake (see APPENDIX B) - Baseline vital signs, level of consciousness, and pain score [0=no pain, 5 (FACES scale) or 10 (all other scales)=worst pain] - Baseline oxygen saturation via pulse oximeter with alarms set 5% below patient's established baseline - Weight - Patency of IV access, when applicable - Location of patient recovery - Name, telephone number or on-site location of a responsible adult (parent, legal guardian, or their designee for any child under 18 years of age) to accompany patients who shall be discharged home.
SEDATION ADMINISTRATION	8. Sedation shall be administered in accordance with the *Guides to Drug Dosages and Rates of Administration* outlined in APPENDICES D & E. 9. If pharmacologic agents used for sedation are administered in doses exceeding the ranges outlined in the *Guides to Drug Dosages and Rates of Administration*, the rationale shall be documented in the medical record by the physician/dentist ordering the medication. 10. Guidelines for drug administration: • Give drug slowly, and in small incremental doses. • Assess therapeutic effect before determining next incremental dose and observe patient for: - Maintenance of adequate oxygen saturation - Ability to maintain a patent airway and appropriate response to physical stimulation and/or verbal command - Adverse effects of administered drug(s) • Adjust dosages per physician/dentist order based on patient's age, level of debilitation, drug combinations, tolerance, pulmonary reserve, previous narcotic usage, and length of procedure. • **SEDATION SHOULD NOT BE USED AS A SUBSTITUTION FOR EFFECTIVE LOCAL ANESTHESIA**.

PATIENT CARE MANAGEMENT	
DURING THE PROCEDURE	11. RN, physician/dentist, nurse practitioner (NP), or physician assistant (PA) shall continuously monitor and observe patient. This shall include: • Continuous pulse oximetry (oxygen saturation) and cardiac rate • Continual assessment of adequacy of ventilation (carbon dioxide detection via capnometer is recommended if continuous direct observation of adequacy of ventilation not possible) • Continuous cardiac rhythm, if patient has significant cardiovascular disease or when dysrrhythmias are anticipated or detected • Continual blood pressure, if measurement shall not interfere with procedure • Continual respiratory rate and character • Continual level of consciousness, if assessment shall not interfere with procedure • Pain score PRN to assure adequate sedation and analgesic supplementation. 12. RN, physician/dentist, NP, PA shall document measurements/observations on the *Sedation Flowsheet* or *critical path* as frequently as appropriate, but at intervals no greater than **15 minutes** for MSA or DSA.
DURING THE PROCEDURE	13. Notify physician/dentist immediately if a patient experiences: • Baseline oxygen saturation of less than 93%, a decrease in oxygen saturation from a low saturation baseline, or a fall in oxygen saturation of 5% or greater • Inadequate ventilation and/or Inability to maintain a patent airway • Inability to respond appropriately to physical stimulation/verbal commands • Other adverse reactions to drugs administered 14. Should any of the changes in patient condition noted in STATEMENT 13 occur: • Give supplemental oxygen as ordered by the physician • If saturation does not improve, implement the following measures: - Stimulate the patient - Halt procedure - Attempt to improve the airway with jaw thrust and/or oral airway - Initiate or assist ventilation with bag/mask and oxygen - Administer naloxone or flumazenil as ordered - Initiate cardiopulmonary resuscitation procedures as needed 15. If endotracheal intubation is employed, determine correct tube placement by carbon dioxide detection, presence of equal breath sounds, and presence of chest rise.

PATIENT CARE MANAGEMENT	
RECOVERY PERIOD	16. The physician/dentist, RN, nurse practitioner, or physician assistant responsible for care of the patient during the recovery period shall not have duties other than patient recovery. Areas that have recovery rooms will follow PACU staffing standards. When an RN, nurse practitioner, or physician assistant is monitoring the patient, the physician/dentist shall be readily available on-site throughout the recovery period. 17. The physician/dentist, RN, nurse practitioner, or physician assistant shall continuously monitor/observe the patient. This includes: • Continuous pulse oximetry (oxygen saturation) and cardiac rate • Continual assessment of adequacy of ventilation (carbon dioxide detection via capnometer is recommended if continuous direct observation of adequacy of ventilation not possible) • Continuous cardiac rhythm, if patient has significant cardiovascular disease or when dysrrhythmias are anticipated or detected • Continual blood pressure • Continual level of consciousness • Temperature PRN • Continual pain assessment, to assure adequate pain management once the effects of sedation/analgesia begin to wear off 18. The physician/dentist, RN, nurse practitioner, or physician assistant shall document measurements/observations (STATEMENT 17) on the *Sedation Flowsheet* or *critical path* at intervals no greater than **every 15 minutes** or more frequently as needed until the patient is at pre-sedation baseline or meets clinical discharge criteria. 19. Intravenous access shall not be discontinued during the recovery period until the patient is at pre-sedation baseline or has met discharge criteria. 20. RN shall notify the physician/dentist if the patient does not return to baseline or meet discharge criteria within two hours post procedure/diagnostic test.
RECOVERY PERIOD	21. OBSERVATION OF INFANTS (< ONE YEAR OF AGE): • The following patients must have a 2 hour (minimum) observation period post last dose of sedation if they are not going to a monitored bed - Infants born ≥ 37 weeks (full term) and are now < 48 weeks post conception - Infants born < 37 weeks (premature) and are now < 60 weeks post conception - Infants born < 37 weeks (premature) and are now ≥ 60 weeks post conception and have lung disease, apnea, or oxygen requirement. • Once infants not going to a monitored bed achieve pre-sedation baseline, observation/monitoring parameters noted in STATEMENT 17 should be documented every 15 minutes until 2 hours post last dose of sedation. • The need for continued monitoring and/or admission shall be assessed and documented by the physician if an infant does not meet discharge criteria or return to pre-sedation baseline by the end of the observation period. • Infants going to a monitored bed shall be transported as per STATEMENTS 27-28 once pre-sedation baseline has been achieved.

PATIENT CARE MANAGEMENT	
DISCONTINUATION OF PROTOCOL/ DISCHARGE OF PATIENT	22. The sedation protocol may be discontinued when: • All clinical discharge criteria in STATEMENT 23 are met, or • Patient has been physically assessed by a physician/dentist who documents that assessment and writes a discharge order. • In either instance, an RN assessment shall be documented on the Sedation Flowsheet along with the name of the responsible physician/dentist who has performed the procedure unless another physician/dentist has assumed responsibility for post-procedure care and discharge. 23. **CLINICAL DISCHARGE CRITERIA** (patient shall meet all criteria or shall have returned to pre-sedation baseline): • Level of consciousness score of 4-5 per PACU scale (APPENDIX F) • Ability to swallow oral fluids/secretions or demonstrate gag reflex • No evidence of severe hypertension or hypotension exists • Pulse is regular and within the range defined for that patient's age group • Respiratory rate and character are within the defined range for that patient age group • Oxygen saturation on room air is ≥95%. 24. Although pain will be assessed in all patients, and treated as necessary, the absence of pain is not a criterion for discontinuation of this protocol. 25. Discharge to home (the following shall be documented on the *Sedation Flowsheet*): • That all clinical discharge criteria in STATEMENT 23 are met • Presence of a responsible adult (family/friend) to accompany patient at time of discharge • Responsible adult has been informed of importance of continued observation • Patient and responsible adult have received information regarding side effects/duration of sedation and have had all questions answered.
TRANSPORTATION OF PATIENT	26. PEDIATRIC PATIENTS: It is strongly recommended that drugs intended to produce moderate or deep sedation be administered at the site of the procedure. 27. POST-PROCEDURE (ALL AGES): before patient is transported, patient shall meet all discharge criteria in STATEMENT 23 and receiving RN shall be notified and shall receive a verbal report. 28. If patient is transported before being discharged from the protocol: • Deeply sedated patients shall always be transported in the presence of a physician credentialed for deep sedation or an anesthesiology staff member • Patient shall be accompanied by an RN and a physician/dentist with the following equipment: - Pulse oximeter if transported outside the immediate area - Oxygen tank (ascertain 1000 psi of pressure in the tank), oxygen tubing - Appropriately sized face mask and self-inflating bag for ventilation - Emergency drug supplies - Oral airways • During transport, the patient shall be monitored via pulse oximeter. A cardiac monitor shall also be required if the patient developed a change in cardiac rhythm from baseline during the procedure. • Transfer of responsibility for patient monitoring and management to the staff of the receiving unit shall be documented in the progress notes by the transport staff and the staff of the receiving unit. • Transport staff shall remain with the patient and continue the protocol per STATEMENTS 16 - 23, until the patient is at pre-sedation baseline, meets clinical discharge criteria, or the staff of the receiving unit determines that they can safely assume responsibility for the continuous monitoring of the patient through the recovery period.

APPENDIX A: ADDITIONAL DEFINITIONS	

CONTINUOUS MONITORING	A level of surveillance of the patient that is prolonged without any interruption at any time, and during which:
	$ a nurse, physician, or dentist is in constant attendance
	$ responsible staff member shall have no other responsibilities that would compromise provision of surveillance and one-to-one patient care.

CONTINUAL MONITORING	A level of surveillance of the patient that is repeated regularly and frequently in steady rapid succession.
LOSS OF PROTECTIVE REFLEXES	An inability to handle secretions without aspiration or to maintain independently an unobstructed airway.
PERFORM SEDATION	The entire sedation process. Requires delineated clinical privileges or immediate supervision in accordance with the written job description.
ADMINISTER SEDATION	The actual administration of the drug. Requires demonstrated competency.
SEDATION RECOVERY PERIOD	The time interval from the end of the diagnostic, operative or invasive procedure until patient is at pre-sedation baseline or meets discharge criteria.

APPENDIX B: FASTING/FEEDING GUIDELINES FOR SEDATION FOR DIAGNOSTIC, OPERATIVE, OR INVASIVE PROCEDURES (These guidelines apply to patients of all ages.)
No SOLIDS for 8 hours prior to sedation **No BREAST MILK for 4 hours prior to sedation** **No CLEAR LIQUIDS for 2 hours prior to sedation**

SOLIDS include solids, formula, juices with pulp, milk products other than breast milk

CLEAR LIQUIDS include tea, soda, non-pulp juices, Jell-O, popsicles

The time intervals given above refer to the time at which the procedure is scheduled, not the time at which the patient is asked to come to the Hospital.

The physician may adjust these NPO requirements if, according to his/her clinical judgment, the recommended length of time without feedings may be harmful to the patient.

These NPO requirements may be made more restrictive at the physician's discretion (e.g. presence of co-morbidities such as hiatal hernia).

APPENDIX C: STRATEGIES FOR DECREASING RISK OF ACID ASPIRATION

PULMONARY ASPIRATION OF GASTRIC CONTENTS	• One of the most serious complications of pharmacologically-induced sedation. • Not limited to children who are deeply sedated or who undergo general anesthesia, but can occur in any patient in whom an underlying medical condition or administered drug(s) results in loss of consciousness/protective airway (gag/cough) reflexes.	
RISK FACTORS: Nature/ volume of gastric contents	• Presence of particulates - Solid or partially digested food - Particulate antacids (magnesium, aluminum) - Barium x-ray contrast	• pH < 2.5 • Volume >0.4-0.8 mL/kg
PATIENTS ALWAYS AT HIGH RISK (full stomach)	• Acute abdominal pathology (e.g., appendicitis, peritonitis, bowel obstruction) • Esophageal dysmotility syndromes • Increased intracranial pressure • Head and/or spinal cord injury • Undocumented/inadequate fasting period • Previous esophageal surgery (e.g., TE fistula repair, esophagectomy with gastric pull-up)) • Poorly-controlled diabetes	• Gastro-esophageal reflux • Peritoneal dialysis • Ascites • Hiatal hernia • Morbid obesity • Severe pain • Multiple trauma • Vomiting

PROPHYLAXIS

In emergency sitations and in the management of patients with the conditions listed above, the prophylactic use of agents aimed at increasing the pH or decreasing the volume of gastric contents may lessen the severity of pulmonary injury if aspiration occurs. These drugs do not reduce the propensity to regurgitation and pulmonary aspiration, but they may limit the damage. They may be administered either intravenously or orally.

Prokinetic, antiemetic drugs*

Drug	Dose	Maximum Adult Dose	Onset Time	Contraindication

APPENDIX E

PEDIATRIC PATIENTS: Guide to Drug Dosages and Rates of Administration

(Reflects drugs that may be used for sedation and analgesia and is not meant to be all inclusive)

CAUTION: SEDATION CANNOT SUBSTITUTE FOR ADEQUATE LEVELS OF INDICATED TOPICAL OR LOCAL ANESTHESIA.

Medical conditions associated with increased risk of cardiorespiratory complications following opioid or sedative administration

- infants < three months of age,
- Premature infants < 60 weeks post conception at time of procedure
- history of apnea or disordered controlle d breathing,
- cardiorespiratory disease,
- hemodynamic instability
- obtundation,
- airway compromise,
- renal or liver disease,
- neuromuscular disease

DRUG/ACTION	PEDIATRICS: MODE OF ADMINISTRATION	COMMENTS
SEDATIVES		
Chloral Hydrate • Hypnotic • Has no amnesic, nor analgesic properties *Pediatric patients sedated with chloral hydrate for diagnostic, operative, or invasive procedures shall be sedated in accordance with this protocol, or another Medical Staff approved protocol specific to a procedure area.	Usually administered **rectally or orally** • Initial dose is 25-100 mg/kg. • The low dose in the range of 25 mg/kg is usually ineffective. • Maximum dose 2 grams.	• Primarily used for diagnostic imaging studies, EEG, Audiology where immobility is not needed (Chloral Hydrate does not provide analgesia). • Patients may be asleep for 2-6 hours. • Studies suggest sedation with chloral hydrate is less effective in older children. • Has a slow onset time 10-20 min and long duration of action. • Depresses respiration • Hypoxia can occur after administration of chloral hydrate (In a study of 854 children receiving a recommended dose of 38-83/mg/kg, 5.4% of patients experienced a decrease in oxygen saturation to #90% of baseline). • **WARNING**: When chloral hydrate is combined with any narcotic, the risk of hypoxia and apnea is increased significantly.
Droperidol (Inapsine®) • Sedative, • Anti-emetic, • Blocks dopaminergic receptors	**IV Administration** ADMINISTER SLOWLY • Initial dose is 0.03-0.07 mg/kg administered over 2 minutes. • Maximum initial dose is 2.5 mg. • Onset of action is 3-10 min. • Wait at least 5 min to assess effect.	• Not the first choice of drug for sedation for procedures. Usually given as an adjunct to other drugs. • Small doses are often adequate. • Markedly enhances effects of narcotics and other sedatives. • Droperidol antagonizes only the nausea and not the depressant side-effects of narcotics and other sedatives.

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- neuromuscular disease

DRUG/ACTION	PEDIATRICS: MODE OF ADMINISTRATION	COMMENTS
SEDATIVES (cont)		
Midazolam Hydrochloride (Versed®) • Short-acting benzodiazepine • Central nervous system depressant • Produces sedation, anxiolysis, amnesia • No analgesic properties • Can be antagonized (reversed) with flumazenil (Romazicon®)	**IV Administration** ADMINISTER SLOWLY • Otherwise healthy patient: initial dose is 0.05 mg/kg. (maximum dose 5 mg. or 0.2 mg/kg) • Administer slowly over a 2 min period with adequate time interval (2-3 min) between doses to assess for effect of previously administered dose. • Additional midazolam may be given in 0.05 mg/kg doses to achieve or maintain desired level of sedation (max dose 5 mg.). This dose may be repeated X 4. • Maximum total dose 5 mg or 0.2 mg/kg **Nasal Administration**: IV form of drug is given nasally, 0.2 -0.3 mg/kg (max dose 5 mg.) **Oral Administration**: oral preparation (2mg/cc), 0.5 -0.75 mg/kg (max dose 15 mg.) **Rectal Administration**: IV form of drug is given rectally, 0.5 -1 mg/kg (max dose 15 mg.).	• Use smaller doses in debilitated, chronically ill patients, patients with a history of disordered control of breathing (apnea), patients with a history of liver or kidney disease, and prematurely born infants < 60 weeks post-conception. • Respiratory depression is potentiated when combined with any opioid/narcotic. • Nasal administration produces sedation rapidly < 5 -10 min • Oral administration produces sedation slowly >20 min. • Rectal administration has an onset of action that is intermediate between oral and nasal. Sedation is produced in 10 min.
Pentobarbital (Nembutal®) • Barbiturate • Hypnotic • No amnestic nor analgesic properties	• Usually administered IM or PO. • **ADMINISTER IV SLOWLY:** rapid administration produces sleep and deep sedation. • Initial dose of pentobarbital is 2-6 mg/kg (IM/PR/PO). IV dose 2 -4 mg/kg/dose. • Maximum dose 150 mg. • Administer very slowly IV, usually over a 2 -5 min period	• Used for diagnostic imaging studies where immobility is essential. • Patients will be asleep for 2-4 hours. • Has a slow onset time, 5 -8 min, and long duration of action. • Depresses respiration and blood pressure. • **WARNING**: When any barbiturate is combined with any narcotic the risk for hypoxia and apnea is increased significantly.

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- neuromuscular disease

DRUG/ACTION	PEDIATRICS: MODE OF ADMINISTRATION	COMMENTS
SEDATIVES (cont)		
Scopalomine • Potent amnestic ,sedative, • anti-sialagogic, anti-cholinergic	• Scopolamine 0.01 mg/kg/IM. Can be given IV. • Maximum scopolamine dose 0.4 mg. • Used with morphine as a premedicant, 1 hour before procedure	• Contra-indicated in glaucoma, GI or GU obstruction, thyrotoxicosis • Antagonized by physostigmine (0.01 mg/kg, max dose 2 mg). • Used with morphine to minimize procedure-related pain for major procedures (cardiac cathete rization, endoscopy).
ANALGESICS		
Fentanyl Citrate (Sublimaze®) • Narcotic/Opioid • Very potent analgesic (80-100 X more potent than morphine) • Minimal sedation • No amnesia • May be antagonized (reversed) with naloxone Narcan® (below)	**IV Administration** ADMINISTER SLOWLY • Initial dose is 0.5 - 1 mcg/kg administered slowly over a 2 minute period. • Maximum total dose is 3 mcg/kg. • Titrate incrementally. Use small doses. • Administer slowly over a 2 min period with adequate time interval (3-4 min) between doses to assess for effect of previously administered dose. **Transmucosal Administration** (Fentanyl Oralet®) • 10-15 mcg/kg administered over 20 min	• Short duration of action ~30-60 min. • Use smaller doses in debilitated or chronically ill patients or in patients with an increased risk of respiratory depression • Respiratory depression is potentiated when fentanyl is combined with Midazolam or any sedative/hypnotic. • Chest wall rigidity can occur when administered rapidly in doses > 5 mcg/kg. • Bradycardia can occur at an y dose.

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DRUG/ACTION	PEDIATRICS: MODE OF ADMINISTRATION	COMMENTS
ANALGESICS (cont)		
Meperidine Hydrochloride (Demerol®) • Narcotic/Opioid • **10 times less potent** than morphine • Minimal sedation • No amnesia • May be antagonized (reversed) with naloxone (Narcan®)	**IV Administration** ADMINISTER SLOWLY • Initial dose is 1 - 2 mg/kg. (max dose 100 mg) • Titrate incrementally. Use small doses • Administer slowly over a 1-2 min period with adequate time interval (2-3 min) between doses to assess for effect of the previously administered dose.	• **Meperidine is not recommended for routine use.** • Use smaller doses in debilitated or chronically ill patients or in patients with an increased risk of respiratory depression • Toxic metabolite, normeperidine can cause seizures if given in repeated doses, particularly in patients with decreased renal function. • **WARNING**: Catastrophic interactions with MAO inhibitors
Morphine Sulfate • Potent narcotic/Opioid • Potent analgesic • No amnesia • May be antagonized (reversed) with naloxone (Narcan®)	**IV Administration** ADMINISTER SLOWLY • Initial dose of morphine is 0.05-0.1 mg/kg • Titrate incrementally. Use small doses. • Administer slowly over a 1-2 min period with adequate time interval (2-3 min) between doses to assess for effect of previously administered dose.	• Use smaller doses in debilitated or chronically ill patients or in patients with an increased risk of respiratory depression • Half life 3-4 hours: first dose may last only 90 min (Half life is longer in neonates and infants).
ANTAGONISTS		
Flumazenil (Romazicon®) • Benzodiazepine antagonist (reverses benzodiazepine-induced sedation and respiratory depression)	**IV Administration** ADMINISTER RAPIDLY • Pediatric dosing is not well established. • Initial dose is 0.01mg/kg (max initial dose 0.1mg) regardless of size. If ineffective, double the dose in 1 min (max dose 1 mg).	• **CAUTION**: Duration of action of this antagonist may be shorter than the agonists. • **CAUTION**: May induce seizures in patients physically dependent on benzodiazepines.

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DRUG/ACTION	PEDIATRICS: MODE OF ADMINISTRATION	COMMENTS
ANTAGONISTS (CONT)		
Naloxone (Narcan®) • Narcotic/opioid antagonist	Initial **resuscitation** dose is 0.01 - 0.1 mg/kg (up to 2 mg/dose) given intravenously, intra-muscularly, subcutaneously, intra-tracheally, or intra-osseously. This dose can be doubled and repeated at 1 -2 min intervals. **IV administration** • Drug provided in ampules; will need to be diluted. • Dilute a 1cc ampule (containing 0.4 mg) with sterile fluid to a total volume of 10cc resulting in a final concentration of 0.04mg/ml. **Intra-tracheal administration** • Give 2 to 10 times the IV dose in 3 -5 mL normal saline solution. **Intra-osseously administration** • Flush with 3-10 mL of normal saline after administration	• Naloxone is used for the reversal of narcotic induced respiratory depression or hypotension. • Lower doses 0.001 mg/kg should be used in patients ta king opioids chronically and in patients being treated for pain. • **CAUTION**: Duration of action of naloxone is < 30 min, which may be less than that of the narcotic with re -appearance of narcosis. • **WARNING: Ampules with 3 different concentrations exist: 1 mg/mL, 0.4 mg/mL, and 0.02 mg/mL (neonatal).**

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October 16, 2006

To Whom It May Concern:

I have discussed the issue of sedation for VCUGs and DMSAs with Dr. Richard Bellah, a radiologist and RIVUR co-investigator at CHOP, as well as Dr. Jan Boswinkel, Medical Director of Procedural Sedation Services at CHOP.

Less than 1% of children are sedated for VCUGs and child life specialists are often present to help allay anxieties about the exam. Sedation is only administered when the referring physician requests it. In these situations the patients are sent to the Sedation Unit where they are evaluated by a nurse practitioner or physician. Generally, oral Versed (midazolam) is used in combination with the child life specialist support. Dr. Boswinkel states that oral Versed is considered anxiolysis (minimal sedation) and does not require monitoring, unless the patient has other medical problems that might compromise cardiorespiratory function.

Approximately 10% of children are sedated for DMSA scans, again at the request of the referring physician. Sedation for DMSA scans involves deep sedation, and therefore is scheduled and managed through the CHOP sedation unit. Patients being sedated for DMSA scans generally receive pentobarbital +/- fentanyl.

Sincerely,

Ron Keren, MD, MPH

Children's Hospital of Pittsburgh

3705 Fifth Avenue
Pittsburgh, PA 15213-2583

September 15, 2006

Myra A. Carpenter, Ph.D.
Research Assistant Professor, Epidemiology
Collaborative Studies Coordinating Center
Department of Biostatistics
137 East Franklin Street, Suite 203, CB # 8030
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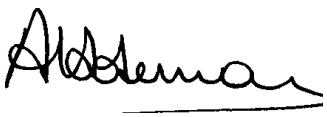
Dear Myra,

As you requested, I am writing to confirm that Chiefs of Radiology and Nuclear Medicine departments have indicated to me that sedation will not be used for either VCUGs or DMSA scans of children enrolled in the RIVUR study. I hope this information is sufficient, please let me know if you need anything else from my end.

Sincerely



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SEDATION GUIDELINES – CHM PEDIATRIC IMAGING

GUIDELINES PRIOR TO SEDATING PATIENT

1. A legal guardian who can sign informed consent for sedation must accompany every outpatient.
2. A history and physical will be completed and signed by the nurse and Sedation Physician.
3. Patients should be NPO according to the department's NPO guidelines.
4. Supportive equipment **must** be readily available.
5. All personnel will be trained in BLS. Physicians and nurses will be trained in PALS.
6. Patients must be monitored by pulse oximetry and, in addition, ETCO2 monitoring when indicated.
7. Sedation Physician must be in the department or readily available during the exam.
8. After assessment the Sedation Physician and nurse will classify every patient according to ASA physical status classification:

Class I:	A normally healthy patient	
	Examples:	*Seizures, headaches, sinusitis, etc.*
Class II	A patient with mild systematic disease	
	Examples	*Developmental Delay, mental retardation, Sickle Cell Disease, mild asthma, congenital heart defect, routine Post-Ecmo babies, etc.*
Class III:	A patient with severe systemic disease	
	Examples:	*On medication for diagnosis, has altered lifestyle, and an acute metabolic problem.*
Class IV:	A patient with severe systemic disease that is a constant threat to life.	
Class V:	A moribund patient who is not expected to survive without the operation.	

*****If classified as III, IV or V, the physician must decide whether the patient may be sedated*****

9. Once patient is assessed the Sedation Physician and nurse must formulate an individualized sedation plan
10. The Sedation Physician (and Radiologist if necessary) should also be made aware of any variations in NPO status; abnormal VS; significant allergies; potential for complications with sedation, etc.

DISCHARGE CRITERIA

1. The patient must be arouseable with all protective reflexes intact (based on a discharge scoring system)
2. All vital signs will be checked immediately prior to discharge.
3. The patient cannot be discharged until 30 minutes has lapsed since sedation was given.
4. Verbal and written instructions will be given to all outpatients with phone numbers.

EMERGENCY DRUGS (available in lock box in each imaging area)

1. **Atropine** - 0.02 mg/kg IV/IM (min = 0.1 mg/dose; max child = 0.5 mg/dose; max adolescent = 1 mg/dose) {may repeat once in 5 minutes}
2. **Diphenhydramine** (Benadryl) - 1 mg/kg IV, PO (max 50 mg/dose)
3. **Epinephrine** - 0.01 mg/kg/dose IV {0.01 mg/kg = 0.1 ml/kg of 1:10,000 dilution}; subsequent dose(s), given every 3-5 minutes, is 0.1 mg/kg/dose IV {0.1 mg/kg = 0.1 ml/kg of 1:1000 dilution}
4. **Flumazenil** (Romazicon) - 0.01 mg/kg/dose IV (max 0.2 mg) {may repeat every minute up to max cumulative dose 1 mg}
5. **Lidocaine** - 1 mg/kg/dose IV or ET (may repeat every 5-10 minutes up to max cumulative dose 3 mg)
6. **Naloxone** (Narcan) - 0.01 mg/kg/dose IV (max 2 mg/dose) {use 1mg/ml concentration} [may repeat every 2-3 minutes based on patient's response]

INITIAL DOSES – Must determine plan for sedation in conjunction with Sedation Physician before administration

1. **Chloral hydrate:** {sedative} (100mg/cc) {given PO}
   - 50, 75 or 100 mg/kg depending upon weight, age and length of exam
   - **One time maximum dose of 1125 mg**
   - Under 12 months
   - Up to 2 years
   - *Sedation Physician approval needed if initial dose needs to be:*
     - between 1125 mg-2000 mg
     - given to a patient over 2 years

2. **Pentobarbital (Nembutal):** {barbiturate} (50 mg/cc) {given as a bolus/may use 0.9 NS flush}
   - 3 mg/kg 12 months and older
   - May give 1 mcg/kg of fentanyl if not asleep 5 minutes after initial dose of pentobarbital
   - Sedation Physicians approval needed if initial dose needs to be greater than 3 mg/kg
   - **One time maximum dosage of 100 mg**

3. **FENTANYL:** {narcotic} (50 mcg/cc) {given slowly in increments, titrate with fast IV rate}
   - 1 mcg/kg any age
   - **One time maximum dose of 50 mcg**
   - Used mostly for pain
   - May be given before midazolam based on individual patient situations and nursing assessment

4. **Midazolam (Versed):** {benzodiazepine} (5 mg/cc) {give in increments with fast IV rate}
   - Use on all children 8 years and older.
   - Sedation Physicians approval needed to use on children under 8 years.
   - Dosage 0.2 mg/kg (if under 50 kg) for first dose, then 0.1 mg/kg – 0.2 mg/kg based on patient's condition and response.
   - If patient is greater than 50kg, use 0.1 mg/kg for first dose, then 0.1 mg/kg - 0.2 mg/kg based on patient's condition and response.
   - **One time maximum dosage of 6 mg for patients ≤ 6 years**
   - **One time maximum dosage of 10 mg for patients > 6 years**

5. **Diazepam (Valium):** {benzodiazepine}
   - Dosage guidelines: 0.04 – 0.2 mg/kg PO
   - *Usual dose = 0.1 mg/kg* PO
   - To be used in anxious older children in MRI
   - **Maximum dose 10 mg P.O.**

SUPPLEMENTAL DOSES – Must have Sedation Physicians approval before administering.

1. **Chloral hydrate:**
   - If not asleep 20 minutes after initial chloral dose, may give an additional 25 - 50 mg (to equal 100 mg/kg as total dose) {up to maximum of 2000 mg}
   - Or give 1 mcg/kg fentanyl IV
   - Or give 2 mcglkg fentanyl IM

2. **Pentobarbital (Nembutal):**
   - If not asleep 5 minutes after first fentanyl dose give another 1 mcg/kg fentanyl or give another dose of pentobarbital, which is given as a split-dose over one minute (based on patient's condition and response)
   - **Guidelines for cumulative maximum = 10 mg/kg**
   - IM pentobarbital can be given if unsuccessful at initiating IV (dosage guidelines as follows):
     6 mg/kg if less than 15 kg
     5 mg/kg if greater than 15 kg
     *Supplemental dose in 1 hour 2 mg/kg if less than 15kg; 2.5 mg/kg if greater than 15kg

3. **Fentanyl:**
   - Give the second dose of 1 mcg/kg fentanyl, 5 to 10 minutes after initial dose
   - Then you may give boost of 1 mcg/kg of fentanyl every 30-45 minutes
   - May give fentanyl if determined that PO diazepam was not effective based on patient's response

4. **Midazolam (Versed):**
   - May give 1 mcg/kg fentanyl IV after the first 2 doses of midazolam or give another dose of midazolam equal to the second in 3-5 minutes (within dosage guidelines)
   - **Guidelines for cumulative induction dose - 1 mg/kg**
   - **Guidelines for cumulative induction and boosting dose - 2 mg/kg**
   - Then may boost every 30 minutes with midazolam dose (based on patient assessment) within guidelines
   - May give midazolam if determined that PO diazepam was not effective based on patient's response

APPROVAL SIGNATURE(S)

_____ _____
Nannette Thibodeau, Clinical Manager, Pediatric Imaging Date

_____ _____
J. Michael Zerin, M.D., Chief, Pediatric Imaging Date

Patient/Family Care Policy

Children's Hospital
Columbus, Ohio

Children's
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Number: XI-30:50	**Originated: 7/93** **Revised:8/200, 3/2001; 6/02, 11/03, 2/05**
Subject:	**SEDATION: USE AND MONITORING IN PEDIATRIC PATIENTS**
Purpose:	To properly and safely manage patients undergoing sedation by assessing THE INTENDED LEVEL OF SEDATION before initiating the procedure, then fulfilling appropriate requirements for personnel, equipment, monitoring, documentation, and pain assessment. Then managing sedation before, during and after the procedure until transfer or discharge. This policy is written with the awareness that regardless of the level of sedation intended or route of administration, sedation represents a continuum from mild sedation through deep sedation. The deepest level of sedation has greater risk of the patient losing protective reflexes. A patient may move easily and quickly from a light level of sedation to obtundation. The distinctions among the levels of sedation are made for the purpose of describing the appropriate physiologic monitoring of sedated patients and are not meant to dictate the utilization of sedation medications. Guidelines for the sedation of patients undergoing mechanical ventilation in a critical care unit or the operating room and/or trauma setting are beyond the scope of this policy. Documentation in shaded areas as required by practitioner or delegate on the Sedation Documentation Record form AM-69 (see Attachment II)
Related Policies:	Patient/Family Care Policy XI-30:30 – Pain Management Protocol
Policy Statement:	*It was assumed for the purposes of this policy that the patient's age, developmental level, biophysical/psychological functioning and pre-sedation or "normal" state of activity (baseline) and a need for pain management would be considered when selecting the desired level of sedation, administering the medication(s), monitoring and discharging the patient. (A post-sedation level of behavior shall be as close as possible to the normal level for an individual prior to transfer or discharge.)*
Definitions:	**I. SEDATION LEVELS** Sedation refers to the intended level of sedation and managing the patient for the level achieved, it is not based on specific medications or route of administration used for a procedure but, rather response of the patient. There are **five levels (0-4)** of sedation on the sedation scale. The following descriptions define each of the levels. **Level 0 ANXIOLYSIS-** Normal response to verbal commands and coordination not affected. **Level I MILD SEDATION** – Normal response to verbal commands; cognition and coordination may be affected; ventilation and cardiovascular are intact; the patient is awake, verbal and cooperative; the goal is to use selected medications to decrease or eliminate anxiety, pain and to facilitate the patient's coping skills. **Level 2 MODERATE SEDATION** –Patient is easily arousable and responds

APPROVED:

David Fisher, MD, Medical Director

Linda Stoverock, RN, MSN, Sr. Vice President
Patient Care Services, Chief Nursing Officer

	purposefully to verbal commands; No interventions are needed to maintain airway; spontaneous ventilation is adequate; cardiovascular function is usually maintained. Sleep deprived patients that require oxygen are moderately sedated. **Level 3 DEEP SEDATION** – Patient cannot be easily aroused and responds purposely only to repeated painful stimuli; ability to maintain airway may be affected; spontaneous ventilation may be inadequate; cardiovascular function is usually maintained. **Level 4 ANESTHESIA** – General, spinal or major regional (Local anesthesia not included) Patients non-arousable to intense stimuli. Ability to maintain airway is often impaired; often require assistance in maintaining airway; positive pressure ventilation may be required because of depressed spontaneous ventilation or depression of neuromuscular function; cardiovascular function may be impaired. DISSOCIATIVE - Trance-like state.
	II. CANDIDATE CLASSIFICATION: A. The responsible practitioner must assess and record each patient's Suitability for sedation using the American Society of Anesthesiologists (ASA) Class I, II, or III on the Sedation Form AM-69. **B.** CLASSIFICATION MODIFIED FROM THE AMERICAN SOCIETY OF ANESTHESIOLOGISTS CLASSIFICATION OF PATIENT STATUS: 1. **CLASS I:** There is no organic, physiologic, biochemical, or psychiatric disturbance. The pathologic process for which operation is to be performed is localized and is not a systemic disturbance. 2. **CLASS II**: mild-to-moderate systemic disturbance caused either by the condition to be treated surgically or by other pathophysiological processes. 3. **CLASS III**: Severe systemic disturbance or disease from whatever cause, even though it may not be possible to define the degree of disability with finality. 4. **CLASS IV**: Indicative of the patient with severe systemic disorder already life-threatening, not always correctable by the operative procedure. Requires additional monitoring, location, and staffing. 5. **CLASS V:** The moribund patient who has little chance of survival without the operation so is submitted to operation in desperation. Requires additional monitoring, location, and staffing.
Policy Statement:	**III. PERSONNEL REQUIRED** Refer to Attachment I 1. The practitioner responsible for the treatment of the patient and/or the administration of sedation drugs and airway management shall be appropriately trained and deemed competent in the use of such techniques (verified by their Section Chief).

2. It is recommended that personnel have specific assignments and current knowledge and competency in response to emergency resuscitation. The sedated patient will be attended by trained personnel at all times. Refer to Attachment I

IV. EQUIPMENT REQUIREMENTS: Refer to Attachment I

Pulse oximeter for non-oral sedation and those patients with a potential for airway obstruction; whereas pulse oximeter is required for ASA class III-IV receiving oral sedation, it is encouraged for oral and nitrous oxide sedation. The pulse oximeter must be on the patient and operating continuously throughout the state of sedation.
Resuscitation bag and mask of age appropriate size and airway equipment must be accessible in the immediate area.
Oxygen flow meter with tubing are required and immediately capable of delivering 90% 0_2 for 60 minutes.
Suction regulator, tubing and catheters, are set up and ready to use.
Reversal agents: Naloxone hydrochloride (narcotic antagonist) and flumazenil (benzodiazepine antagonist) must be available in the immediate area to be used in the event a reversal agent is needed.
An emergency cart including the necessary drugs and equipment must be maintained in the immediate area
IV access is required; ECG monitor and defibrillator should be readily available.

IV. MONITORING REQUIREMENTS FOR ALL LEVELS:

PRE-PROCEDURE Refer to Attachment I:

An initial baseline oxygen saturation for non-oral sedation and those patients with potential for airway obstruction; blood pressure, heart rate, respiratory rate, pain assessment and sedation scale are recorded immediately prior to the sedation. .

The practitioner should consider the risks vs the benefits in the timing of the procedure in relation to oral intake. Patients being scheduled for general anesthesia fall under NPO guidelines for the Anesthesia Dept. The current standard of practice in Children's Hospital for NPO status prior to conscious sedation (levels 1,2 or 3) varies by patient age.

Adults (> 18 years of age) are NPO for 6 hours or nothing after midnight.
Children older than 6 months of age are NPO for 6 hours.
Children younger than 6 months of age are NPO for 4 hours.

All patients may be given clear liquids (7 up, water, pedialyte, clear apple juice) up to 2 hours prior to sedation. Infants younger than 6 months may also receive breast milk up to 2 hours prior to sedation. If the sedating practitioner, in

	conjunction with the attending clinician, deems it necessary to proceed under urgent or emergent circumstances without a full NPO time period, then documentation of need should be reflected in the medical record. **DURING THE PROCEDURE Refer to Attachment I:** The oxygen saturation for those patients with potential for airway obstruction, heart rate, pain level and the sedation level as needed, based on response and level of intended sedation, see pain and sedation scales. **TRANSFER OR DISCHARGE Refer to Attachment I:** • If the patient is to be transferred or discharged, blood pressure, respiratory rate, heart rate, pain scale and sedation level are recorded immediately before transfer or discharge and vital signs must be stable. *(A post-sedation level of behavior shall be as close as possible to the normal level for an individual prior to transfer or discharge.)* .
	UPON ARRIVAL TO FLOOR/UNIT: Refer to Attachment I: **FOR ALL LEVELS:** Blood pressure, heart rate, pain assessment and respiratory rate are recorded according to practitioner order on the floor or unit. The responsibility for the sedated child rests with the sedating physician. Transfer of sedated patients from a procedure site to the inpatient floor requires close communication between the sedating physician and the floor accepting care. If the floor is not equipped to accept the patient, then the transferring physician retains responsibility for monitoring unless an alternate unit can be found to accept the patient (i.e., PACU, ED observation, etc.). Monitoring of the child and documentation of the child's status must be uninterrupted during transfer. **DISCHARGE CRITERIA:** Cardiovascular stability is achieved: the blood pressure, heart rate, and respiratory rate have returned to pre-procedure baseline. Airway/respiratory stability is achieved: the patient can take a deep breath and cough (if age appropriate infants and toddlers do not always cough on demand) the respiratory rate and depth have returned and pre-procedure baseline. The patient is in or has returned to the baseline interactive state: can talk, lift head and sit up unaided, has controlled movement of extremities, can follow commands, is awake, alert, oriented for age or pre-sedation state. • The post-procedure discharge criteria must be met by assessing the vital signs, pain scale and sedation scale.

Patient/Family Care Policy

Children's Hospital
Columbus, Ohio

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NUMBER: XI-30:50	ORIGINATED: 7/93 Revised: 8/00, 3/01, 6/02, 11/03, 2/05
SUBJECT:	SEDATION: USE AND MONITORING IN PEDIATRIC PATIENTS

Special Instructions:

ALL LEVELS:

- Practitioners must discharge patient from hospital (may be by criteria).
- When the treatment or procedure has been completed, the practitioner (or designee) who shall assess and discharge the patient when the post-procedure discharge criteria are met by the vital signs, pain scale and sedation scale.
- Patients are returned to the level of care provided prior to the procedure before transfer back to floor/unit. For both outpatients and inpatients the same discharge criteria apply.

V. **FACILITY:**

Sedation shall be performed only in areas of the hospital that can accommodate the necessary personnel, equipment for monitoring, and for emergency intervention if needed.

VI. **DOCUMENTATION Refer to Attachment II (Sedation Form AM-69)**

1. All shaded areas are to be completed by the practitioner or delegate. Documentation in shaded areas as required by practitioner or delegate on the Sedation Documentation Record form AM-69
2. PRE-SEDATION ASSESSMENT IS LABELED ON THE LEFT MARGIN AND INCLUDES THE UPPER HALF Refer to form AM-69
   a) A pre-sedation blood pressure, heart rate, pain assessment, respiratory rate, temperature and intended level of sedation are documented immediately prior to sedation on the form.
   b) Procedure related benefits / risks, options and alternatives explained and accepted
   c) A history and physical is complete, a diagnostic history is documented, the airway is assessed, a risk assessment is completed with an ASA score assigned.

d) All menstruating females and any girls older than 12 years of age will receive a urine pregnancy test before undergoing sedation or anesthesia unless the testing is refused by the parent or legal guardian and the consent form (AM-20) so initialed.

e) A Time out is conducted immediately prior to procedure being performed. Patient, procedure and site are all verified.

3. SEDATION MEDICATION ORDERS:

A practitioner's order is required for medication used for sedation. Practitioner' orders will be carried out in accordance with existing standards, policies, procedures, bylaws of Children's Hospital and state laws and regulations.

a. Verify allergy, weight, right patient, right medication, right dose, right route, right site of administration, and time of administration will be documented and calculated in milligrams per kilogram or per square meter of body surface area. When prescriptions are used, a copy or a note describing the content of the prescription should be in the patient's chart along with a description of the instructions given to the parent.

4. DURING SEDATION: Refer to Attachment I for monitoring requirements

5. POST-SEDATION DOCUMENTATION:

Record time, blood pressure, heart rate, 0_2 sat and patient response to pain, and level of sedation.

The patient is in or has returned to the baseline interactive state; can talk, lift head and sit up unaided, has controlled movement of extremities, can follow commands, is awake, alert, oriented for age or pre-sedation state.

VII TEACHING:

Teaching related to sedation and pain management will be provided to the patient and family and documented, as needed.

Patient/Family Care Policy

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NUMBER: XI-30:50	ORIGINATED: 7/93 Revised: 8/00, 3/01, 6/02, 11/03, 2/05
SUBJECT:	SEDATION: USE AND MONITORING IN PEDIATRIC PATIENTS

Special Instructions:

VIII. THERAPEUTIC HOLDING

Devices should be age appropriate and used judiciously and if used checked frequently to prevent chest or limb restriction. The child's head position should be checked frequently to ensure a patent airway.

IX. EDUCATION AND CREDENTIALING:

The purpose of this policy is to ensure one standard of care throughout the institution. Any sedation medication given by any chosen route can result in a state of clinical unconsciousness (level 4 general anesthesia). Therefore, practitioners and staff must be prepared through training for the possibility of unintentional deeper levels of sedation (especially level 3). The following stipulations are made to safeguard against adverse or sentinel events.

1. Practitioners may use any sedative medication approved by the Pharmacy and Therapeutics Committee and dosages for which they have been trained and credentialed.
   The process entails:
   - Training in use of the sedation policy and pain management policy
   - Current PALS or ACLS/ATLS training
   - Knowledge and mastery of the medications being used
   - Credentialing to be verified by the Department or Section Chief.
2. The practitioner (attending) who is supervising sedation must be present on the unit or in the immediate vicinity during the time that the patient is sedated. Sedation performed in the Emergency Department is performed under the direction of the ED physician staff.
3. Healthcare staff will be trained in sedation policy and procedure and code blue and will have at least BCLS (PALS, ACLS or NRP for the ED and Intensive Care Units is recommended)
4. Adverse drug reactions, sentinel events, or near miss/medication errors will be reported as incident reports and reviewed by the Pharmacy and Therapeutics Committee in conjunction with Quality Improvement Services and Legal Services.

X CREDENTIALING CRITERIA:

The Department or Section Chief for each area is responsible for verifying the capability of each member administering sedation. Thus, credentialing of section members rests with their chief, based on the following credentialing criteria.

1. For Attending Practitioners to administer or supervise sedation:
   - Educational materials must be reviewed and mastered concerning the sedation policy as well as and all available sedative medications (sedation policy educational materials prepared by the Sedation Committee).
   - Current PALS verification, ACLS or NRP.
   - Procedural, sedation, and verification of airway management skills observed and verified by Section Chief.

- QI data will regularly be presented to the medical staff for their review (adverse drug reaction incident reports or sedation audits).
- Educational material for sedation shall be reviewed and updated at least every three years.

2. For Housestaff, Fellows and Advanced Practice Nurses to administer sedation:
   - Educational course must be completed covering sedation policy, documentation, and the performance of sedation at Children's (created by the Sedation Committee).
   - Education course must be completed about sedative medications. Sedation in the ED performed by Housestaff and rotating residents is done under the direction of the attending practitioner.

The Sedation Department Chief will sign off on the sedation training prior to the residents, fellows, or Advanced Practice Nurses administering sedation.

Children's Mercy
HOSPITALS & CLINICS
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November 1, 2006

RIVUR Data Coordinating Center
Collaborative Studies Coordinating Center
Department of Biostatistics
137 E Franklin St.,Ste 203,CB#8030
The University of North Carolina at Chapel Hill
Chapel Hill, NC 27514-4145

To Whom It May Concern:

Sedation is not used during the performance of a VCUG in our institution. However, children under the age of 5 may receive sedation during a DMSA scan. Our hospital uses an individualized plan of care for each child. The medications that may be used during sedation consist of Fentanyl, Versed, or Pentobarbital. Sedation is provided for as long as the scan lasts. Credentialed physicians and nurses provide the sedation and all of the joint commission requirements are followed by our institution.

Sincerely

Bradley A. Warady, M.D.
Chief, Section of Pediatric Nephrology
The Children's Mercy Hospital

Sedation Process for Nuclear Medicine Procedures

- The decision to book a patient for sedation should be made at the time the appointment is scheduled due to the preparation necessary. See the attached requirements.

- The criteria to sedate a patient are as follows:
  1. Bone scan (TBS) - patient is under the age of 4 years
     - scan for ? child abuse
     - known to need sedation from previous experience in NM or other modality

  2. Any SPECT – if the patient is very uncooperative and is under 25 kg.

  3. Bone scan (Local views only) – normally sedation is not used for a limited bone scan, however, if pinhole hip views are required, the NM physician should be consulted for approval.

- Obtain patient's weight.
- Before proceeding with IV placement ensure that the patient can in fact be sedated by obtaining the following information from the parent:
  - at what time did the child last eat & drink
  - what did the child drink? Was it a clear fluid?
  - any allergies? Any medication?
  - does the child have a cardiac condition?
  - does the child have asthma? Does he/she need ventolin?
  - inquire about the child's general health, such as ;
    have a cold, runny nose, cough, fever?
- If any of the information from the preceding list contraindicates the administration of sedation, then consult the CT nurse or the NM physician. If the patient is suspected of having a cold then ask the CT nurse to listen to his/her chest to assess for congestion.
- If there are no problems present, proceed with the IV insertion and inject the patient for the procedure.
- Following the injection call the CT nurse and inquire when the patient can have the sedation workup. It might be convenient for the nurse to do the workup right away, so take the patient along with the NM requisition to the CT nursing station. Be sure to tell the parent what time they should return to the DI reception desk. If the workup cannot be done right away, ask when the patient should return for the sedation workup and instruct the parent. Reinforce the need to keep the child NPO during the waiting period.
- When the child returns and has had the sedation workup, call the CT nurse to inform when the scan will commence. If the workup has not been done, take the patient along with the NM requisition to the CT nursing station. Inform the nurse when the room will be available to commence the scan.
- Prior to the scan, the CT nurse will obtain the sedation order from the NM physician (or covering physician).
- The CT nurse will bring a blood pressure monitor but the MRT should have the NM pulse oxyimeter ready in the room.
- Once everything is in place, the nurse will administer the sedation and the scan can commence.
- On completion of the procedure the child is taken to appropriate recovery area before discharge.
- The above information outlines the process for out patients. If an in patient requires sedation, the ward nurse will be given the NPO instructions and request for an IV. If there is a contraindication to sedation the ward nurse or physician should inform us. The patient can be returned to the ward following the injection &/or workup to wait for the return to NM.

Dietary Guidelines For Children Undergoing Sedation or General Anaesthetic for Diagnostic Imaging Exams

These guidelines are simply for the protection of your child. Should your child eat or drink after the indicated time, the test will be cancelled. If you have any questions regarding these guidelines, please call CT/Nuclear Medicine/GI/GU@813-6070 or MRI/MEG@813-5774.

8 hours before the scan, your child must finish eating any solid food. This includes orange juice, chewing gum and candy.

6 hours before the scan, your child must finish drinking milk or infant formula.

4 hours before the scan, you must stop breast feeding your baby.

3 hours before the scan your child must stop drinking clear fluids. Clear fluids are water, apple juice, or Jell-O. If you can't see through it, don't let your child drink it.

Children taking medicine can generally continue taking them with only a small sip of water. Please call and ask to speak with a nurse before you give your child their medicine.

Thank you for following these guidelines. We will be happy to answer any questions or concerns you may have.

Department of Diagnostic Imaging
The Hospital For Sick Children

Chapter 2: Recruitment, Screening, and Eligibility

Table of Contents

Chapter 2: Recruitment, Screening, and Eligibility

2.1 Overview

Recruitment and retention of an adequate number of study participants are critical to the success of any clinical trial. To try and maximize the number of eligible participants enrolled into the RIVUR study, and to help enroll children from a broader spectrum of severity of illness, RIVUR clinical sites will be recruiting as either primary (acute) care sites, or subspecialty (referral) care sites. This chapter outlines the steps leading up to randomizing a participant into the RIVUR trial.

2.2 Recruitment

2.2.1 Recruitment Materials

Each participating clinical center will have developed its own preferred mechanism for recruiting participants, developing multiple strategies tailored to their catchment areas and the populations served. Brochures describing the RIVUR study will be provided to each site to facilitate their recruitment.

Investigators should consider sending brief information letters or study brochures to all physicians in the catchment area, describing the goals and methods of the study. This should be done before the study starts, and periodically throughout the recruitment phase. Referring physicians should be supplied with materials that detail the study requirements for medical record documentation. It will be important to maintain a good relationship with referring physicians, keeping them informed of the study and their participants' progress. In addition, educational presentations to medical, nursing and other health professional groups should be scheduled to help with recruitment. There is available to RIVUR Steering Committee members a Powerpoint presentation that describes RIVUR.

The role of the Study Coordinator is crucial. The most successful person for recruitment is an energetic and dedicated Study Coordinator who plays a central and multifaceted role. This individual is trained on all protocol details and is the local resource person for RIVUR physicians, referring physicians, participants and their families, the Data Coordinating Center and the NIH/National Institute of Diabetes and Digestive Kidney Disease. The Study Coordinator should show dedication, honesty, and deal sympathetically with potential participants and their families. Concern for the overall health and well-being of the study participants is their highest priority.

2.1.2 Recruitment Goals

The goal of recruitment is for each of five core clinical site to recruit and randomize 120 patients over an 18-24 month period, for a total of 600 randomized patients. Each core site will recruit approximately 60 participants per year for the first two years. Those core sites with affiliated satellites will contribute equally to the expected 60 participants. The recruitment at the core sites is estimated to be 5 participants per month for 24 months while the satellite sites' recruitment is estimated to be ~1 participant per month for 24 months.

2.1.3 Minority Recruitment

RIVUR clinical sites should strive to recruit all available minority participants that meet the eligibility criteria. Because minorities have generally been under-represented in previous clinical trials, they are less likely to be familiar with medical terminology, may not know anyone who has been in a 'good' clinical trial, and may be suspicious of the medical system. Additional time may be required to educate potential participant families prior to the participant's enrollment. Sites may be required to enlist the services of an interpreter to facilitate recruitment in non-English speaking participants.

Study Coordinators and other personnel with whom the participants will have contact should be sensitive to different cultural and ethnic attitudes and practices. For example, personnel should be aware of days of special significance when scheduling follow-up visits; this may help improve participant compliance. Whenever possible, individuals from different minorities should be represented in the study staff.

2.3 Screening

2.3.1 Overview

In brief, the screening process will identify potential study participants who appear to meet the RIVUR eligibility criteria. The most critical screening factor for RIVUR recruitment is timing. In order to be considered for study inclusion, a child (aged 2 to <72 months) who has been recently diagnosed with their first or second urinary tract infection (UTI) and has documentation of fever or symptoms within $\pm$24 hours of the beginning date of UTI work-up will need to have been appropriately treated and have been scheduled for a renal ultrasound and a voiding cystourethrogram (VCUG). In the event that the child has had more than one UTI, there can be noVUR diagnosis between the first and second UTI and no intervening treatment for VUR with prophylactic anti-microbial treatment. An ultrasound and VCUG must be performed within 16 weeks of the date of the index UTI diagnosis. Another timing consideration is that the randomization procedure must be carried out within 16 weeks of the index UTI diagnosis.

2.3.2 Screening Tools

A RIVUR eligibility summary card (Figure 1.) will be distributed with the recruitment materials to each site prior to study start-up. The card summarizes the RIVUR eligibility criteria as well as lists out most of the exclusion criteria for study participation. Another tool that will be helpful in screening is the Eligibility and Randomization Form. This form may be used on paper to track a subject's eligibility, but ultimately, its main purpose is to verify eligibility and after deeming a child to be eligible, randomize him/her to a treatment group. Do not begin data entry of this form during the screening process.

A log has been developed for those sites whose IRB requires tracking of potential participants. The Participant Screening Log (PSL) is a required form and will be entered into the RIVUR DMS. The data collected on the PSL will enable the sites to determine where their efforts in screening will be the most effective.

2.3.2.1 Documentation and Screening Timeline

The child is eligible for RIVUR if they have had 1 or 2 UTI's. In the event that more than one UTI has occurred, in order for the child to be eligible, he/she may not have been treated with prophylactic anti-microbials nor had a VUR diagnosis. The UTI immediately preceding the enrollment into RIVUR will be called the index UTI. The date of the index UTI diagnosis is defined as the collection date of the urine sample that resulted in the positive urine culture.

In order to complete the screening within the randomization time restriction (16 weeks since the index UTI diagnosis), the study staff will need to be able to determine that the index UTI meets the RIVUR–designated UTI definition (≥38°C fever OR symptoms occurring within 24 hours of medical care related to urinary tract, i.e. dysuria, urgency, frequency, abdominal pain, foul-smelling urine, and in infants, dehydration, hypothermia, and failure to thrive), was caused by a single primary organism, was appropriately treated, and that the child has vesicoureteral reflux (VUR) in at least one ureter. A list of exclusion criteria must also be reviewed, most of which may be determined from a child's medical history and ultrasound results.

Figure 1. RIVUR Prescreening Summary Card

RIVUR
Randomized Intervention for Children with Vesicoureteral Reflux

Inclusion – child must meet all

- ☑ Age: 2 months to less than 6 years (72 months) at randomization
- ☑ **First or second** UTI with ≥ 38°C fever **OR** symptoms related to urinary tract documented within ± 24 hours of UTI work-up (symptoms include dysuria, urgency, frequency, abdominal pain, foul-smelling urine, and in infants, dehydration, hypothermia, and failure to thrive)
- ☑ Index UTI diagnosis occurred within 112 days of randomization
- ☑ Pyuria on UA shown in 1 of 3 ways:
  - ≥ 10 WBC/mm^3 **OR**
  - ≥ 5 WBC/HPF **OR**
  - Leukocyte esterase ≥ trace on dipstick
- ☑ Culture proven infection with single primary organism:
  - ≥ 50,000 CFU/mL (cath or aspirated) **OR**
  - ≥ 100,000 CFU/mL (clean void)
- ☑ Index UTI treated for 7+ days with effective drug OR test of cure (neg urine culture) post treatment
- ☑ VUR grade I-IV in at least one ureter

SEE OTHER SIDE FOR EXCLUSION

RIVUR
Randomized Intervention for Children with Vesicoureteral Reflux

Exclusion – child meets one or more

- ☒ If child < 6 mos old, gestational age <34 wks
- ☒ VUR diagnosed or treated between 1st and 2nd UTI
- ☒ Greater than two organisms present on index UTI urine culture
- ☒ Second organism present at >10,000 CFU/mL
- ☒ Consent not obtained OR inability to complete protocol
- ☒ Allergy to TMP/SMZ
- ☒ Grade V VUR in either ureter
- ☒ Co-morbid urologic anomalies: hydronephrosis, ureterocele, urethral valve, solitary or profoundly small kidney, multicystic dysplastic kidney, neurogenic bladder pelvic kidney or fused kidney.
- ☒ History of other renal injury/disease
- ☒ Any bladder or renal surgeries
- ☒ Congenital or acquired immunodeficiency
- ☒ Underlying anomalies or chronic diseases that could potentially interfere with response to therapy such as gastrointestinal conditions (malabsorption, inflammatory bowel disease), liver/kidney failure or malignancy
- ☒ Complex cardiac disease
- ☒ Family hx of anaphylactic reaction to sulfa

SEE OTHER SIDE FOR INCLUSION

The documents necessary for eligibility determination consist of the child's medical records from the index UTI visit, including medical history, documentation on fever, symptoms, urine specimen type, urinalysis results, urine culture results including anti-microbial sensitivity results, and local reports from the ultrasound and VCUG. Timely collection of supporting documentation and direct action regarding scheduling of radiographic procedures following a child's first UTI will increase the success of RIVUR recruitment. Source documents are required to document that the eligibility criteria have been verified.

The progression of events leading up to randomization include early identification of a child who has recently been diagnosed with his/her first or second UTI, scheduling of radiographic procedures, documentation collection, eligibility determination, consent, and scheduling of the randomization visit.

2.4 Eligibility

2.4.1 Inclusion Criteria

2.4.1.1 Age of Participant

Date of birth is obtained to calculate age. At the time of randomization, the patient must be older than 2 months of age, but less than 6 years of age (72 months). If the prescreening indicates that a patient is between 1 and 2 months of age, but will be at least 2 months when randomization occurs, the Study Coordinator should continue to collect eligibility documentation for the child. If the prescreening indicates that the patient will be 6 years of age or greater at the time of randomization, then the patient should not be screened any further.

If a child is less than 6 months of age, their gestational age must be greater than or equal to 34 weeks in order to be accepted into the study.

2.4.1.2 First or second Febrile or Symptomatic UTI

The child who is being considered for inclusion into RIVUR will need to have been diagnosed with either a febrile UTI or a symptomatic UTI ($_{F/S}$UTI) that fits the definition that follows. The UTI must meet one of the two criteria (febrile or symptoms) listed under section I AND meet one of the three pyuria criteria listed under section II AND meet one of the two criteria for proof of infection listed in section III. This UTI definition remains constant for all RIVUR UTIs.

I. Fever[1]

- Documented temperature of at least 100.4 °F or 38°C, measured anywhere on the body either at home or at doctor's office

OR

Symptoms[1]

- Suprapubic, abdominal, or flank pain or tenderness, or urinary urgency, frequency, or hesitancy, or dysuria, or foul smelling urine, or in infants ≤ 4 months old, failure to thrive, dehydration, or hypothermia

[1] Must occur within ± 24 hours of initiating workup for UTI.

AND

II. Pyuria on urinalysis

- ≥10 WBC/mm^3 (uncentrifuged specimen) OR
- ≥5 WBC/hpf (centrifuged specimen), OR
- positive leukocyte esterase on dipstick

AND

III. Culture proven infection with a single organism[2]

- ≥5 x 10^4 CFU/mL (catheterized or suprapubic aspiration urine specimen) OR
- ≥10^5 CFU/mL (clean voided specimen).

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[2] One contaminating organism may be present at colony count of ≤ 10,000 CFU/ml.

2.4.1.3 Appropriately-Treated Index UTI

In order for a child to be considered eligible for RIVUR, there must be documentation that the index UTI was appropriately treated. Study Coordinator will need to acquire the urine culture results including anti-microbial sensitivity results for the index UTI. Treatment for the index UTI will be considered appropriate if antibiotic therapy continues for a minimum of 7 days and:

1) There is documented sensitivity of the organism to the antibiotic used for treatment OR
2) There is a documented test of cure (negative urine culture) 1-14 days after completion of therapy.

Note: A UTI will be considered appropriately treated by a cephalosporin if the sensitivity panel of the UTI shows the bacteria sensitive to the same or earlier generations of cephalosporin used to treat the UTI.

2.4.1.3 VCUG Radiographic Scan Results

Central to the RIVUR study is the presence of grade I-IV VUR in either ureter. The VUR diagnosis will come from a local radiologist's VCUG report. VUR will be graded according to the five-grade system of the International Reflux Study Group. Note: any child with grade V VUR in either ureter will be excluded from the study.

Timing of the VCUG is critical for entry into the RIVUR trial. The scan must be obtained and interpreted within 16 weeks of the index UTI diagnosis.

2.4.2 Exclusion Criteria

In addition to documenting that the child being screened meets all of the inclusion criteria for the trial, there is a list of exclusion criteria that will eliminate the child's eligibility if one or more criteria are met.

2.4.2.1 Renal Ultrasound Results

Many of the exclusion criteria may be documented from the renal ultrasound results. The renal ultrasound will be performed to screen for obstruction or other anatomic abnormalities of the urinary tract, such as urologic anomalies (hydronephrosis, ureterocele, urethral valve, solitary or profoundly small kidney, multicystic dysplastic kidney, pelvic kidney, or fused kidney).

The ultrasound scan must also have been obtained and interpreted within 16 weeks of the index UTI diagnosis.

2.4.2.2 Sulfa Allergy

If the child has any known allergy to sulfa medications or has G6PD deficiency or other conditions that are contraindications for the use of trimethoprim-sulfamethoxazole (TMP/SMZ), RIVUR's active study medication, he/she will be excluded from the study. Further, if the child being screened has a parent or sibling with a known anaphylactic reaction to sulfa medications, he/she will be excluded from the RIVUR trial.

2.4.2.3 Other Medical Conditions

Any child who has any one of the conditions listed in Table 2.1 will be excluded from the study. There may be information in the child's medical records about these exclusion criteria, but the Study Coordinator may only have the parent's report as the supporting documentation.

QxQs for the ERF will include specific definitions or other information necessary to make these assessments.

Table 2.1. RIVUR Exclusion Criteria

1. History of renal disease or injury
2. Bladder or renal surgery
3. Grade V VUR in either ureter
4. Congenital or acquired immunodeficiency
5. Anomalies or chronic diseases that interfere with response to therapy such as chronic gastrointestinal conditions (i.e. malabsorption, inflammatory bowel disease)
6. Liver or kidney failure
7. Any malignancy
8. Any known syndromes associated with VUR or bladder dysfunction
    a. VATER - VACTERL association
    b. Townes-Brock syndrome (*SALL1* mutation)
    c. Cat eye syndrome (tetrasomy, chromosome 22)
    d. Casamassima - Morton-Nance syndrome
    e. Renal coloboma syndrome (*PAX2* mutations)
    f. Branchio-oto-renal syndrome (*EYE1* mutation)
    g. Frasier syndrome (*WT1* mutation)
9. Complex cardiac disease, defined as any cardiac anomaly where the child requires regular medication or where the child's cardiologist would prescribe perioperative antibiotics

10. Continued use of drugs that are contraindicated with sulfatrim (atropine, bezoic acid, hyoscyamine, methenamine, methylene blue, phenyl salicylate, benzocaine, butamben, tetracaine topical, dofetilide, lidocaine/prilocaine topical)

2.4.2.4 Inability to Complete the Trial

Another exclusion criterion for the RIVUR trial includes a family's inability to complete the study protocol. This includes whether or not the family has given consent for the child to participate in the study. Once consented and randomized into the trial, the child will be followed for a minimum of 2 years. If the family has any reason to move from the study area within 2 years following study enrollment, the child should be excluded. Hardships with regard to clinic transportation should be considered when discussing the family's ability to participate in the RIVUR trial.

2.4.2.5 Participating in Other Trials

Eligible participants who are currently participating in any other research study are welcome to participate in the RIVUR trial if the other study does not include medication or preclude the child from adhering to the RIVUR protocol in any way.

2.4.2.6 Pyuria or Evidence of UTI on Day of Randomization

For a child to be eligible there cannot be pyuria or evidence of a UTI on the day of randomization. To rule these out, the coordinator must ask the parent about any recent fever or symptoms and collect urine on the day of randomization to dip for pyuria. This can be performed on a bag specimen. If result is trace or higher, coordinator should obtain a cathed specimen and dip again. If still positive, coordinator should order a stat microscopy from local lab on the cathed urine. A microscopy result of $\leq$10 WBC/mm3 (uncentrifuged specimen) OR $\leq$5 WBC/hpf (centrifuged specimen) trumps the dipstick result and means the child is eligible. A positive microscopy result will require that the urine be cultured to rule out a UTI. In this situation, the coordinator should tentatively reschedule the randomization visit and wait for the result of the urine culture.

If the culture results from the previous randomization attempt show no bacteria, then the child may return to the clinic for randomization. The coordinator should obtain a urine specimen and dip as usual during the second randomization attempt. Even if the dip shows pyuria, the coordinator may continue with the randomization if there has been no recent fever or UTI symptoms.

In rare situations a child may normally demonstrate positive pyuria. If the dip from the second randomization attempt shows greater pyuria than the dip from the first attempt, the coordinator should be careful to rule out the possibility of UTI.

2.5 Consent

2.5.1 Participant Informed Consent

Informed consent is a legal condition whereby a person can be said to have given consent based upon an appreciation and understanding of the facts and implications of an action. The individual

needs to be in possession of all of his faculties, such as not being mentally retarded or mentally ill and without an impairment of judgment at the time of consenting. Impairments include illness, intoxication, drunkenness, using drugs, insufficient sleep, and other health problems. In RIVUR, the parent(s) or guardian of the participant will be consenting for the child.

Informed consent is a process, not just a form. Information must be presented to enable persons to voluntarily decide whether or not their child will participate as a research subject. It is a fundamental mechanism to ensure respect for persons through provision of thoughtful consent for a voluntary act. The procedures used in obtaining informed consent should be designed to educate the subject population in terms that they can understand.

Included in the 'informed' process:

1. Description of the overall experience that will be encountered.
2. Description of the risks and benefits that subjects may reasonably expect to encounter.
3. The parents or legal guardian must be told the extent to which their personally identifiable private information will be held in confidence**.**
4. Identification of contact persons who would be knowledgeable to answer questions of subjects about the research, rights as a research subject, and research-related injuries.
5. Explanation of the right to withdraw at any time without penalty. It is equally important to explain any foreseeable consequences to them should they unilaterally withdraw while dependent on some intervention to maintain normal function.

Eligible children invited to participate in the RIVUR study will be consented for study enrollment. Each site's Project Coordinator or other trained study staff member must perform the formal process of obtaining informed consent from the parent(s)/legal guardian of the child for enrollment. Failure to obtain informed consent and a signed consent form from the parent(s)/legal guardian of each potential participant before screening and/or before enrollment is a serious protocol violation. Note: Foster parents are not considered legal guardians.

The informed consent process must include an explanation of the nature of the study and its rationale, examination procedures, specimen and data collection procedures, randomization, the duration of the study, the importance of compliance to study procedures, and the potential risks and benefits. Parents and/or guardians must be told that they are not obligated to participate, that there will be no penalty for declining to participate, and that their treatment will not be compromised if they choose not to participate or cease participation at any time.

Ample time must be provided for each parent or guardian to read and understand each site's IRB-approved consent form, and to ask questions. If a parent or guardian cannot read, clinic staff must read the consent form for the adult, or use an audiotape of the consent form. Parents or guardians who do not understand English should have the consent process administered in the participant's language in the presence of the Project Coordinator or appropriate recruitment staff, and the consent form must be translated in the language spoken by the patient and approved by the IRB at that clinical center.

2.5.1.1 Consent for Specimen Storage at the Repository

NIDDK/NIH has included in the RIVUR trial the opportunity for the participants to contribute to the NIDDK biosample and genetics repositories. Some of the specimens collected during the study will be stored at the central repositories to be used for future research. Each participant must be separately consented to contribute specimens to the NIH-designated repositories. These consents may be covered during the RIVUR consenting process. If a family has any desire to limit the specimens to be stored, they should be free to do so without repercussion. Each specimen collected has a 'date for use by' if the family does not wish for an open-ended time period of specimen retention.

2.5.1.2 Consent Tracking Form (ICT)

Each consented parent or guardian should receive a signed copy of the study consent. The site's signed consent form copy is to be filed with other confidential participant information. Upon completion of the consenting process, an Informed Consent Tracking (ICT) form is to be completed for each participant **prior** to randomization. It is again completed on any contact occasion when the parent or guardian notifies the study that they would like to modify their consent, or withdraw from the study.

It is imperative that the Study Coordinator keeps track of what specimens have been consented for collection. It is a serious protocol violation to collect a specimen and ship it to a repository if the family has not consented. The report from the DMS will be able to keep the Coordinator informed, but the Coordinator will need to inform the phlebotomist about repository restrictions.

2.5.2 Obtaining a Medical Release

Endpoint data collection as well as adverse event reporting will require review and abstraction of medical records for health care received outside the clinical center's hospital. Study personnel must obtain a medical record release form to obtain data from the outside care provider. Medical release forms should include the purpose of the request, the information that will be requested, and the time period related to the request. The release form should be reviewed with the participant during the informed consent process, prior to the participant signing the form.

2.5.3 Health Insurance Portability and Accountability Act (HIPAA)

The Health Insurance Portability and Accountability Act (HIPAA) require that all research collecting identifiable health information on an individual be in compliance with HIPAA standards and regulations. HIPAA regulations specifically apply to research studies collecting Protected Health Information (PHI). PHI is defined by HIPAA as health information transmitted or maintained in any form or medium that:

1) Identifies or could be used to identify an individual; and
2) Is created or received by a healthcare provider, health plan or employer, and
3) Relates to past, present or future physical or mental health or condition of an individual.

Compliance for each Center will require that each participant read and sign a "HIPAA Authorization to Use and Disclose Individual Health Information for Research Purposes" form.

These forms must receive IRB approval at the clinical site prior to their use and thus, prior to the enrollment of any RIVUR participant. The participant should receive a copy of her signed authorization.

In addition, all study personnel who have contact with potential participants or data are required to complete a course on human subjects' protection. Each Center PI and the directors of the Coordinating Center and Central Laboratories are responsible for ensuring that their personnel have completed an approved training program.

2.6 Scheduling a Randomization Visit

Once a child is determined to be eligible for participation in RIVUR, and appropriate data is collected, the randomization and baseline visit should be scheduled for the child's enrollment. Informed consent can occur at this time, or at the beginning of the randomization visit.

Chapter 3: Radiology
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Chapter 3: Radiology

3.1 Overview

Renal/bladder sonograms will be used to screen participants for obstruction or other anatomic abnormalities of the urinary tract. DMSA renal scans will be used to determine the presence and/or worsening of cortical defects, and to assess the severity of renal damage. Contrast VCUGs will be used to identify and grade the severity of VUR. Results of all images will initially be interpreted at participating institutions. RIVUR study evaluations will be made through independent readings by reference radiologists and nuclear medicine investigators using standardized grading systems. These reference radiologists will make up the Imaging Studies Reading and Classification Committee.

3.2 Radiographic Images

3.2.1 DMSA

DMSA scans will be used to determine the presence of cortical defects. Renal images should be obtained 1 ½ - 3 hours after IV administration of an age-appropriate dose of DMSA. Administered dose of 3-5 mCi/1.73 m2 body surface area or 50-100 µCi/kg body weight (minimum dose of 0.5 to 1 mCi) is advised. Planar images obtained with parallel-hole collimator, with or without pinhole magnification, are acceptable. SPECT images are not acceptable for this study.

Planar Imaging without pinhole magnification:
Posterior and both posterior-oblique renal images should be obtained using a high-resolution collimator, 256 x 256 matrix, and 500,000 - 1,000,000 counts per image. Appropriate zoom should be used to eliminate bladder activity from the field of view. Differential renal function should be calculated on the posterior image by background subtracted number of counts in each kidney as percentage of total number of counts in both kidneys.

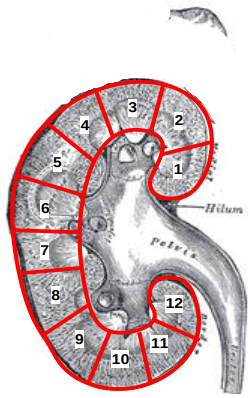
Pinhole Imaging:
A posterior image of the kidneys using a parallel-hole collimator (300,000-500,000 counts) should be obtained for calculation of the renal differential function. Magnified posterior and posterior-oblique images of each kidney are then obtained using a pinhole collimator with a 4 mm insert. 120,000-150,000 counts should be accumulated for each pinhole image.

Interpretation of DMSA scans:
Cortical defects (dysfunction) will be defined as focal or diffuse decreased uptake with or without volume loss. Using criteria established by Majd (1) defects with preserved contour (without volume loss) will be classified as acute pyelonephritis and those with obvious volume loss/cortical thinning will be classified as cortical scar. The cortical defects will be assessed semi-quantitavely by dividing the renal cortex into 12 equal segments. The location and number of renal parenchymal segments affected will be determined and the extent of the renal abnormality will be graded as outlined in Figure 1.

These evaluations will be made by two reference nuclear medicine investigators on the Imaging Studies Reading and Classification Committee.

See Appendix 1 for an example of a DMSA image.

F… …ystem for characterizing extent of renal scarring

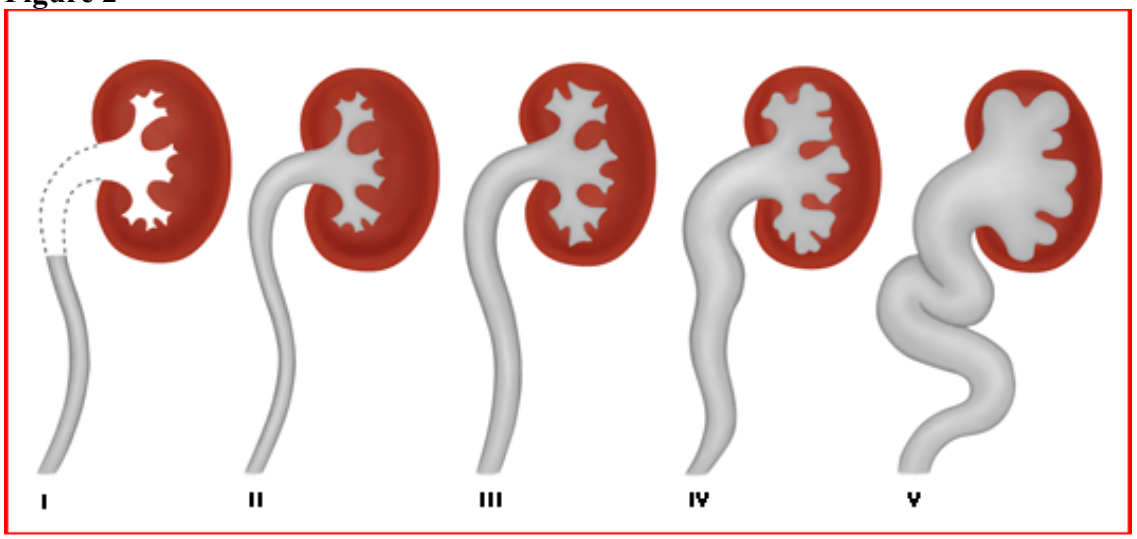


Grade	Description
0	No kidney segments affected
1	1-2 kidney segments affected
2	3-4 kidney segments affected
3	>4 kidney segments affected
4	Global atrophy characterized by a diffusely scarred and shrunken kidney.

3.2.2 VCUG

A contrast VCUG will be used to identify and grade the severity of VUR. Morphological abnormalities of the bladder and the appearance of the urethra will be noted. VUR will be graded according to the five-grade system of the International Reflux Study Group (see Figure 2 below): Grade I, reflux into ureter only; Grade II, reflux into ureter, pelvis and calyces without dilation; Grade III, mild to moderate dilation and/or tortuosity of the ureter and moderate dilation of the renal pelvis but little or no blunting of the fornices; Grade IV, moderate dilation and/or tortuosity of the ureter and moderate dilation of the renal pelvis and calyces; and Grade V, gross dilation and tortuosity of the ureter and gross dilation of the renal pelvis and calyces.

Figure 2



International classification of vesicoureteral reflux (VUR) Modified from International Reflux Committee. Medical versus surgical treatment of primary vesicoureteral reflux. Pediatrics 1981; 67:392.

Sedation during performance of VCUG is neither expected nor required as part of this trial. Institutional policies on sedation will not be modified for study participants. However, the study will record whether or not sedation is used and, if used, the name of the medication(s).

Results of the VCUG will be initially interpreted at participating institutions; the digital image will be acquired for verification of the degree of VUR by two reference radiologist investigators on the Imaging Studies Reading and Classification Committee.

3.2.3 Renal/Bladder Sonogram (Ultrasound)

Renal/bladder sonograms will screen for obstruction or other anatomic abnormalities of the urinary tract, such as ureteropelvic junction obstruction, a posterior urethral valve, or hydronephrosis associated with an ectopic ureter or ureterocele.

3.2.4 References

1. Majd, M, Seminars in Nuclear Medicine 1992. 22: 98-111.

2. Rushton, H.G., et al., *Evaluation of 99mtechnetium-dimercapto-succinic acid renal scans in experimental acute pyelonephritis in piglets.* J Urol, 1988. **140**(5 Pt 2): p. 1169-74.

3. Andrich, M.P. and M. Majd, *Diagnostic imaging in the evaluation of the first urinary tract infection in infants and young children.* Pediatrics, 1992. **90**(3): p. 436-41.

4. Goldraich, N.P., O.L. Ramos, and I.H. Goldraich, *Urography versus DMSA scan in children with vesicoureteric reflux.* Pediatr Nephrol, 1989. **3**(1): p. 1-5.

3.3 Clinical Site Procedures

3.3.1 Obtaining Scans

Coordinators should schedule and/or obtain radiographic images on participants as required per protocol and described in the MOP Chapters on baseline, follow-up, and endpoints data collection.

Non-protocol interim DMSA scans, requested by the DCC following a febrile UTI or treatment failure determination, are to be scheduled within 7 days of notification. Since assessment of these images is time-critical, images must be obtained and mailed to the reference radiologists as soon as possible. The DCC will notify sites of treatment failure determinations within 2 weeks after the images are received by the reference radiologists. Sites are asked to notify parents of any change in status within 3-4 days.

The images can be obtained either as electronic images on CD (preferred) or films. Electronic images should be collected as DICOM format with the site‟s local reading software. Coordinators will need to obtain one copy of all digital images, as well as associated local radiology reports. One copy is stored at the clinical site as study source documentation after using it to upload to the RIVUR PACS (see Section 3.3.4).

3.3.2 Identification / De-identification and Encryption

Images, films, and reports are to be de-identified of patient information as required at each individual site prior to upload for the reference radiologists.

If you are unable to upload an image then you should de-identify the data sufficiently or you may use Winzip Pro 11.2 to encrypt the files before you send them to the reference radiologists.

If your institution is unable to include the DMSA report in DICOM format then you will need to convert it and upload it into the PACS. You will need to convert the report into either a pdf file or scan in as an image file. Please see Appendix 3.5 for further instructions. Ultrasounds and VCUG reports are not required unless specifically requested by a reference radiologist or DCC staff.

3.3.2.1 ID Labels

The DCC will provide pre-printed ID labels for each site. The ID labels correspond to the participant ID numbers, and include contact occasion and sequence number pre-filled for baseline, 12-month (CO=07) and end-of-study 24-month (CO=13) scans. Additional labels are included for non-protocol interim DMSA‟s. These will require recording of contact occasion and sequence numbers as appropriate. These radiographic labels will be used to identify the radiographic scans and allow us to identify studies that belong to a single patient.

The preprinted labels with participant ID numbers are to be affixed to CD cases, on every page of film, the local report pages, and the inventory and shipping logs. ID numbers

including contact occasion and sequence number (see Section 5.2) also need to be written on the CD, marking on the top of the CD with a black sharpie.

3.3.3 Data Collection Forms at the Clinical Sites

- DMSA Sedation Form (DSF)
- DMSA Scan Shipping Form (DSS)
- VCUG Sedation Form (VSF)
- VCUG/US Scan Shipping Form (VUS).

3.3.3.1 Sedation Forms

A sedation form is to be completed for each DMSA and VCUG image, using the VCUG Sedation Form (VSF) or DMSA Sedation form (DSF) to document sedation used during the scanning. These forms are to be completed for each participant and scan, regardless of whether sedation was used. This is information the Coordinators must request at the time they are requesting the scans.

3.3.3.2 Shipping and Inventory Logs

When preparing to mail or upload images to the reference radiologists you will need to complete the DMSA Scan Shipping Form (DSS) and/or the VCUG/US Shipping Form (VUS), providing an inventory of the collection and including the shipping/upload date that correspond to the images being mailed/uploaded. Each scan being shipped must be accompanied by an appropriate study shipping log.

Data from these shipping and inventory logs must be entered into the study DMS. Copies of completed logs associated with a shipment are to be included with each mailing. Coordinators can complete the accompanying logs by hand, or print off the data screen from the DMS.

3.3.4 Mailing Instructions

DMSA Images and corresponding local reports that are NOT ABLE TO BE UPLOADED are to be mailed to:

Massoud Majd, MD
mmajd@cnmc.org
Children's National Medical Center
Department of Radiology
111 Michigan Ave., NW
Washington, DC 20010-2970
Phone: 202-884-5088

and

Harvey A. Ziessman, MD
hziessm1@jhmi.edu
Professor of Radiology
Director of Nuclear Medicine Imaging
Johns Hopkins Outpatient Center
601 North Caroline Street, Suite 3231
Baltimore, MD 21278
Phone: 410-955-5152
Fax: 443-287-2993

VCUG and Ultrasounds Images and corresponding local reports that are NO ABLE TO BE UPLOADED are to be mailed to:

J Michael Zerin, MD
jzerin@dmc.org
5021 Champlain Circle
West Bloomfield, MI 48323
Phone: 248-538-9260 (home)
313-745-7080 (work)
Fax: 313-993-0393

and

Jeanne Chow, MD
Jeanne.Chow@childrens.harvard.edu
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Main 2
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300 Longwood Avenue
Boston, MA 02115
Phone: 617-355-4631 (Rhonda Johnson assistant)
Fax: 617 730 0573

When mailing or uploading scans, please send an email notification to each radiologist and the DCC using the preprogrammed email group available on the RIVUR Website for "DMSA Reference Radiologists" or "VCUG/US Reference Radiologists." The email should be titled „RIVUR Radiology Shipment" and indicate the number of studies included, the date shipped, and the site sending the shipment.

There are no specific requirements regarding how to mail (i.e. US mail, FedEx) baseline scans; sites can choose the system convenient for them. Interim DMSA scans that indicate scarring on the local report will require a more time urgent procedure for shipping, analysis and reporting. These need to be collected as soon as possible and mailed FedEx overnight.

3.4 Radiologist Procedures

3.4.1 Storage and Extraction of Images/Films

If the files arrive from the site in an encrypted zip file format on CD then unzip the file to enable reading.

If files are downloaded from CD‟s to the radiologist‟s computer, folders must be created and named to match the ID label on the CD, indicating the ID number, contact occasion and sequence number (i.e. MA02062_01_00). If possible, files on the CD should also be renamed when saved on the computer/laptop in the folders. **It is critical that there is a link from the images on the computer to the Participant ID number**.

All laptops and computers containing study data should be stored in a secured location.

3.4.2 Reading and Recording Scans

Each member within a pair of reference radiologists will read either via the RIVUR PACS or cd and record reading results independently onto separate forms in the Web based data management system (DMS). Images should be viewed via the RIVUR PACS system. See Appendix 3.4 RIVUR PACS Viewing Instructions for more information. Images are to be read within 10 days of receipt or notification of upload. Interim images following a febrile UTI or treatment failure determination are time critical and must be assessed as soon as possible, within 7 working days.

Reading results can be recorded either on the paper data collection forms then entered, or entered directly into the DMS. At any time when reading results are recorded on paper prior to entry in the DMS, the paper is considered source documentation and must be saved for at least 2 years following the termination of the study.

3.4.3 Data Collection Forms needed by the Radiologists

Each image type has a data collection form associated with it, copies are included with the MOP and are also available on the study website.

- DMSA Results Form (DMF)
- VCUG Results Form (VRF)
- Ultrasound Results Form (URF)

3.4.4 Adjudication

Paired readings of images with any discrepant data items will require adjudication. The Data Management System (DMS) will have reports available that will identify images and reading results that need adjudication. These reports will be available to both members of the pair of radiologists. Section 3.5.5 will be added to this chapter at a later date and will contain a description of the DMS reports regarding radiology.

Adjudication of images is done by telephone conference, set up by the lead adjudicator. The DCC may occasionally sit in on the adjudication calls monitoring the process.

One member within each pair of reference radiologists will take a lead in managing the adjudication procedure, assuring the database reflects the adjudicated results. The lead adjudicator is responsible for setting up the communication for any needed adjudications twice monthly, and for the final data entry of the adjudicated results into the newly created adjudicated record (see Section 3.5.4).

The lead adjudicator is also responsible for keeping documentation on the decision making processes used in adjudicating results and on the comparing of notes taken during the individual readings. This documentation will be shared with the DCC and used to modify the forms or procedures used in the main study and provide the appropriate documentation on the decision making of this study endpoint.

The assignment of the lead adjudicator can be alternated/shared among the pairs of radiologists, throughout the study. Notification to the DCC is required when making a change in assignment so that privileges to the DMS adjudication functions can be transferred.

3.5 Data Management for Reference Radiologists

3.5.1 Identification of Images

The clinical sites are responsible for labeling all images with the participant ID, contact occasion, and sequence numbers. These 3 numbers assure each image is uniquely identified. All participants will have DMSA"s at baseline, 12-months, and 24-months, VCUGs at baseline and 24-months, and ultrasounds at baseline.

Contact Occasion numbers are as follows:

Contact Occasion	Visit
01	Baseline
07	12-Month Follow-Up
13	24-Month Follow-UP

Participants who are deemed treatment failures may require DMSA scans at other times during follow-up in the study. These will be labeled appropriately by the clinical site with the correct contact occasion and sequence number.

The information that identifies each data collection form and/or each data record as a unique record in the RIVUR DMS is the key field information contained in the “header” box at the top of the first page on all forms.

Example Header:

ID NUMBER:							

FORM CODE: DM1
VERSION: A 11/13/06

Contact Occasion			SEQ #		

ID Number – This is the first part of the ID label on each image received from the clinical centers, which corresponds to the participant ID. All RIVUR ID"s are 7 fields long and include a site mnemonic as the first 2 fields, followed by 5 numbers that include a check digit for quality control.

Form Code / Version – identifies a unique data collection form. The results from reading the radiographic images are recorded on 3 data collection forms, one for each scan type. Versions will change as revisions are made to the data collection forms.

Contact Occasion and Seq# - These are the 2nd and 3rd numbers after the ID that is contained on the ID label of each image. For example: PT01515_01_00, the participant ID is PT01515, contact occasion 01 (baseline), and seq# 01 (the first occurrence within the ID and CO.

Each image reading is entered into 2 different files, one for each member of the radiologist pair. For data entry, the reference radiologists are assigned the following codes, which identify the form code for entry, providing unique records for each reading:

DM1 – Massoud Majd
DM2 – Harvey Ziessman
VR1 and UR1 – Michael Zerin
VR2 and UR2 – Jeanne Chow

In the event that adjudication between the paired readings is necessary, a 3rd file is created that will have form codes DM3, VR3, and UR3. Only the lead adjudicator (Majd and Zerin) can modify data in the 3rd form. See Section 3.5.4 for specific instructions on how the adjudication process works in the DMS.

Administrative Information
The last set of questions on each RIVUR data collection form contains administrative information. This includes the date of data collection (image reading), the method of data collection (by paper recording first or directly into DMS), and the initials of the Radiologist. Entering the last field, initials of the radiologist into the DMS is the flag to the DMS and DCC that the image reading is complete and reports can be run. Until this section is entered, it is assumed that readings of this scan are not complete.

3.5.2 Official Study Documents

All current versions of the study MOP and data collection forms are available on the study website at http://www.rivur.net. Documents are stored as PDF files to retain formatting.

3.5.3 Data Management System User's Guide

The RIVUR Data Management User"s Guide is located in Chapter 14 of the RIVUR MOP. All DMS users should be familiar with this document.

3.5.4 DMS Query Resolution - Adjudication

Adjudication is a function performed under "Query Resolution." Only the lead adjudicator has write access to the adjudicated records, while the other radiologist has browsing privileges.

Once in the "Query Resolution" screen, the left hand panel will indicate the ID numbers of any images requiring adjudication of at least one data item. Clicking on the ID will identify the contact occasion and adjudication forms associated with the image.

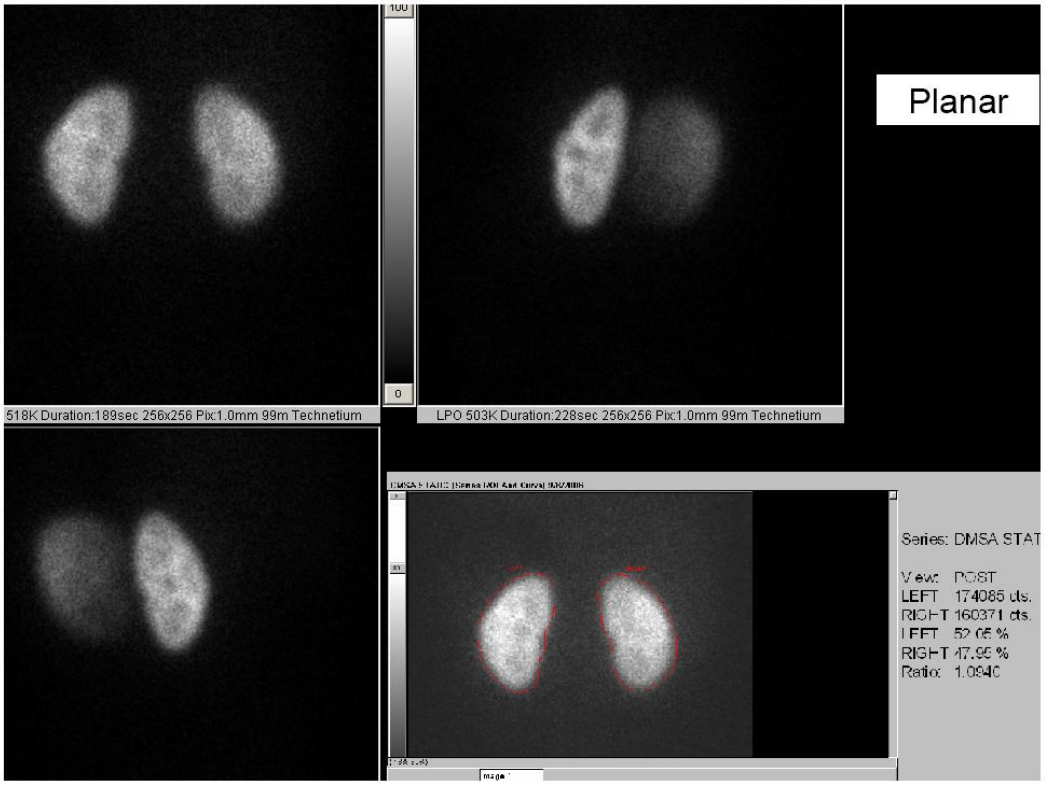
Clicking on a file, will bring up an adjudication record (DM3, VR3, or UR3), which will be pre-filled with the values entered originally by the lead adjudicator. Fields that are in agreement will appear with shading and will not allow modification. Fields requiring adjudication will be blank. When the cursor is on each of these fields, pressing F1 will cause a comment to pop on the screen that provides the previous data values from both radiologists that are in need of adjudication.

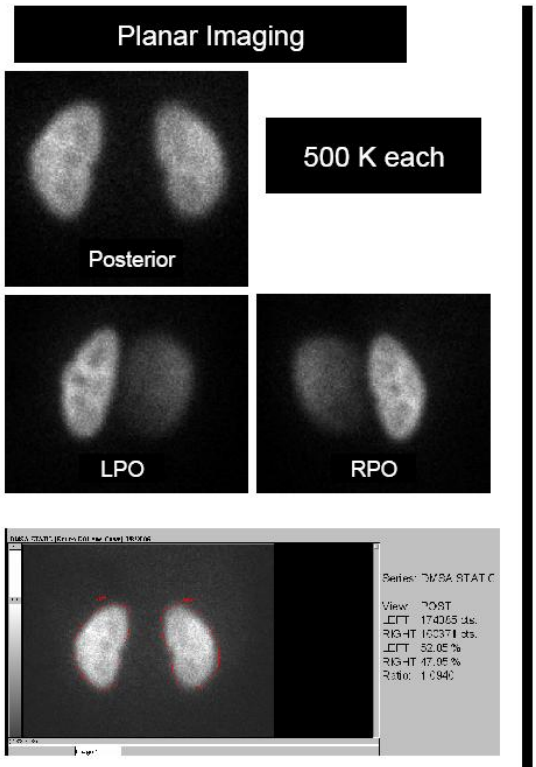
In the event that the adjudication process results in needing to change values on other fields that were not discrepant, that modification must be made through the normal "Remote Data Entry" process on the adjudicated file (DM3, VR3, or UR3), after resolution is complete. Changes needed on images reviewed that did not require adjudication are done in the original DM1-2, VU1-2, and UR1-3 files, which could result in adjudication if there are any new discrepancies.

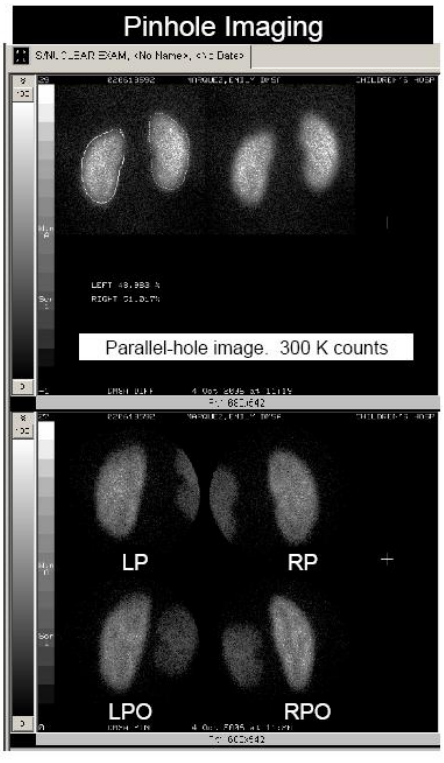
The DMS will have reports that will list out images and data items needing adjudication for both radiologists review.

Appendix 3.2 contains an FAQ providing more information on the adjudication process in the DMS.

Appendix 3.1 – Example DMSA Images







Pinhole images. 150 K counts each

Appendix 3.2 – RIVUR Image Adjudication FAQ

1) What images need to be adjudicated?
Any image result with one or more discrepant values between the 2 radiologists is flagged for adjudication. Currently, the adjudication system looks for a 1:1 exact match.

2) How are images determined to require adjudication?
Each night a process runs that looks for completed and matched records (matched on ID, Contact Occasion (CO), sequence number (Seqno), and form version), compares all data items, and assesses if there is the need to adjudicate any of the results. A completed record is one that has had the radiologists initials entered into the last administrative field of the image records.

If an adjudication is determined to be needed, the original records are locked (DM1, DM2, VR1, VR2, UR1, UR2) from additional entry or modification, and a new record is created for adjudication (DM3, VR3, UR3). The adjudicated record is pre-filled with data that is not discrepant. These fields are also greyed out. The fields requiring adjudication have been left blank and are easily identified. With the cursor on a blank field, typing „F1", the help key, produces a pop-up window that contains both radiologists original and discrepant responses.

3) How do the radiologists know an image needs to be adjudicated?
Both pairs of radiologists can find out which images need adjudication by viewing the DMS reports „DMSA Adjudication Report", or the „VCUG and Ultrasound Adjudication Report". This report will list each scan (ID, contact occasion, sequence number) needing adjudication, and the fields requiring adjudication.

Recall that field names in the system correspond to the form name, and the question number on the form. Example DM1A2 refers to the DMSA Results form, version A, question #2.

The adjudicator (Majd or Ziessman) also knows what images require adjudication through access to the „Query Resolution" function in the DMS. All images (identified by ID, CO, Seqno) requiring adjudication is listed in the left hand hierarchical menu (similar to the „Data Entry" function).

4) What is the process for the radiologist to adjudicate?
One of each pair of radiologist is predetermined to be the adjudicator. It is expected that adjudication is done over the telephone with both radiologists communicating during the process. In this way, the adjudicator can document rules and standards that are derived during the process. Documentation of these rules and standards will be needed to assure consistency of image assessments throughout the study, and provide information on the process for future manuscripts.

5) How does the 'Query Resolution' system work to allow adjudication?
Adjudications and the entry of data resolutions are performed in „Query Resolution" mode in the DMS. This is one of the features offered when you enter the RIVUR DMS. It is very similar in look and appearance to „Data Entry" mode.

Appendix 3.2 – RIVUR Image Adjudication FAQ

Only the adjudicator has access to records in „Query Resolution, and accesses them using the familiar hierarchical menu on the left hand side. This menu only lists records needing adjudication. The 2nd radiologist cannot access these records, but is able to go into „Data Entry" and browse his original image assessment during the adjudication procedure.

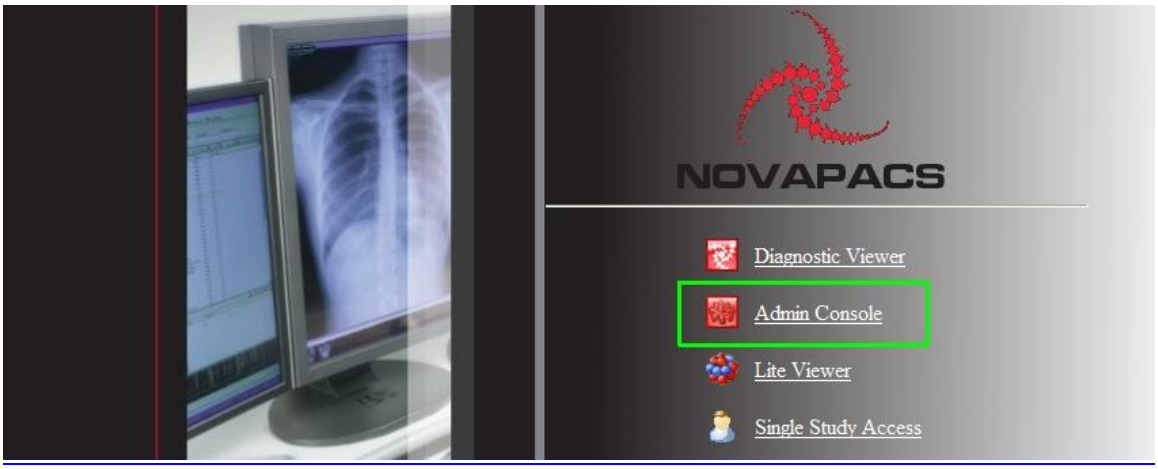
Once an adjudicated record is open, the adjudicator moves through the new record (DM3, VR3, or UR3), and at each blank field, reviews each radiologists result (F1 for this information), then through discussion, the radiologists agree on the final result. The adjudicator enters this result in the field. All the same rules of data entry apply in the „query system" as in the „data entry system" (except that the fields not requiring adjudication are not accessible).

Once an image has completed adjudication, the adjudicator enters the administration data, date of adjudication, and their initials. This signals the system that the adjudication process is complete for this image. The evening process will then move the completed adjudicated records from the „query resolution" system back into the „data entry' system.

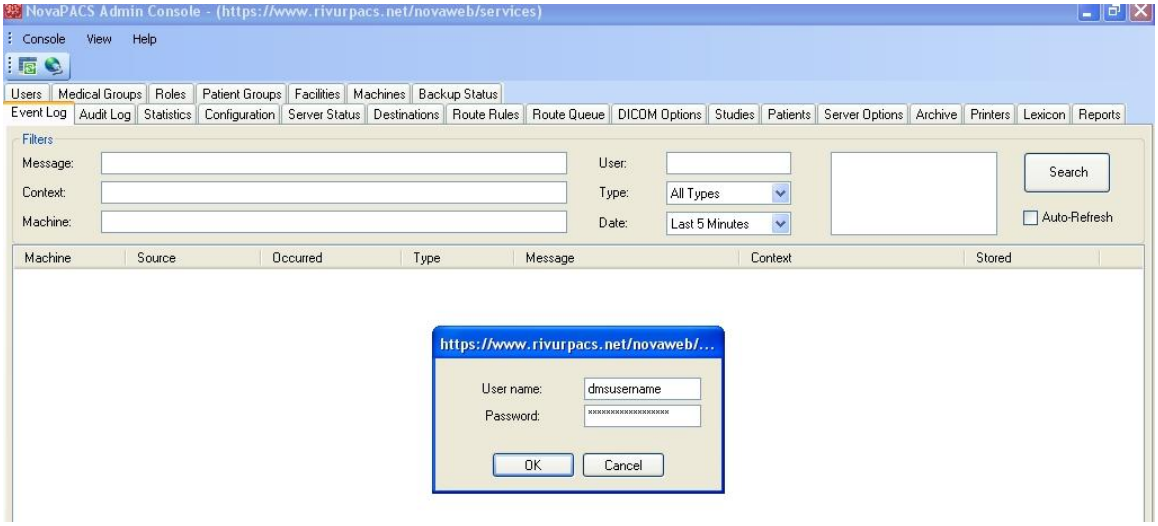
6) Can data be modified or updated after an assessment is entered as complete?
An assessment is considered complete when the radiologist enters their initials into the data form. Data can be modified or updated until the nighttime process determines adjudication is needed. If adjudication is needed, the original records are locked, and updates or modification can then only be made through the adjudicated records (DM3, VR3, and UR3).

Appendix 3.3: RIVUR PACS Uploading Instructions

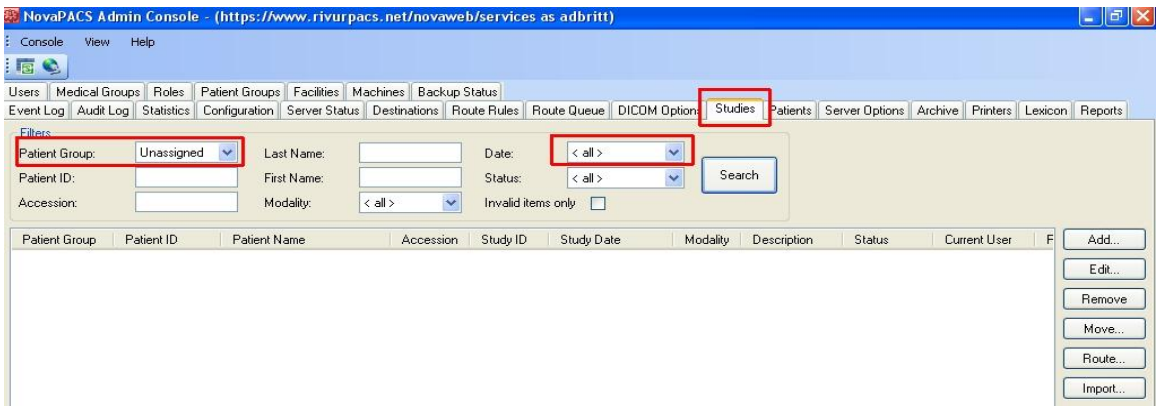
1. Once you have the radiology cds and converted DICOM reports for DMSAs - Go to PACS website: https://www.rivurpacs.net/novaweb/defaultadmin.aspx



2. Click on "Admin Console" and log in using your username and password (same as DMS, if no #"s in DMS password then add 600 to end of password)



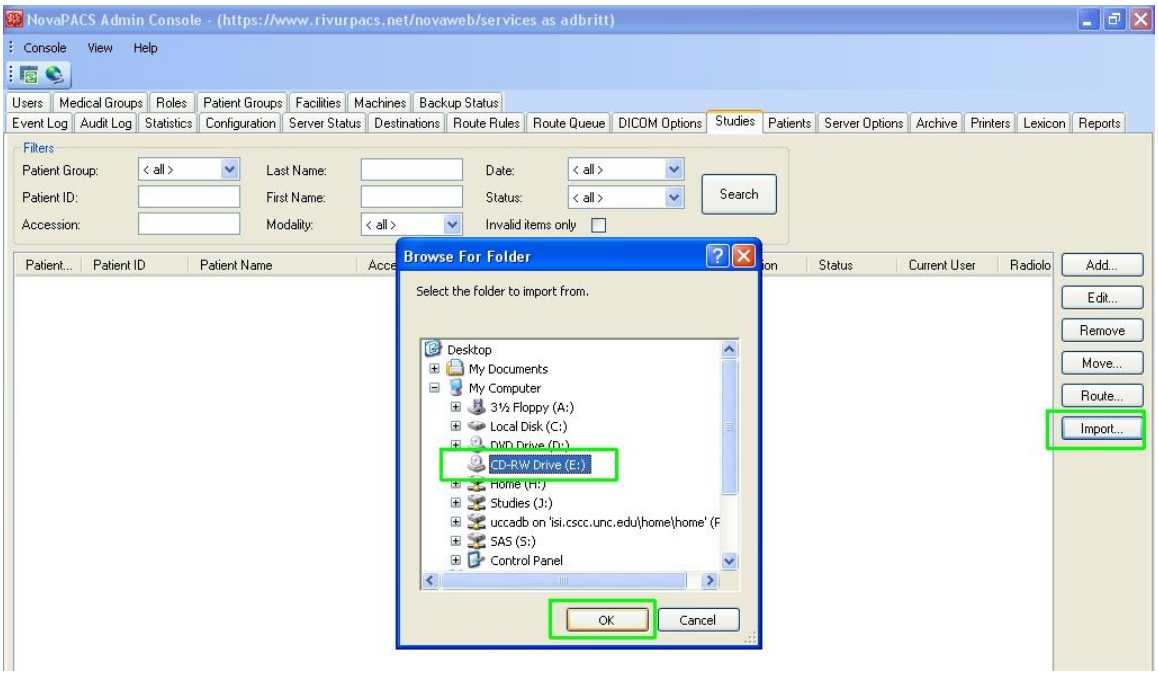
3. Go to the "Studies" Tab and make sure you have set the "Patient Group" to Unassigned, and the Date to "all".



Appendix 3.3: RIVUR PACS Uploading Instructions

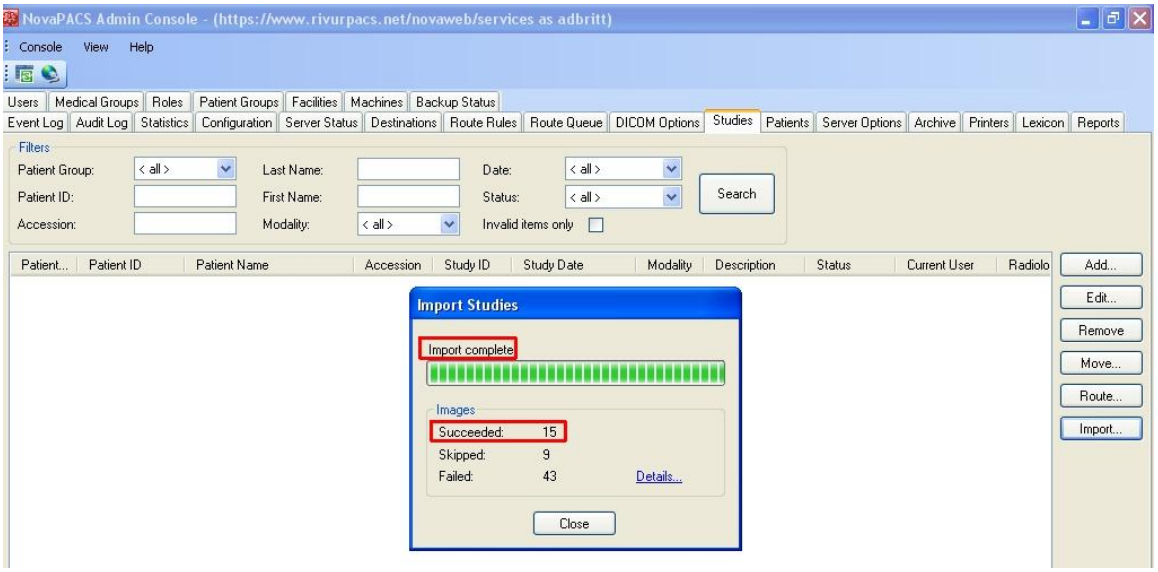
4. Insert the CD into the computer. Wait to see if it loads a viewer program (if so close it).

5. Click on "Import" in the lower right hand menu



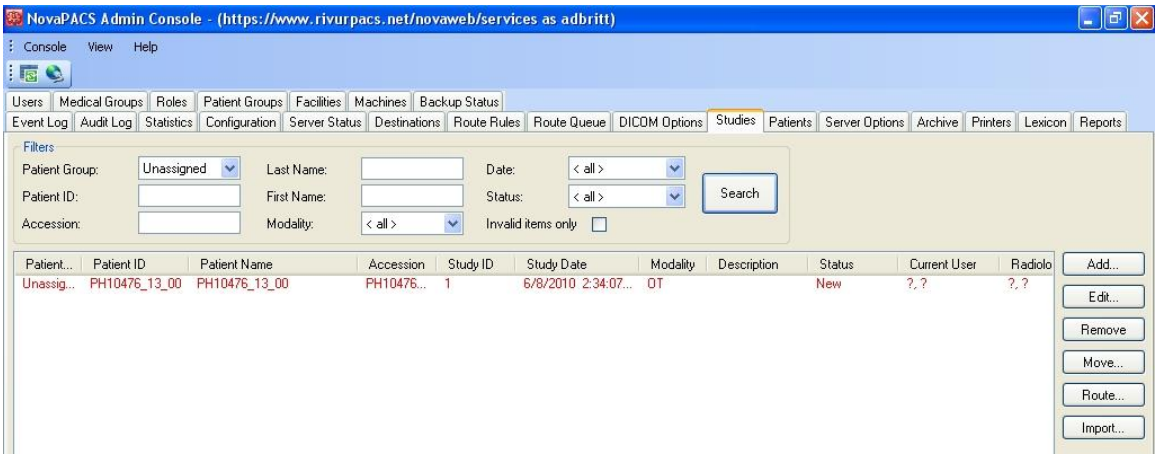
6. Select the entire CD drive (or the specific report image if importing report) and click "OK"

7. Allow to import and wait until it says "import complete" in the box itself. (Make sure it has some amount by Suceeded.)

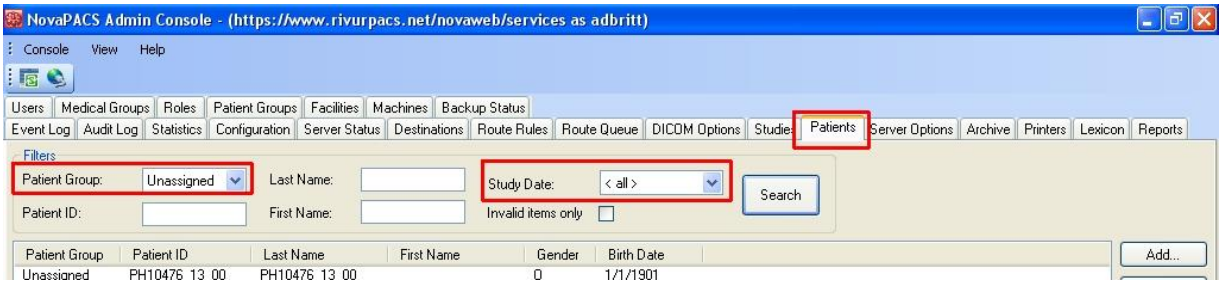


8. You should now see the file you just imported pop up as the only patient in your studies list. Note the information that is listed under Patient name etc. (if more

than one site is importing at a time double check that it is the correct child"s information that you are importing – this is why it"s good to NO LONGER have your hospital deidentify images unless IRB requires it)



9. Click to the Patient tab. Make sure you have set the "Patient Group" to Unassigned, and the Date to "all". – You should see the file you just uploaded here as the only one listed unless others are uploading (see #8 above).

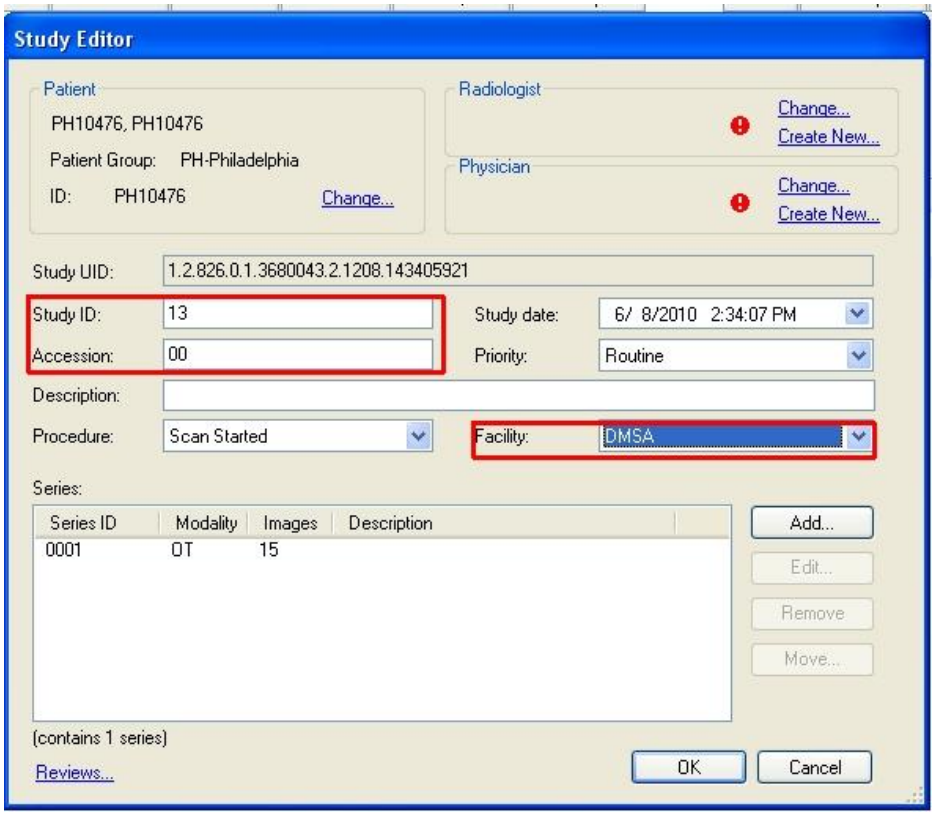


10. Double click on patient and select your site for Patient group, then enter the RIVUR study ID for Patient ID, First name, and Last name. (If it asks you to merge files answer yes)

11. Click to the Studies Tab and select your patient.

Appendix 3.3: RIVUR PACS Uploading Instructions

12. Delete whatever is entered for Study ID and enter the Contact Occasion (2 digits) and Accession = Sequence number (2 digits).



13. Select the type of SCAN for "Facility" and hit enter. (Click "yes" when asked about updating all files for the study)

    a. DMSA = Any type of nuclear medicine scan– If you have to view in the viewer they look like two light gray beans.

    b. VCUG = Voiding cystourethrogram– if you have to view in viewer it looks like xrays of a child's lower body with dark blob over their bladder area that changes size.

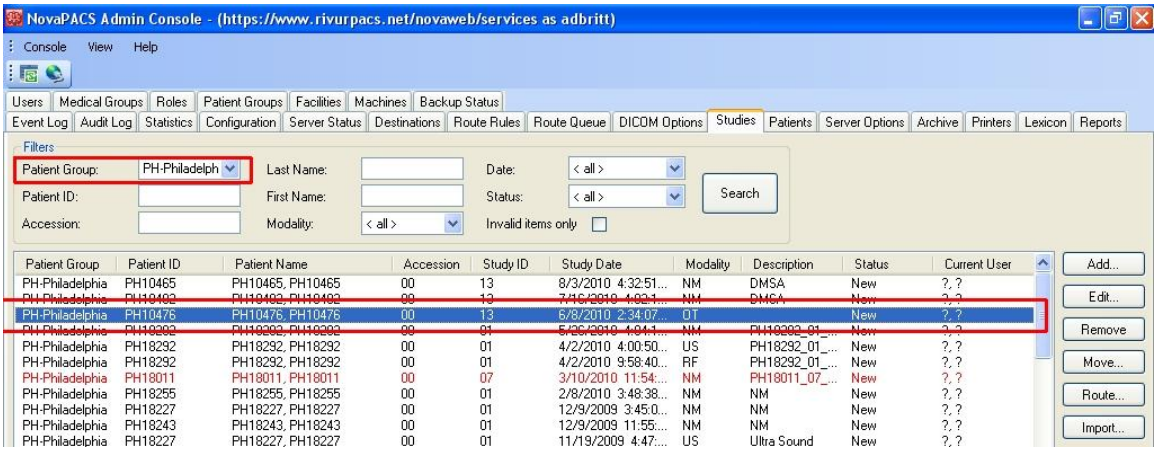
    c. US= Renal ultrasound – if you have to view in viewer it looks like a baby sonogram with random colors on some images.

    d. Other = Abdominal or other X-rays, CAT scabs etc. Some disks have other random images that are not used in our study. Please label these as Other if they are not one of the three above.

    e. If importing a report – select: Report-DMSA, Report-VCUG, Report-US for whichever type you are importing. (NOTE: We only require that you uploading DMSA Reports. VCUG and US are uploading upon request only)

Appendix 3.3: RIVUR PACS Uploading Instructions

14. To double check your upload, go back to the studies tab and select your site from Patient group and make sure this scan is listed under the appropriate study id.

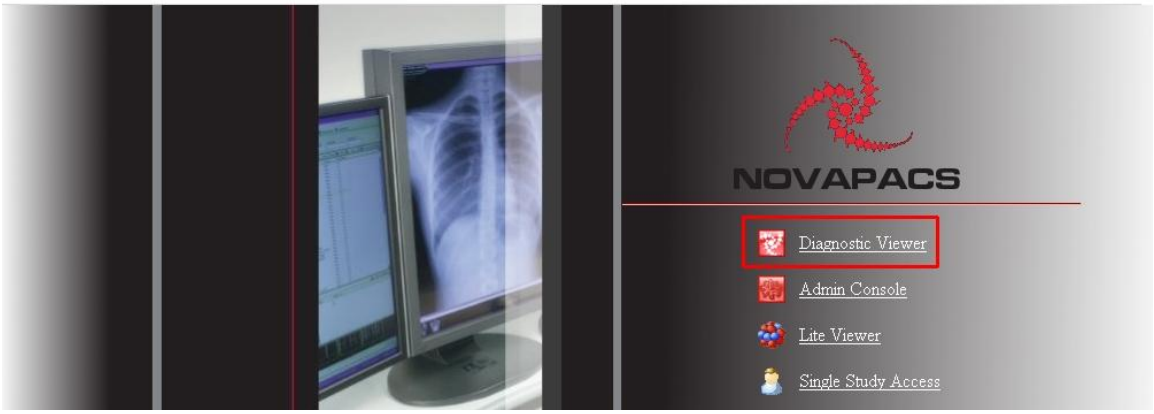


15. If disk doesn"t import and you run into errors – then contact the DCC hotline.

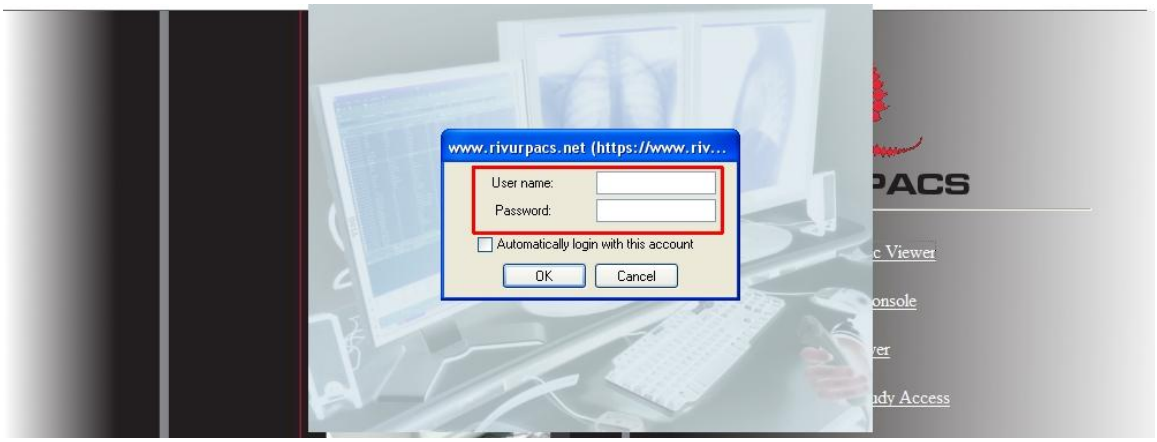
Appendix 3.4: RIVUR PACS Viewing Instructions

1. Go to DMS -> Select Reports -> select "Radiologist to Read Report" , Print report

2.Go to PACS website: https://www.rivurpacs.net/novaweb

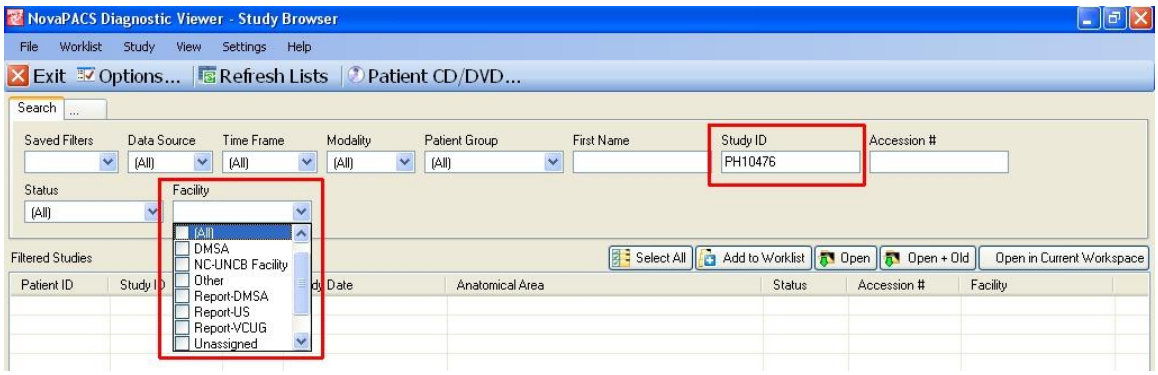


3. Click on "Diagnostic Viewer" and log in using your username and password (same as DMS EXCEPT add 600 to end of DMS password)



4. Go to the Facility Tab and select whatever types of images you would like to read (including their corresponding reports).

5. Enter the study id you would like to view under "Patient ID"



Appendix 3.4: RIVUR PACS Viewing Instructions

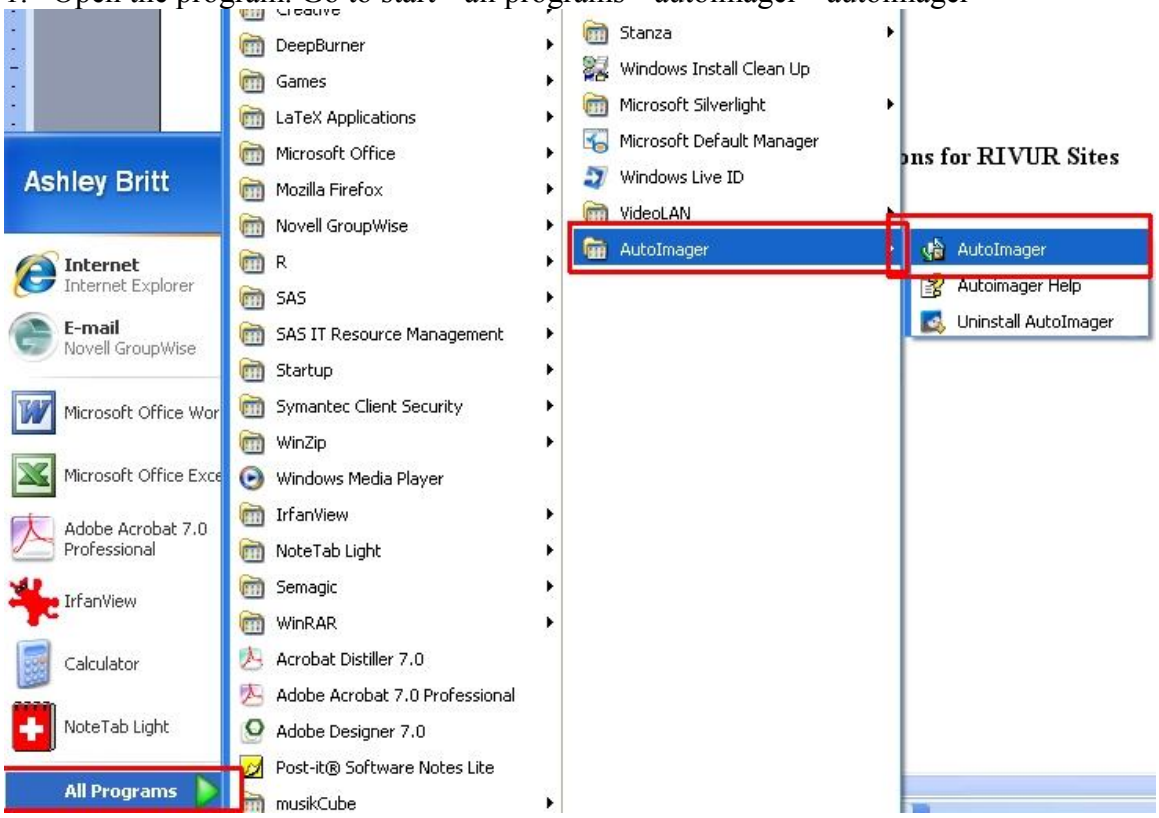
6. Select the scan you would like to view - Study ID = Contact Occasion and Accession = Sequence number

7. Enter your reading form in DMS as usual.

8. If you run into errors or need more information please email rivurpacs@mail.cscc.unc.edu or call the hotline 1-866-257-7242

Appendix 3.5: AutoImager by Mystic Media Conversion Instructions

1. Open the program. Go to start->all programs->autoimager->autoimager



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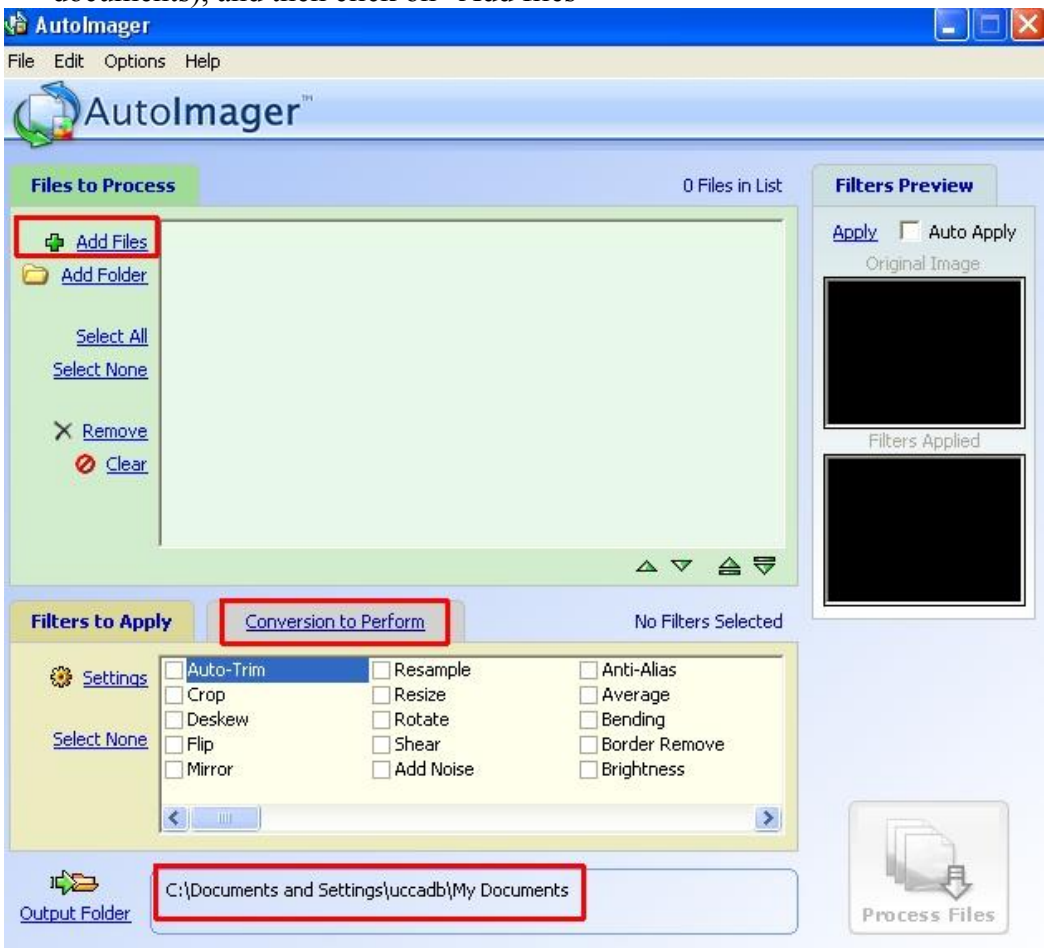
Appendix 3.5: AutoImager by Mystic Media Conversion Instructions

2. Click on “Conversion to Perform”, note what the Output folder is (default is my documents), and then click on “Add files”



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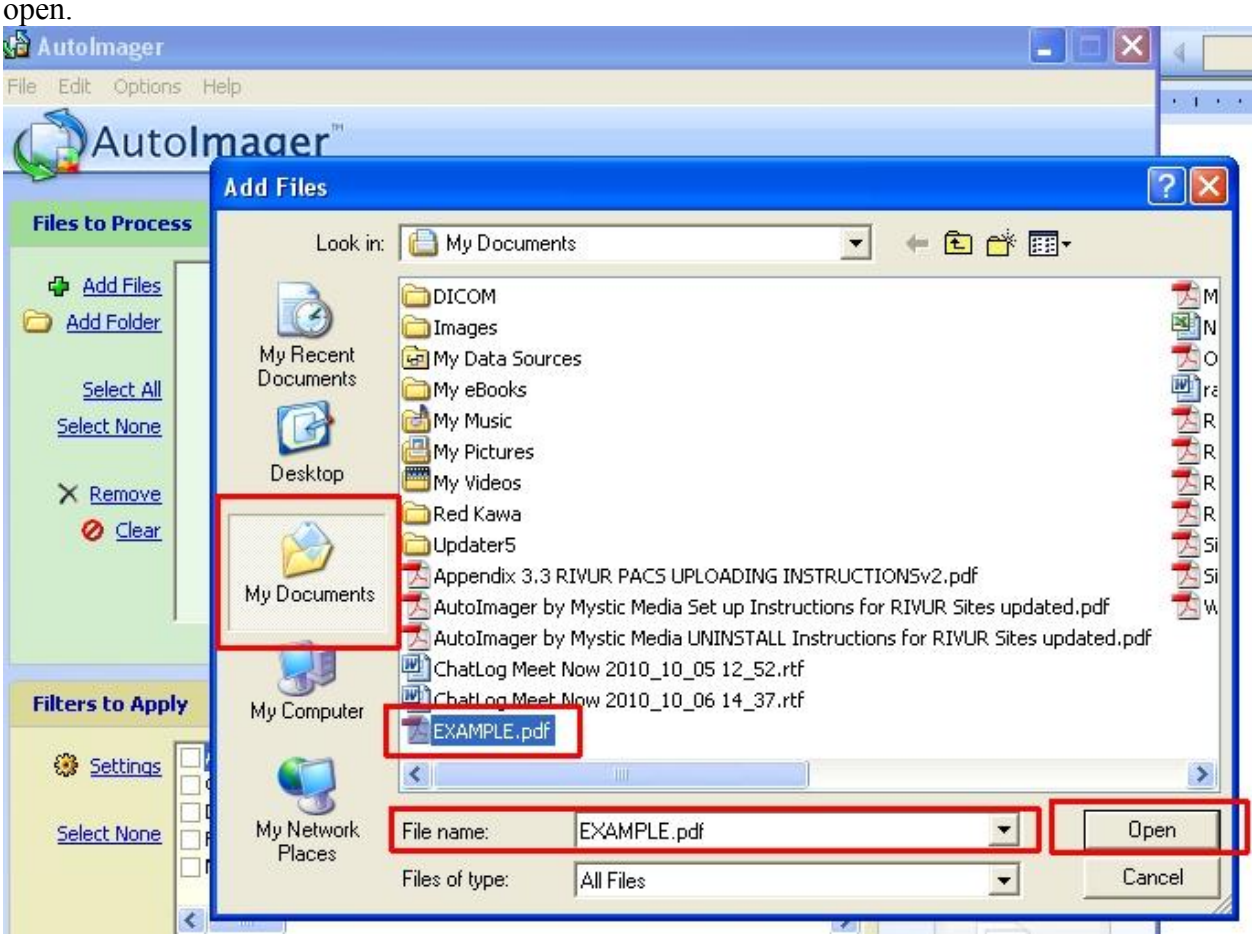
Appendix 3.5: AutoImager by Mystic Media Conversion Instructions

3. Select your *** 1 *** page DMSA local report pdf document you've created earlier and select open.



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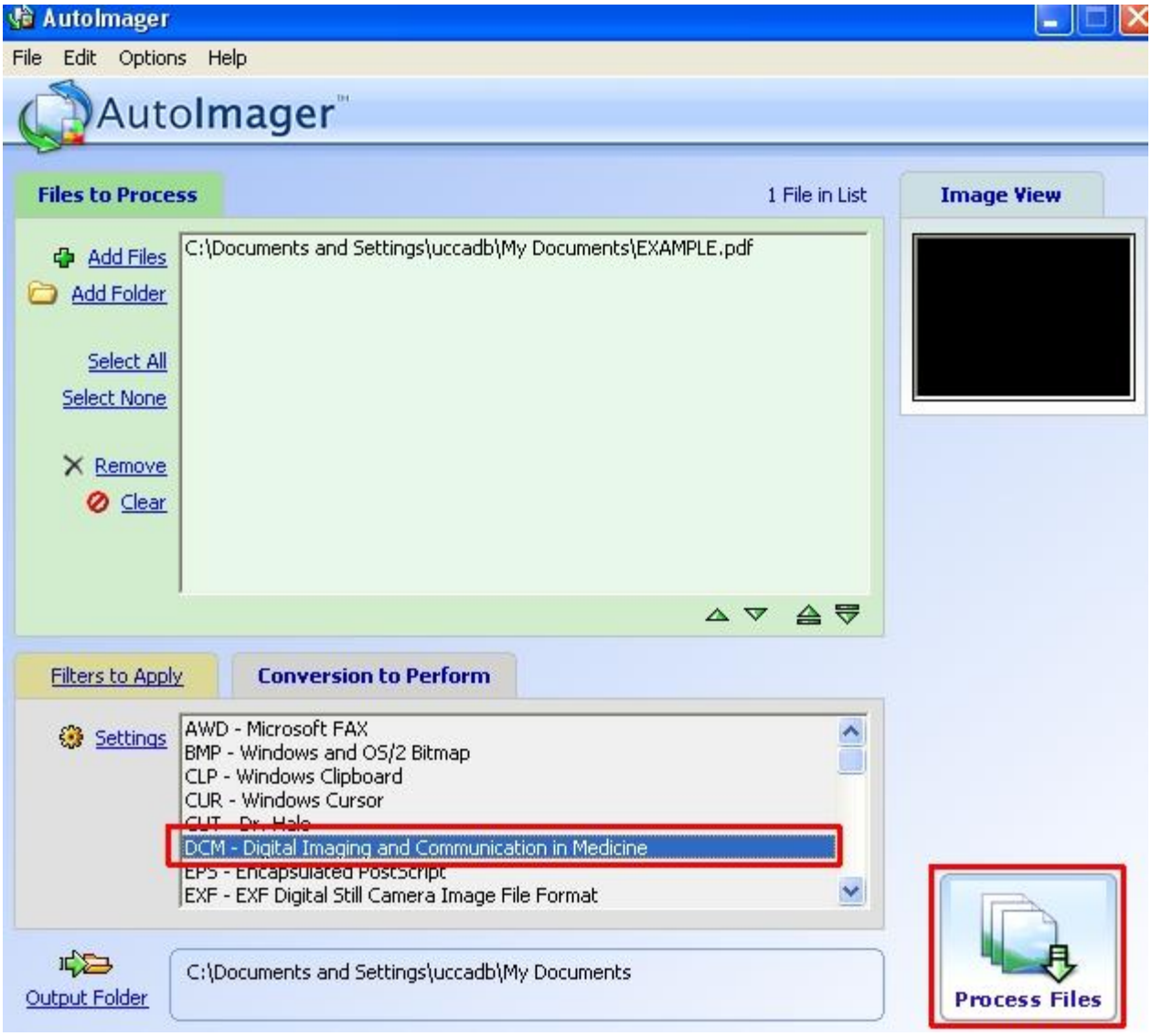
Appendix 3.5: AutoImager by Mystic Media Conversion Instructions

4. Select “DCM – Digital Imaging and Communication in Medicine” then click “Process files”



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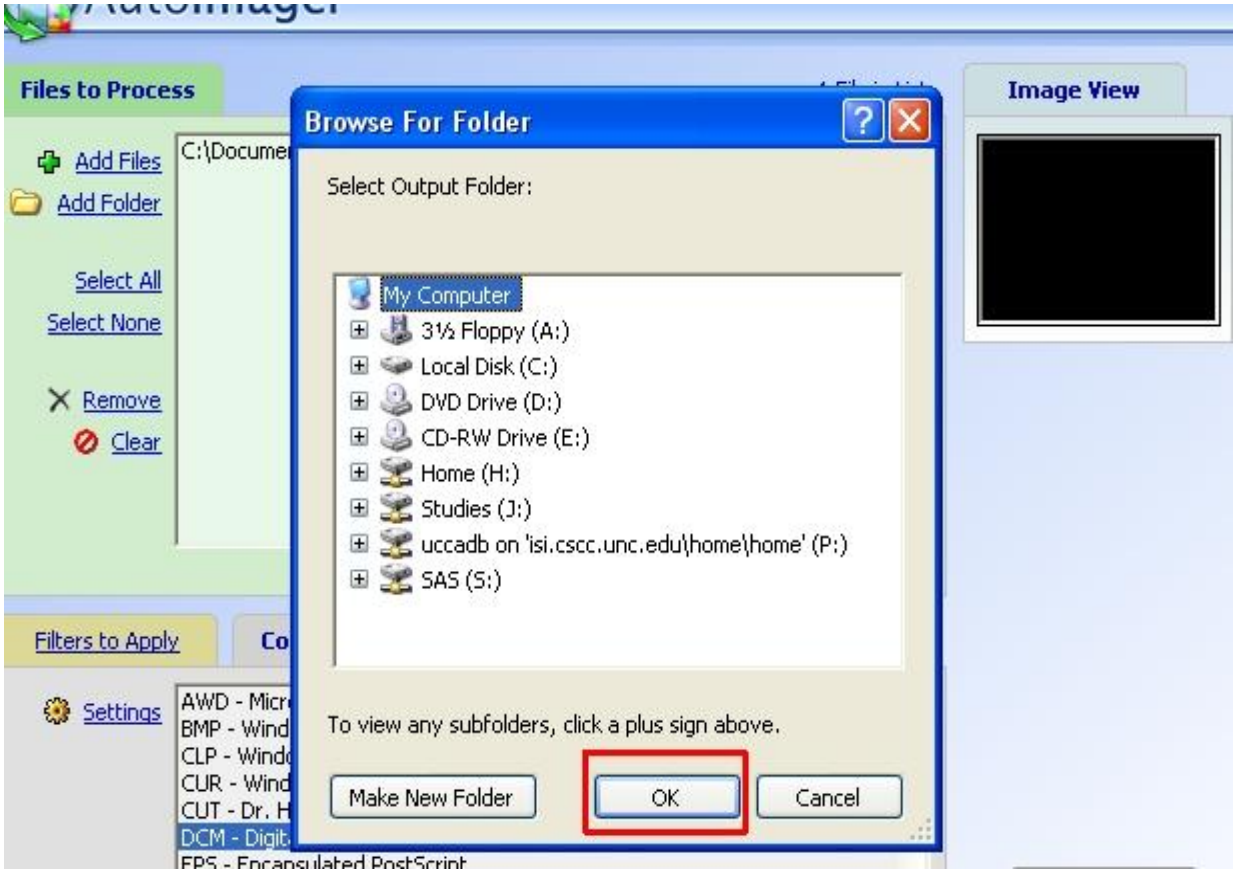
Appendix 3.5: AutoImager by Mystic Media Conversion Instructions

5. Select where you"d like to output the files then click "Okay"
   (if you want to skip this step you can select options at the top and uncheck "Show output folder selection")



6. You have converted the report. You can convert another or exit (select "no" you don"t want to save list).

7. Now upload into PACS like you would a cd (except select whatever folder and file you saved into instead of the CD drive).

Chapter 4: Randomization and Baseline

Table of Contents

Chapter 4: Randomization and Baseline

4.1 Overview

The goal of recruitment, eligibility determination, and randomization is to enroll eligible children as quickly and efficiently as possible for inclusion into the study. The overall goal of RIVUR is to randomize 600 children (300 per arm) over a 24-month recruitment period.

This chapter describes the procedures, data collection forms, and the ordering of procedures and data collection that must be followed for randomization and baseline data collection.

4.2 Prior to the Randomization Visit

4.2.1 Initial screening and Informed Consent (ICT)

Prior to randomization, all potential participants must be initially screened, have local renal ultrasound and VCUG results (with images and VCUG sedation information), and been appropriately treated for their first or second $_{F/S}$UTI.

Informed consent procedures must be completed with the child's parents or legal guardian prior to randomization.

Refer to Chapter 2: Recruitment, Screening and Eligibility for full details on eligibility, inclusion and exclusion criteria, and the process of informed consent.

4.2.2 Modification of Informed Consent

A participant may modify their Informed Consent at any time during the study. If a participant indicates a change in their consent to participate in the study, complete another Informed Consent Tracking Form (ICT).

4.3 Randomization and Baseline Components

The primary objectives of the randomization and baseline visit are to re-confirm eligibility, randomly assign participants to the study medication (active treatment or placebo), obtain baseline information, and distribute study medication. The randomization and baseline visit is composed of the following parts:

1) Re-assessment of all inclusion and exclusion criteria
2) Randomization using the web-based DMS during entry of the ERF form
3) A brief physical examination
4) Collection of participant demographic characteristics and medical history
5) Collection of concomitant medication data
6) Collection of baseline blood, urine, and a rectal swab specimen
7) Parental completion of the self-administered questionnaires
8) Dosing assessment and distribution of study medication

4.3.1 Data Collection Forms

The data collection forms required to complete the randomization and baseline data collection are the listed below in Table 4.1.

Table 4.1 Randomization and Baseline Data Collection Forms

Forms Collected Prior to Randomization:

- Informed Consent Tracking Form (ICT)
- VCUG Sedation Form (VSF)

Forms Collected During Randomization/Baseline Contact:

- Eligibility and Randomization Form (ERF)
- Baseline Demographic Form (BDF)
- Physical Exam Form (PEF)
- Baseline Medical History Form (BMH)
- Concomitant Medication Listing/Coding Form (CMF)
- LIA (Life Impact Assessment) Questionnaire (LIQ)
- Dysfunctional Voiding Questionnaire (DVQ) – if toilet trained
- Medication Dispensing and Dosing Form (MDD)
- Medication Distribution Log (MDL) *
- Specimen Collection Form (SCF)
- Participant Contact Form (PCF) *
- Biospecimen Repository Shipping Log (NIDDK-USL) *
- Genetics Repository Shipping Log (NIDDK-BSL) *
- Rectal Specimen Shipping Log (RSL) *
- Central Blood Lab Shipping Log (CSL) *
- VCUG / Ultrasound Inventory and Shipping Log (VUS)

Forms Completed after the Baseline Visit (though still contact occasion = 01)

- Blood Specimen Results Form (BSR)
- Urine Specimen Results Form (USR)
- DMSA Sedation Form (DSF), unless collected prior to baseline
- DMSA Imaging Inventory and Shipping Log (DSS)

Reference Radiologist Forms (completed and entered by the radiologists)

- Ultrasound Results Form (URF)
- VCUG Results Form (VRF)
- DMSA Results Form (DMF)

* Not data entered

4.3.2 Ordering of Data Collection during the Visit

Sites may organize the Randomization and Baseline data collection to accommodate their own staffing and organization needs. There are, however, a few things that are required and need to be considered:

1. Consent must be obtained and the ICT entered prior to any study data collection or randomization.

2. A urine dipstick negative for pyuria is required prior to randomization to assure no new infection is present. If pyuria is positive on dipstick (leukocyte esterase ≥ trace), a negative WBC (**WBC < 10 WBC/mm^3 or WBC < 5 WBC/hpf**) obtained on this same urine may trump the dipstick to document absence of pyuria. At this same time, urine for local chemistries (creatinine and microalbumin) and repository storage should also be collected.

3. Weight measurement during the physical exam must have been taken prior to blood specimen collection, medication dosing, and distribution.

4. Randomization must occur before medication dosing and distribution.

4.3.3 Data Entry during Visit

RIVUR data collection can be recorded on paper data collection forms, or entered directly online into the RIVUR data management system (DMS). Four forms are required to be entered at the randomization/baseline visit: the ICT must be entered as documentation of participant consent, the ERF must be entered to randomize the participant, the PEF must be entered to provide appropriate weight measurement for dosing, and the MDD must be entered to provide the study medication prescription including dose, number of medication bottles, and bottle numbers to be distributed to the parent/guardian.

All other data collection forms can be entered after the clinic visit is completed. The DCC requires all data collection forms to be entered within 5 working days of data collection.

4.4 Randomization

The process of randomizing participants in RIVUR is the official confirmation of all eligibility criteria, and a final ruling out of potential exclusions. Randomization also assigns each participant to either the active medication or placebo.

In order to enroll and randomize a child, he or she MUST be present in the clinic. You cannot run the eligibility algorithm in the web-based data management system prior to the clinic visit.

4.4.1 Verifying no new UTI prior to Randomization

Prior to randomization, you must verify that the child has not experienced a temperature (≥100.4˚F or 58˚C) anytime in the last 24 hours; this could be done by a telephone call the day before the scheduled visit. If the child has been sick with fever, the Coordinator will need to verify that this is not another UTI. Randomization must be rescheduled.

A urine dipstick test must also be performed and be negative for pyuria. In the event that the dipstick is positive for pyuria, that same urine may be spun and checked for the presence of WBC using microscopy. If pyuria is present, you must obtain a catheterized urine

specimen for culture to verify that the child does not currently have a UTI. This would require rescheduling of the randomization and baseline data collection. If the urine culture results are negative, the child should be scheduled for randomization. During the randomization, the urine should be dipped for pyuria, but the child may be randomized, even if pyuria is present at the second attempt of randomization.

4.4.2 Eligibility and Randomization Form (ERF)

Eligibility verification is completed upon data entry of the ERF form, at this randomization visit. You may have used this form initially as a tool to pre-screen or screen the child for consideration. However, it is critical that this form is completed appropriately at **this** clinic visit to officially verify all eligibility criteria. Some criteria may have changed since pre-screening and screening.

Particular attention must be made to accurately assess the number of UTI's that the child has experienced. The child is eligible for RIVUR if they have had 1 or 2 UTI's. In the event that more than one UTI has occurred, in order for the child to be eligible, he/she may not have been treated with prophylactic anti-microbials nor had a VUR diagnosis. The UTI immediately preceding the enrollment into RIVUR will be called the index UTI. You must have medical record documentation of the diagnosis of the index UTI, documentation of fever or symptoms occurring within $\pm$24 hours of the beginning of the index UTI workup, and documentation showing appropriate treatment for at least 7 days with an effective drug.

Refer to Chapter 2: Recruitment, Screening and Eligibility, and the ERF QXQ for specific details regarding eligibility and the ERF form.

At the time of randomization, verify that the child is at least 2 months of age, and less than 72 months and the index UTI had occurred within 112 days of randomization. All VCUG and U/S images must be collected prior to randomization, must also have been collected after the index UTI and within the 112 days of the randomization date. The baseline DMSA must be collected within 2 weeks of randomization and no more than 112 days from the index UTI.

4.4.3 The Randomization Procedure

In order to satisfy assumptions necessary for the validity of the statistical analysis that will be used to evaluate the RIVUR trial, eligible participants must be randomly assigned to one of the two treatments groups (active or placebo control).

Randomization occurs during the data entry process of the ERF form.

The randomization process does not result in the prescription or bottle number assignments for study medication. This occurs only after the physical exam is completed, the Physical Exam form (PEF) is data entered, and the Medication Dosing and Distribution form (MDD) is completed and data entered.

Refer to Chapter 2: Recruitment, Screening, and Eligibility for specific details on eligibility and the ERF form.

4.4.3.1 Randomization Procedure Using the Data Management System

The Coordinator enters the data from the ERF into the DMS. As the ERF form is data entered, the DMS will validate all responses. If an edit fails, the DMS will provide an automatic query message and skip the entry to the end of the form, bypassing the randomization. If all edits pass, the form asks "Do you wish to randomize this child to a treatment group?" Entering a "Y' in this field automatically runs the randomization.

The eligibility/randomization program verifies the patient's eligibility status based on the entered responses. At this time you will the system will let you know that the randomization was successful. You will not be provided with a treatment assignment. A successful randomization will automatically send an email to the DCC notifying them of the randomization.

In the event that the randomization program aborts and does not run, you will receive an error message explaining the reason for the random information in the ERF. Make the necessary corrections to the ERF begin the randomization procedure again.

4.4.3.2 Randomization and/or Drug Dosing Procedure when the Data Management System is Not Functional

Since the randomization procedure requires entry through an internet connection, a backup procedure is necessary for cases in which the clinic's computer system is not functional, or the WEB is inaccessible or not operating appropriately.

As soon as it is realized that a randomization is anticipated and the DMS is nonfunctional, contact the DCC to arrange a remote randomization. Emergency randomization procedures will be done over the phone with the DCC.

The DCC will provide the randomization, drug dosing and bottle number distribution over the phone in this case:

- All necessary data collection forms must be completed on paper.
- The Eligibility and Randomization Form (ERF) must be completed to provide final assessment, verification, and review of randomization eligibility.
- The Physical Exam Form (PEF) must be completed to provide the weight measurement for dosing.
- The Medication Dispensing and Dosing Form (MDD) must be completed to provide information for drug distribution.
- The Study Coordinator (or other appropriately trained staff member) can call the DCC at 866-257-7242, normally staffed from 8AM – 5PM EST, Monday through Friday. Randomizations at other times must be arranged in advance.

- The DCC must receive faxed copies of completed ERF, PEF, and MDD data collection forms prior to the randomization call.
- The Study Coordinator should have the Medication Distribution Log (MDL) available during the call with the DCC (refer to Chapter 6).
- Participant baseline data collection can be ongoing while the process of emergency randomization and drug distribution is being completed.

First, the DCC will attempt to solve the computer problem, if it relates to the RIVUR DMS. If this fails, the Study Coordinator and the DCC will review the participant's eligibility forms over the phone, and obtain the participant's weight. The DCC will then randomize the participant and provide drug distribution information to the Study Coordinator. (**Note:** Since chances for error are increased by transmitting eligibility data over the phone, this system should only be used when absolutely necessary.)

As soon as the system at the clinical center becomes operational, entry of the ERF, PEF, and MDD must be completed in the DMS system BEFORE ANY FURTHER RANDOMIZATIONS CAN OCCUR, and the contact person providing the phone randomization must be notified that this has happened. It is essential to enter any remote randomizations into the RIVUR DMS in the order in which they were randomized by phone, before using it for any further randomizations.

4.5 Baseline Data Collection

Baseline data is collected in order to adequately describe the population in the trial. This includes demographic variables of gender, ethnicity and race, and includes socio-economic factors such as income and education. Some baseline data includes collecting known factors that may influence the outcome, such as concomitant medications being taken by participants, and medical history information.

Baseline data collection can be obtained in any order that is efficient at the clinical sites. Except for urine collection (required for final eligibility assessments) it is recommended that the blood and rectal swab specimens not be collected prior to randomization. Any baseline data collected prior to randomization will have to be repeated if the randomization is rescheduled.

4.5.1 Physical Exam (PEF)

The physical exam includes temperature, blood pressure, height and weight measures as well as a short abdominal exam, all reported on the Physical Exam Form (PEF). The weight measurement taken during the physical exam will be used to assess the amount of blood drawn for laboratory specimens and is used to determine the dosing and amount of study medication to be distributed. Data entry of the PEF is required before drug distribution.

Refer to the PEF QxQ for item-specific instructions regarding administration.

4.5.2 Baseline Data Collection Interviews

Much of the baseline data collection is done through interviewing the parent/guardian. Parent/Guardian interview forms include the Baseline Demographic Form (BDF), the Baseline Medical History Form (BMH) and the Concomitant Medication Form (CMF).

Section 13.9 of Chapter 13: Data Management and Administrative Procedures, includes techniques for conducting questionnaire interviews.

Refer to the QxQ documents for the BDF, BMH, and CMF for item specific instructions regarding administration.

4.5.2.1 Concomitant Medication Form (CMF)

Concomitant medications are often collected on patients involved in a clinical trial. This data is collected based on parent/guardian's report. Parents will be requested to bring in medication bottles of any medications their child is currently, or has taken since the last contact, or to record and bring in this information in the Participant Handbook/Diary.

Of particular interest are anti-microbial medications in addition to any other prescription medications for chronic conditions, or medications for constipation or over-active bladder. At baseline, only those medications currently being taken and the prophylactic antimicrobial the child had been taking following his/her VUR diagnosis will be recorded along with the start dates for the medication(s). In the case of the antimicrobial prophylaxis taken prior to randomization, the date the medication was completed will be the day of randomization. The RIVUR study medication does not need to be included on the CMF at any visit.

Concomitant medications are coded in order to summarize the data by a preferred term. Coding of concomitant medications is assigned into the DMS at the time of CMF data entry, using a drug dictionary (Master Drug Data Base v2 from Medi-Span) lookup table in the DMS. The CMF fo every RIVUR protocol-scheduled contact.

Refer to the CMF QxQ for more instructions on reporting concomitant medications including instructions on coding a stop date for continuing medications, and Chapter 14: DMS User's Guide for information on coding.

4.5.3 Self-Administered Forms

4.5.3.1 Life Impact Assessment Questionnaire (LIQ)

The Life Impact Assessment Questionnaire (LIQ) is a quality of life and resource utilization instrument that is a self-administered questionnaire for the parent/guardian to complete. This questionnaire can be administered with help, and must be used with an interpreter for families who do not speak English.

Refer to the LIQ QxQ for form specific instructions.

4.5.3.2 Dysfunctional Voiding Questionnaire (DVQ) and the DES Treatment Form (DTF)

The DVQ questionnaire derives from a standardized scale and is designed to evaluate voiding dysfunction and assess constipation. This is a self administered questionnaire for the parent/guardian to complete with their child, if their child is already toilet/potty trained. The questionnaire is intended to obtain information about the child and is worded for a child respondent. This questionnaire can be administered with help, and must be used with an interpreter for families who do not speak English.

After the DVQ has been completed by the family, the Coordinator should run the DMS report entitled DVQ Score Report. The report will yield the score of the dysfunctional voiding instrument. If the DVQ score for a girl is >6, or for a boy >9, the DES Treatment Form (DTF) should be collected on the participant. The DTF is designed to give information on DES treatments.

A child is considered toilet/potty trained when he or she is urinating and defecating in the toilet or potty by themselves during the day.

Refer to the DVQ QxQ for form specific instructions.

4.5.3.3 Challenges with Self Administered Questionnaires

In any survey, whether interview or self-administered, comprehension of the question is the first challenge. However, the task is different in a self administered survey. In a self-administered survey, respondents must first perceive the information before they can comprehend it. Once respondents perceive the information, they must comprehend the layout (the visual aspect) of the information as well as the wording (the verbal aspect). Furthermore, respondents must comprehend much more than just the wording of the survey questions and response categories.

In a self-administered survey, respondents are often given introductory material and instructions. They must comprehend the instructions or directions that are meant to guide them through the questionnaire. In an interviewer-administered questionnaire, the interviewer plays a critical role in this perceptual process. In contrast, the entire onus of perception is on the respondent in a self-administered format.

When respondents are asked to complete a self-administered questionnaire, they are being asked to perform a task that from their perspective may be different from the task we wish them to perform. From the respondent's perspective, the task may be similar to asking them to view a picture, in which they are free to start anywhere and to make their own decisions as to which parts of the picture to examine in what order.

However, from our perspective, this viewing method is detrimental, for it gives us very little control over the perceptual process. From our perspective, it would be best if respondents started at a specified place, read prescribed words (in order to comprehend the question or stimulus) in the order in which we intend, provide answers to each stimulus, and move sequentially through the questionnaire. In general, we do not want respondents to mark

answers without having fully read and understood the questions and accompanying instructions, nor do we want them to pick and choose which questions get answered and in which order.

Advantages of self-administered questionnaires include anonymity and privacy which may encourage more candid and honest responses, and lack of interviewer imposed biases. They are attractive in that they can be given to a respondent to complete while staff continues with other necessary tasks. However, disadvantages include no interviewer intervention available for probing or explanation, respondents may feel they cannot ask for clarification, and respondents are more likely to stop participating mid-way through a self administered questionnaire.

For these reasons it is important that the Coordinator remain accessible to the parent/guardian during the DVQ and LIQ completion. Instructions on how to appropriately fill out the form should be provided, asking that respondents start with the first question and work down through the form, completing all questions as best they can. Let the parent/guardian know that there is no right or wrong answer to these questions. It is acceptable to provide clarification on words or questions within these forms when necessary. However, parents/children should be encouraged to respond based on their personal experience and the way they think the answer best applies to them.

4.5.4 Laboratory Specimen Forms

4.5.4.1 Baseline Specimen Collection (SCF)

Refer to the detailed procedures on specimen collection, identification, processing, and shipping documented in Chapter 5: Specimen Collection. Specimen collection and shipping is documented on the Specimen Collection Form (SCF). The SCF QxQ provides specific item instructions.

Urine and rectal swab specimens must all be collected at the baseline visit on each participant. The urine collection should have occurred prior to randomization as part of the eligibility check verifying pyuria does not exist at the time of randomization. All other specimen collections should occur after eligibility is verified through entry of the ERF form and randomization. Blood collection, also a part of baseline collection, can be scheduled during the DMSA imaging if this occurs after the randomization visit. Section 5.5.3 in Chapter 5 Specimen Collection, describes the blood specimens to be collected, and the priority of collection.

4.5.4.2 Baseline Specimen Shipping Logs

Specimens shipped to central labs or repositories must also have shipping logs completed. These logs are mailed with the specimens, providing an inventory of the shipment. They are not data entered.

There are four specimen shipping logs:

- Biospecimen Repository Shipping Log (NIDDK-USL)
- Genetics Repository Shipping Log (NIDDK-BSL)

- Rectal Swab Specimen Shipping Log (RSL)
- Central Blood Lab Shipping Log (CSL)

4.5.5 Medication Dispensing and Dosing Form (MDD, MDL)

Study medication is dispensed at the end of the randomization and baseline clinic visit.

At the end of the baseline visit, the participant/guardian should be given the study medication bottles or the prescription to collect the bottles from the site's pharmacy.

Medication dosing and bottle identification for dispensing is done through data entry of the MDD form, using the participant's weight measured during the physical exam. This weight provides the dosing necessary for the participant. A DMS report will provide a prescription with dose, number of bottles to be dispensed, and the bottle numbers to be dispensed for the next 7 months until the next clinic visit. Section 4.4.3.2 addresses drug dosing when the DMS is non-functional.

Distribution of study medication should be recorded by the Coordinator on the participant's Medication Distribution Log (MDL). If a pharmacist dispenses the study medication, the pharmacist should record the date of distribution on the pharmacy's MDL (MDL-P).

Refer to Chapter 6: Study Medication for detailed instructions on study medication distribution procedures, and the MDD QxQ for form specific information.

4.5.6 Radiographic Images (VSF, VUS, DSF, DSS)

Results of the renal/bladder ultrasound and VCUG are required as part of the study eligibility criteria, and must be completed prior to randomization for eligibility criteria, and within 112 days after diagnosis of the index UTI. In addition, a Baseline DMSA scan is required for all participants. The Baseline DMSA must be completed within 2 weeks of randomization (before or after), and no more than 16 weeks (112 days) after diagnosis of the index UTI. Some participants may already have had the DMSA study completed at the time of randomization. If the Baseline DMSA has not already been performed at the time of randomization, the Coordinator should schedule one immediately, in order to adhere to the 8-week window.

Images of all three scans are required, as are the local reading reports, and information on sedation used during the VCUG or DMSA. Data collection forms VSF and DSF are required to document sedation use (or non-use) during the procedures. Data collection forms VUS and DSS are required to document the shipping of images to the study reference radiologists.

Refer to Chapter 3: Radiology Imaging for detailed study procedures, forms required, and shipping instructions to the reference radiologists. Baseline images should not be shipped prior to randomization, but should be shipped within a week of randomization, or within a week after having a scan performed.

Note: DMSA images collected during a participants' follow-up, and especially after a UTI, follow a different shipping schedule due to the time urgency of these images.

4.6 Participant Handbook/Diary

Each participant's parent/guardian is to be given a participant handbook/diary, and a RIVUR Participant Follow-up Schedule (a DMS report). The handbook provides a summary of procedures associated with each follow-up contact. The handbook also functions as a diary for recording any fever or illnesses, medical care visits, and changes in concomitant medications that need to be reported to the Coordinator at each follow-up contact. Other important information and instructions for the parents regarding their child's participation in the study is also documented in the handbook. The Coordinator should review the handbook with the parent/guardian and instruct them on the use of the diary.

4.7 Participant Contact Information (PCF)

The Participant Contact Form (PCF) provides vital contact information on each randomized participant, his or her parent/guardian, and a second backup contact person. The participant's primary physician is also recoded along with his or her contact information.

This form should be completed by study personnel with the parent/guardian present, providing the information. Contact information on previously obtained medical records may not be current. All sections for which the participant is willing and able to provide information should be completed. It is critical to obtain information for an additional 2nd "contact person", who will know the health status and/or location of the participant in the event that they are difficult to follow-up with.

This form is not data entered, and should be stored with other confidential materials to maintain the confidentiality of the study participants. If your clinic or hospital has a system in place that collects this information (including 2nd contact person), you will not need to complete this study form, however, you will need to be able to demonstrate that this information is readily available to you during a monitoring visit.

4.8 Scheduling follow-up Contacts

At each contact, the Coordinator should make a point of scheduling the next two study contacts. At the baseline visit, this would be telephone contacts at two and four months of follow-up since randomization. Contacts are expected within a 20 day window, 10 days on either end of the target date (target date is determined based on the number of months since randomization).

The DMS contains a RIVUR Participant Follow-up Schedule Report that lists all follow-up contact target dates, contact type (telephone or clinic visit), and the protocol allowed contact window. A copy of this report would have been first provided to the parent/guardian at the time of randomization, and the information may have been written into the patient handbook/diary.

RIVUR would rather have data outside the time period than no data at all, but it would be a waste of resources to schedule two contacts too close together. Scheduled contacts for randomized participants should be at least 30 days apart.

4.9 Local laboratory results (BSR, USR)

Reporting of local laboratory results will most likely occur after the participant's clinic visit when results are received in the RIVUR clinic.

Data from the local lab reports are to be transcribed/entered into the Blood Specimen Results Form (BSR) and the Urine Specimen Results form (USR).

Refer to the BSR and USR QxQ for form specific instructions.

4.9.1 Alert Notifications

If clinically significant findings are identified in the local laboratory reporting, Coordinators must promptly notify the participant's primary care provider. In addition, Coordinators must complete an Adverse Events Form (AEF) for the clinically significant findings.

Refer to Chapter 9: Participant Safety and Adverse Event Reporting for procedures related to laboratory alerts

Appendix 4.1 – Baseline Visit Checklist of Procedures and Forms

RIVUR
Randomized Intervention for Children with Vesicoureteral Reflux

Baseline Visit Checklist

Preparations		Associated Forms
Participant Contact Information (preliminary)		PCF
Urine culture and urinalysis results from index UTI		
Baseline Ultrasound report (performed within 16 weeks after diagnosis of index UTI)		
Baseline VCUG scan report (performed within 16 weeks after diagnosis of index UTI)		VSF
Medical records and reports from index UTI		
Task / Procedure		**Associated Forms**
Begin with…	Informed Consent	ICT
Items that must be performed in the specified order	1. Physical Exam	PEF
	2. Study Eligibility and Randomization	ERF
	3. Study Medication Assignment	MDD, MDL
Data to be collected at any time during the visit	Participant Contact Form	PCF (paper only)
	Baseline Demographic Form	BDF
	Baseline Medical History	BMH
	LIA Questionnaire	LIQ
	DV Questionnaire (if toilet-trained)	DVQ
	Concomitant Medications	CMF
Materials to be distributed to parent / participant	Medication, dosing cup and syringe	
	Participant Handbook/Diary	
	Copy of signed consent form	
Specimen Collection (see reverse)	Urine Collection (collected at randomization)	SCF, USR, BSR, RSL, NIDDK-USL, NIDDK-BSL
	Peri-rectal Swab Collection (collected at randomization)	
	Blood Collection (collected within 14 days of randomization)	
Baseline Imaging	Baseline DMSA scan (performed within 16 weeks after diagnosis of index UTI and within 2 weeks after date of randomization)	DSF, DSS
	Baseline VCUG and Ultrasound scans shipping	VUS

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Appendix 4.2 – Baseline Visit Specimen Collection Scheme

RIVUR
Randomized Intervention for Children with Vesicoureteral Reflux

BASELINE Specimen Collection Scheme

Urine Collection - Collect at Randomization

A. Dipstick

If leukocyte esterace Negative (-)
(Proceed with normal randomization)

B. Order local **microalbumin** & **creatinine** on collected urine

C. 4-10 ml in orange-top cup, unfrozen
⇨ Ship to **Biosample Repository**
(U label)

If leukocyte esterase Positive (trace to +++)*
Collect catheterized or clean-catch specimen & dip again for leukocyte esterase (LE)

If LE negative (-)
Proceed with normal randomization steps B & C to the left.

If LE positive (trace to +++)*
B. Order culture to determine if recurrent UTI
C. Tentatively reschedule randomization

* WBC count obtained on dipped urine trumps dipstick results (i.e. if LE positive on dip, but WBC is negative, then child is eligible)

Peri-rectal Swab - Collect at Randomization

⇨ Ship to **Central Lab in Pittsburgh, PA** (R label)
(If shipping delayed for more than 20 minutes, then refrigerate prior to shipping)

Blood Collection - Collect within 14 days of Randomization

1) 

0.5ml in purple EDTA tube for **CBC** ⇨ Send to **Local Lab** (no label)

2) 

1.5ml in yellow SS tube, aliquot serum

Priority 1: 0.5ml for **Cystatin C** and **Creatinine**
⇨ Batched & FROZEN at -70 , ship every 3 months to **Central Lab in Kansas City, MO** (C label)

Priority 2 (collect if enough in *this* SS tube): 0.1ml serum for **Electrolytes**
⇨ Send to **Local Lab** (no label)

3) 

For kids ≤ 20lb: collect ONE 3.0 ml ACD tube
For kids > 20lb: collect TWO 3.0 ml ACD tubes, $^{2}/_{3}$ full
⇨ Ship room temperature to **Genetics Repository** (B label)
If ACD tube(s) not collected at Baseline, then collect at a later clinic visit.

4) 

*Collect **ONLY** from kids >20lb*
4.0ml in yellow SS tube ⇨ ***Spin*** and Ship unfrozen (with frozen gel pack) to **Biosample Repository** (S label)

Central Lab in Pittsburgh: Karen.Barbadora@chp.edu
Central Lab in Kansas City: Nancy Wilson nwilson@cmh.edu
Genetics Repository: Dana Witt witt@biology.rutgers.edu
Biosample Repository: BIO-NIDDKRepository@thermofisher.com

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Appendix 4.3 – Antibiotic/Antimicrobial Code List

Antibiotic/Antimicrobial	Code
Amikacin	010
Amoxicillin	100
Amoxicillin-clavulanate	110
Ampicillin	120
Ampicillin/Sulbactam	011
Aztreonam	121
Cefadroxil	130
Cefazolin	141
Cefepime	131
Cefixime	170
Cefotaxime	140
Cefotetan	171
Cefoxitin	142
Ceftazidime	150
Ceftriaxone	160
Cefuroxime	180
Cefuroxime-Axetil	172
Centamicin	181
Cephalexin	190
Cephalothin	191
Ciprofloxacin	200
Clindamycin	201
Ertapenum	202
Erythromycin	203
ESBL/Beta Lactamase	204
Gemifloxacin	205
Gentamicin	210
Imipenem	212
Levofloxacin	213
Linezolid	211
Loracarbef	220
Meropenem	221
Nalidixic acid	230
Nitrofurantoin	240
Norfloxacin lz	244
Oxacillin	245
Ozacillin	241
Penicillin	242
Piperacillin	246
Piperacillin/Tazobactam	243
Rifampin	247
Sulfisoxazole	250
Tetracycline	251
Ticabcillin cla	252
Ticarcillin/ K Clavulanate	253
Tigecycline	254
TMP-SMZ	270
Tobramycin	255
Trimethoprim	260
Tripenem	271
Vancomycin	280
Other	500

Chapter 5: Specimen Collection

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Chapter 5: Specimen Collection

5.1 Overview

Urine and blood specimens are collected for local clinic laboratory analysis. Blood serum and peri-rectal swab specimens are collected for central laboratory analysis. Among those participants who appropriately consented for DNA extraction and storage of biological specimens, additional blood and urine is collected and stored in NIDDK repositories for future studies.

Table 5.1 provides a summary of specimen collection during the study. All specimens are collected at the baseline and end-of-study clinic visits. Blood is also collected for a local CBC at the follow-up clinic visits. For patients designated as treatment failure during the study, an additional interim rectal swab specimen will be requested for central analysis.

This chapter provides instructions on procedures for the collection, processing, shipping, and reporting of laboratory specimens. Study participants may have additional blood and urine studies as part of their routine and emergency clinical care. In the event that these data are reported at alert levels, they would need to be reported as part of adverse events or endpoint data collection, but are not normally considered part of the routine protocol specimen collection, and are not required to be collected and processed as described below.

Table 5.1 Summary of specimen collection

Type of Specimen	Baseline	6-mo Clinic Visit	12-mo Clinic Visit	18-mo Clinic Visit	End of StudyVisit	As Needed
Urine for local dipstick and local lab	X				X	
Urine for Biosample Repository	X				X	
Rectal Swab for Central Lab	X				X	X*
Blood for Local Lab**	X	X	X	X	X	
Blood for Central Lab	X				X	
Blood for Genetics Repository	X***					
Blood for Biosample Repository	X				X	

* Required if treatment-failure criteria have been met

** CBC and Electrolytes at baseline and end-of-study, CBC only at 6, 12, and 18 months.

*** If blood for genetics repository not collected at baseline, it may be collected during a later blood draw

5.2 Data Collection Forms

The required study data collection forms associated with specimen collection and shipping are listed and described below:

- Specimen Collection and Processing Form (SCF)
- Central Blood Lab Shipping Log (CSL)
- Rectal Swab Shipping Log (RSL)
- NIDDK Genetics Initiative Phlebotomy Mailing Form (NIDDK-BSL)
- NIDDK Biological Specimen Repository Mailing Form (NIKKD-USL)
- Blood Specimen Results Form (BSR)
- Urine Specimen Results Form (USR)
- Rectal Swab Specimen Results Form (RSR)*
- Central Blood Lab Form (CLR)*

* entered at central labs

5.2.1 Specimen Collection and Processing Form (SCF)

All specimen collection is documented onto the SCF. Through this form, the DCC tracks the collection date, collection time, volume, and type of specimens collected, as well as the date of shipment to the study central labs and repositories. Anticipated results are then closely monitored. Note: this form will need to be updated to record shipping dates for those specimens not shipped at the time of collection and initial recording of the SCF. Refer to SCF QxQ for item specific instructions. Note: If baseline blood collection is split between the Randomization visit and a Baseline DMSA visit, then update the SCF form to show the shipped date of the specimen(s) and note the additional collection date(s) in Item 4.

5.2.2 Central Lab Shipping Logs (CSL, RSL)

The Central Lab Serum Specimen Shipping Log (CSL) and the Rectal Swab Shipping Log (RSL) are shipping logs that accompany specimens being sent to the study central labs. They are not data entered.

5.2.3 NIDDK Genetics Initiative Phlebotomy Form (NIDDK-BSL)

This is the NIDDK Genetics Repository shipping log, which is to be completed at the time of blood specimen collection using ACD tubes for eventual DNA cell lines. It is included in the mailer box with the specimen being shipped to the Rutgers Cell and DNA repository. In addition, a shipment notification is to be made to the Repository on the day of shipping, either by email, fax, or through the Repository web portal (as instructed on this form). This form is not data entered.

5.2.4 NIDDK Biosample Repository Mailing Form (NIDDK-USL)

This is the NIDDK Biosample Repository shipping log to be sent with the urine specimen, and serum separator tube (if child >20 lbs) to Fisher Bio-repository. A shipment notification to the repository on the day the FedEx shipment is required by email or fax (see packing and shipping instructions listed on this form). This form is not data entered.

5.2.5 Blood Specimen Results Form (BSR)

This data collection form reports on the local lab CBC and electrolyte studies done at the baseline and the end-of study clinic contact. This form is data entered at the site upon receipt of results.

Any clinically significant findings in local laboratory results should be reported on an adverse event form.

5.2.6 Urine Specimen Results Form (USR)

This data collection form is used to report the urinalysis and urine culture results from baseline and end-of study data collection. In addition, coordinators will use this form to document findings during the study from medical records abstraction of urinalysis or urine culture results for potential study UTI endpoints data collection. This form is data entered at the site.

Any clinically significant findings in local laboratory results should be reported on an adverse event form.

5.2.7 Rectal Swab Specimen Results Form (RSR)

This form is completed and data entered at the Central Lab for rectal swab analysis.

5.2.8 Central Lab Blood Results Form (CLR)

This form is completed and data entered at the Central Blood Lab for cystatin-C, creatinine, and high sensitivity C-reactive protein results.

5.3 Specimen ID labels

The DCC will supply labels for all specimen tubes and containers, as well as shipping logs, for specimens that are shipped from the sites to the study central labs and repositories. Sites are responsible for appropriate labeling and tracking of specimens analyzed locally. Locally analyzed specimens must be identified at each site in such a way that the local lab report can be easily linked to the participant study ID number.

Prior to collection, place the appropriate specimen collection label onto the appropriate collection receptacle (tube or cup). All labels will contain the following information:

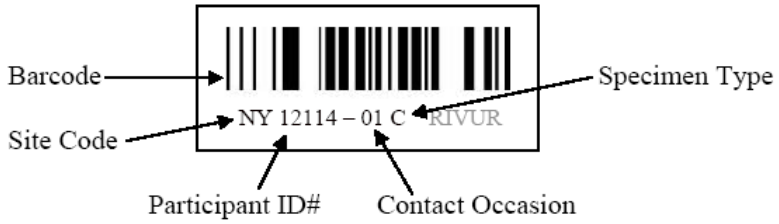
- Barcode
- Participant ID number

  Note: On the repository specimen labels, the participant ID number has been modified and begins with an NIDDK 3-field numeric site code, as shown in some of the example labels in Table 5.2 below. This replaces the usual 2-character RIVUR site code. The central labs use labels with the original RIVUR ID structure.
- Contact Occasion number

- Specimen type
  - U = Urine for biosample repository
  - R = Rectal swab
  - C = Serum for Central Blood Lab (cystatin C and creatinine)
  - B = Blood in ACD tube(s) for genetics repository
  - S = Blood in SS tube for biosample repository

  If no specimen type is indicated, this label is provided for use on shipping logs, or as an extra. If used to replace a label, please record the specimen type code using a permanent marker.

Diagram 5.1 Breakdown of a RIVUR Baseline specimen label



There are a maximum of 6 labels needed at the baseline (visit=01). If the participant weighs less than or equal to 20lbs, only 5 labels are needed at Baseline because Coordinators will collect only 1 ACD tube for the Genetics Repository (See Section 5.5.3. Blood Collection).

In addition, 4 extra labels have been included for each visit to use on shipping logs. These labels do not specify specimen type. If no specimen type is indicated, the label can be used as an extra or on paper shipping logs. If used in place of a specimen label, please record the specimen type code using a permanent marker.

It is critical that the correct labels are used on the specimens. To ensure appropriate labeling, coordinators and assisting personnel should become completely familiar with the codes being used.

Table 5.2 shows sample specimen labels. The actual label is NOT identical to the table, so care should be used when choosing the correct label for the correct specimen.

Table 5.2 Sample specimen labels for study clinic in Buffalo (RIVUR site code = NY, NIDDK site code = 616)

Baseline Labels

 616-12114-01 RIVUR (for repository shipping logs)	 616-12114-01 RIVUR (for repository shipping logs)	 616-12114-01 RIVUR (for repository extra)
 NY12114-01 RIVUR (for central lab shipping logs)	 NY12114-01 RIVUR (for central shipping logs)	 616-12114-01 RIVUR (for repository shipping logs)
 616-12114-01S RIVUR (Biosample Repository SS tube)	 NY12114-01C RIVUR (Central Lab serum)	 NY12114-01R RIVUR (Central Lab rectal swab)
 616-12114-01U RIVUR (Biosample Repository urine)	 616-12114-01B RIVUR (Genetics Repository blood #1)	 DE20103-_ RIVUR (Genetics repository blood #2)

End-of-Study Labels

 616-12114-13 RIVUR (for repository shipping logs)	 616-12114-13 RIVUR (for repository shipping logs)	 616-12114-13 RIVUR (for repository extra)
 NY12114-13 RIVUR (for central lab shipping logs)	 NY12114-13 RIVUR (for central shipping logs)	 616-12114-13 RIVUR (for repository shipping logs)
 616-12114-13S RIVUR (Biosample Repository SS tube)	 NY12114-13C RIVUR (Central Lab serum)	 NY12114-13R RIVUR (Central Lab rectal swab)
 616-12114-13U RIVUR (Biosample Repository urine)	 NY12114-_R RIVUR (Treatment Failure rectal swab)	 NY12114-_ RIVUR (for central shipping logs)

5.4 Specimen Storage at the Clinical Sites

The repository urine, rectal swab, and repository blood specimens will be shipped fresh (not frozen), but may require refrigeration for a couple of hours prior to actual shipping, or overnight for specimens collected on non-shipping days. Please note: gel packs must be frozen prior to shipping to ensure refrigeration during transit. Processing and shipping instructions for each specimen type are detailed in section 5.5 below.

Serum shipped to the Blood Central Laboratory for cystatin-C and creatinine analysis will be shipped frozen in batches every 3rd month. These specimens must be frozen in an ultra-low freezer prior to shipping, see section 5.4.1.

5.4.1 Ultra-Low Freezer

The serum for cystatin-C and creatinine analysis must be stored at - 70˚ C. Frozen specimens must be stored upright in an appropriate ultra-low freezer. Each site Coordinator must make arrangements at their clinical site for this storage. An "appropriate" ultra-low freezer is a freezer that is monitored daily for temperature changes and control, has electrical power, alarm battery, and has major adverse events documented.

Each Study Coordinator must develop and document a clearly defined backup plan in the event of prolonged power and/or temperature failure to ensure the stability of the stored samples. Arrangements must be made such that the Coordinator is notified when an alarm is activated and there is a problem with the freezer. A specific alternative ultra low freezer must be identified (location and area documented) in the event that the specimens must be removed. The conditions in which specimens will be moved, who will move them, and the procedure for transport should be included, contact persons and phone numbers should also be documented in this plan. This plan needs to be developed and in place before an incident occurs.

5.5 Specimen Collection

5.5.1 Urine Collection

Urine is collected for study analysis at the Baseline and End of Study Visits. Additionally, if at an interim protocol visit a child presents with fever and/or UTI symptoms, coordinators should collect urine to determine if a UTI is present. When a catheterized specimen is not indicated, urine should be collected in a sterile plastic or glass container. A clean-catch sample should be collected mid-stream, i.e. the initial small quantity of urine should be discarded and the remaining sample to be collected in the sterile container. For children who are not yet toilet trained, a bagged specimen can be obtained, if catheterization is not standard.

5.5.1.1 Urine for Local Lab

Urine is collected for immediate dipstick, and local laboratory microalbumin and creatinine. If pyuria is present at randomization then a local laboratory urine microscopy and culture is also required using a catheterized (cath-ed) urine specimen. In addition, 4-10ml of the collected urine specimen should be reserved for the Biosample repository

Urine specimens for local analysis should be delivered to the site's local laboratory within 1 hour of collection, or kept in a bag containing ice cubes or refrigerated until delivered. Urine remaining after local analysis should be transferred to the urine container provided by the Biosample repository. If a cath-ed specimen was obtained, Coordinator should use cath-ed urine for Biosample repository specimen. Once repository container is filled according to the laboratory procedure, tighten the cap on the container and store refrigerated until the shipper is ready to go.

5.5.1.2 Urine for Biosample Repository

Urine for Biosample Repository is collected at the Baseline and End-of-Study visits. The urine samples for the National Institutes of Health Biosample Repository at Fisher BioServices should be kept unfrozen, in the container provided by the Biospecimen Repository. The Repository expects a urine sample to be 4 mL if collected by the coordinator, but should be 10 mL if specimen is provided by the participant. The Repository's absolute minimum volume to be shipped is 1 mL. Any amount less than 1 mL will not be kept by the Repository. If shipping more than an hour after collections, sample should be refrigerated until time of shipping.

The Biosample repository will provide collection and shipping kits including the urine collection container, an SS tube for repository serum collection (see section 5.5.3.4), packing and shipping materials, and pre-printed Federal Express labels for shipping of the samples. The collection container should be labeled with the participant ID label provided by the DCC, bar-coded and indicating specimen type 'U'. The Biosample repository sample collection kits will be shipped directly to each participating clinical site. To order more collection kits or shipping supplies, send an email to: BIO-NIDDKRepository@thermofisher.com.

Full processing and shipping instructions for the Repository are provided in the document 'Instructions for Shipping Urine and Blood for the NIDDK BioSample Repository' (NIDDK-USL), see Appendix 5.2. This form is completed for both urine and blood shipments to the Biosample Repository. It also functions as the shipping log, and must be completed and included in the shipped package. Coordinators should keep a copy of all shipping forms on site. Data recorded on this form is not data entered into the DMS.

Shipments are to be made Monday through Thursday only, and should not be shipped on Fridays. Specimens collected on Friday will have to be refrigerated over the weekend and shipped on Monday.

Send a shipment notification to the repository via email at BIO-NIDDKRepository@thermofisher.com or fax (301-515-4049) on the day the package is picked up by FedEx. Include the 12-digit FedEx tracking number in the notification. Contact the NIDDK Repository via email or call Heather Higgins (240-793-0353) or Sandra Ke (240-686-4702) regarding questions about packaging and shipping.

5.5.2 Rectal Swab Specimen

A rectal swab specimen to determine antimicrobial resistance (TMP/SMZ-resistant E coli, and other organisms) is to be collected on all participants at both baseline and at the end-of-

study clinic visit. In addition, a rectal swab specimen is to be collected on all participants who meet treatment failure criteria. In this event, sites will be notified by the DCC.

The preferred rectal swab collection modes are listed here in order from most preferred to least preferred, but still acceptable: 1. stool on the rectal swab taken from a recent stool sample, 2. rectal swab, and 3. peri-rectal swab. If stool is available in the diaper, it should be smeared on the swab. A rectal swab is the next preferred specimen, but if the parents decline, then it would be appropriate to collect a peri-rectal swab. We want to make the parents comfortable and willing to enroll their children into our study. Study staff should use a dry swab to collect the sample. Note: The goal is to collect a little "brown" on the swab. Please verify that there is stool on the swab.

The Sites are responsible for ordering collection kits and shipping materials for the rectal swab specimens.

5.5.2.1 Equipment needed for peri-rectal swabs

- Amies without charcoal, Fisher Scientific, item No 220116, https://www1.fishersci.com/Coupon?gid=180558&cid=1340
- Participant specimen label provided by the DCC for specimen type 'R'
- Specimen Packaging, see Appendix 5.1 Pointers on Shipping Clinical Specimens
- Ziploc bag or biohazard bag
- Cold paks
- Paper towels
- Shipping box/envelope
- Specimen Shipping Log

5.5.2.2 Procedures for Rectal Swab Collection and Shipping

1. Stool culture for E. coli will be obtained using a sterile, leak-proof Amies without Charcoal swab for rectal specimens.
2. A stool sample from a soiled diaper will be obtained as the specimen of choice. The next choice for specimen collection is the rectal swab. If parent or guardian is unwilling to allow rectal swabs, a peri-rectal swab may be obtained by swabbing the area around the anus, but not beyond the anus. Study staff should use a dry swab for sample collection.
3. Place the swab into the Amies transport tube so that the tip is immersed in the media.
4. Place label provided by the DCC (specimen type 'R'), on the swab transport tube.

5. The tube is placed in a biohazard bag or Ziploc bag for transport within two hours of collection, or refrigerate prior to shipment. **The swab can be kept at room temperature for up to 20 minutes, and then must be refrigerated.**

6. For stool swabs, if more than a 2 hour delay in transporting the specimen is expected, the specimen must be kept on an Amies without Charcoal culture swab at 4˚ C (~40˚ F – normal refrigerator temperature) until overnight shipment the following day. Cultures obtained on Friday or Saturday should be refrigerated and shipped on Monday morning.

7. Specimens should be transported to the Central Laboratory as soon as possible by overnight carrier. Consult with your institution's safety officer about the shipping classification they would advise you to use. RIVUR's Rectal Swab Central Lab recommends using UN3373 Biological Substance Category PI 650 Packing Instructions. Basic packing instructions include:

   a. primary receptacle (swab)

   b. secondary packaging with cold packs (zip lock bag) – primary receptacle packed in the secondary packaging in such a way that under normal transportation, they will not be crushed, broken or punctured

   c. rigid outer packaging (Exact-pak)-container must hold secondary packaging with suitable cushioning material so that if any leakage occurs the integrity of the outer packaging will not be compromised

8. The Exact-pak is placed in the shipping package and shipped overnight to Central Laboratory. Include the RIVUR Rectal Swab Shipping Log (RSL). Keep a copy of the RSL on site. A biohazard label is not required for semisolid materials unless there is evidence that the specimens contain an infectious agent.

9. Cultures can be shipped Monday through Thursday. Do not ship on Fridays. Specimens collected on Fridays must be refrigerated over the weekend and shipped on Monday.

   The cultures will be sent overnight to:

   The Children's Hospital of Pittsburgh c/o Karen Barbadora
   Rangos Research Center of UPMC
   ID Research Lab 9th Floor Bay 10A
   4401 Penn Avenue
   Pittsburgh PA. 15224.

10. Send a shipment notification email to Karen Barbadora (Karen.Barbadora@chp.edu)

11. Questions regarding this policy should be referred to Karen Barbadora: call 412-692-9390 or page 412-456-1582.

5.5.3 Blood Collection

The blood collection protocol for RIVUR is dependent on each child's weight. The participant's weight determines the volume of blood that can be drawn. Diagram 5.2 shows the distribution of blood collected among the local lab, central lab, and repositories at the baseline visit. Diagram 5.3 shows the End-of Study collection scheme. The collection scheme for End-of Study differs only in that no blood is collected for the Genetics Repository.

The priority for blood collection is as follows:

1. CBC (local analysis)
2. Blood serum for cystatin C and creatinine (central analysis)
3. Blood for the Genetic Repository
4. Blood for the Biosample Repository
5. Blood serum for electrolytes (local analysis)

Coordinators should meet and work with their local labs to discuss the blood collection protocol for RIVUR. Volumes approved for the study are very small and need to be drawn, distributed, and used very carefully. The labs will first insist they need more blood, however, these are the volumes that have been identified as workable by laboratory consultants on the study.

Diagram 5.2 Blood Collection Scheme for BASELINE VISIT

RIVUR
Randomized Intervention for Children with Vesicoureteral Reflux

BASELINE Specimen Collection Scheme

Urine Collection - Collect at Randomization

A. Dipstick

If leukocyte esterase Negative (-)
(Proceed with normal randomization)

B. Order local **microalbumin** & **creatinine** on collected urine using the volume required by local lab

C. 1-10 ml in orange-top cup, unfrozen
⇨ Ship to **Biosample Repository**

If leukocyte esterase Positive (trace to +++)*
Collect catheterized or clean-catch specimen & dip again for leukocyte esterase (LE)

If LE negative (-)
Proceed with normal randomization steps B & C to the left.

If LE positive (trace to +++)*
B. Order culture to determine if recurrent UTI
C. Tentatively reschedule randomization

* WBC count obtained on dipped urine trumps dipstick results (i.e. if LE positive on dip, but WBC is negative, then child is eligible)

Peri-rectal Swab - Collect at Randomization

⇨ Ship to **Central Lab in Pittsburgh, PA** (R label)
(If shipping delayed for more than 20 minutes, then refrigerate prior to shipping)

Blood Collection - Collect within 14 days of Randomization

1) 
0.5ml in purple EDTA tube for **CBC** ⇨ Send to **Local Lab** (no label)

2) 
1.5ml in yellow SS tube, aliquot serum


Priority 1: 0.5ml for **Cystatin C** and **Creatinine**
⇨ Batched & FROZEN at -70 , ship every 3 months to **Central Lab in Rochester, NY** (C label)


Priority 2 (collect if enough in *this* SS tube): 0.1ml serum for **Electrolytes**
⇨ Send to **Local Lab** (no label)

3) 
For kids ≤ 20lb: collect ONE 3.0 ml ACD tube
For kids > 20lb: collect TWO 3.0 ml ACD tubes, $^{2}/_{3}$ full
⇨ Ship room temperature to **Genetics Repository** (B label)
If ACD tube(s) not collected at Baseline, then collect at a later clinic visit.

4) 
*Collect **ONLY** from kids >20lb*
4.0ml in yellow SS tube ⇨ ***Spin*** and Ship unfrozen (with frozen gel pack) to **Biosample Repository** (S label)

Central Lab in Pittsburgh: Karen.Barbadora@chp.edu
Central Lab in Rochester: gfr@urmc.rochester.edu
Genetics Repository: Dana Witt witt@biology.rutgers.edu
Biosample Repository: BIO-NIDDKRepository@thermofisher.com
01/11/10

Diagram 5.3 Blood Collection Scheme for END-OF-STUDY Visit

RMuR Randomized Intervention for Children with Vesicoureteral Reflux

END OF STUDY Specimen Collection Scheme

Urine Collection - Collect at END OF STUDY visit

A. **Dipstick** to screen for leukocyte esterase
If trace or positive, send urine for culture.

B. Order local **microalbumin** & **creatinine** on collected urine using the volume required by local lab

C. Send collected urine (1-10 ml) in orange-top cup, unfrozen
⇨ Ship to **Biosample Repository** (U label)

Peri-rectal Swab* - Collect at END OF STUDY visit

⇨ Ship to **Central Lab in Pittsburgh, PA** (R label)
(If shipping delayed for more than 20 minutes, then refrigerate prior to shipping)

*** If off study medication for > 6 months, then swab is not required, however it is required for Treatment Failures**

Blood Collection - Collect at END OF STUDY visit

1) 

0.5ml in purple EDTA tube for **CBC**† ⇨ Send to **Local Lab** (no pre-printed label)

† **If Treatment Failure or off study medication for > 6 months, then CBC is not required**

2) 

1.5ml in yellow SS tube, aliquot serum

Priority 1: 0.5ml for **Cystatin C, Creatinine and C Reactive Protein**
⇨ Batched & FROZEN at -70° C, ship every 3 months to
Central Blood Lab in Rochester, NY (C label)

Priority 2 (collect if enough in *this* SS tube): 0.1ml serum for **Electrolytes**
⇨ Send to **Local Lab** (no pre-printed label)

3) 

Collect ONLY from kids >20lb
4.0ml in yellow SS tube ⇨ ***Spin*** and Ship unfrozen (with frozen gel pack) to
Biosample Repository (S label)

NOTE: If ACD tube(s) for Genetics Repository not previously collected, then collect at exit visit.

Central Swab Lab in Pittsburgh: Karen.Barbadora@chp.edu
Central Blood Lab in Rochester: paula_maier@urmc.rochester.edu
Genetics Repository: Dana Witt witt@biology.rutgers.edu
Biosample Repository: BIO-NIDDKRepository@thermofisher.com
10/12/11

5.5.3.1 Local Laboratory Blood

Blood is to be drawn for local CBC and electrolytes analysis at baseline and end-of-study, then for CBC only at each follow-up clinic visit. If the participant has discontinued RIVUR medication and has not taken any doses since the previous CBC, the CBC will not be

collected. RIVUR medication discontinuation may be either physician-directed as a result of a change in prescribed medical care, an adverse event, or treatment failure, or a decision made by the parents or caregivers to not administer study medication to the child.

Volumes are specified to assure enough blood is drawn to allocate to the central labs and repositories, within the total protocol specified allowance. The baseline and end-of study collection includes 0.5mL of blood in an EDTA tube for the CBC, and 1.5 mL collected in a serum separator tube, of which 0.1mL is analyzed locally for the electrolyte study and remaining 0.5 mL is shipped to the Central Blood Laboratory (Section 5.5.3.2). Note that not all electrolytes in a standard panel are included as study data, this might help to negotiate blood volumes (refer to the Blood Specimen Results Form, BSR). However it also might be cheaper to order the full panel, or preferred for clinical care, even though not all analytes are reported to the study.

At interim follow-up visits, only a blood draw for the local CBC is required.

Local specimens must be identified at each site in such as way that the local lab report can be easily linked to the participant study ID number. The DCC does not provide labels for specimens analyzed locally.

5.5.3.2 Central Blood Laboratory

The Central Blood Laboratory performs cystatin-C, serum creatinine, and high sensitivity C-reactive protein (hs-CRP) studies on the frozen 0.5mL serum collected at baseline and end-of-study.

5.5.3.2.1 Equipment Needed

Participating sites are responsible for all collection and shipping supplies:

- 0.5mL Nalgene Cryogenic Vials, catalog number 5000-1012 from Nalge Nunc International 1-800-625-4327 (tubes will hold 1cc and are freezable).
- Participant specimen label provided by the DCC, specimen type ‘C’
- Biohazard packaging, see Appendix 5.1 Pointers on Shipping Clinical Specimens
- Specimen tube box or biohazard bag
- Styrofoam cooler for shipping
- Cardboard shipping box
- Dry ice for shipping
- Specimen Shipping Log

5.5.3.2.2 Instructions for central lab specimen collection and shipping

Collection:

1. 0.5 mL of serum aliquot is needed, taken from a centrifuged serum separator tube. Serum should be clear. Slight to moderate hemolysis is acceptable but lipemia is NOT; lipemia interferes with the analysis. Milky-white, lipemic serum should be clarified by high speed (3000 rpm) centrifugation capable of separating lipid from the serum.
2. The serum should be transferred to a dry Nalgene cryovial or another tube which can withstand - 70˚ and labeled with the 'C' label..
3. The tube should be frozen at - 70˚ C. If there is to be delay in freezing at - 70˚ C, place in ice and keep refrigerated until the specimen can be frozen at -70˚ C.

Shipping:

1. Remove specimens from the -70˚ C freezer. Do not let the samples thaw. Frozen serum may be batched and shipped to the central blood lab (CBL) in batches of no more than 20 tubes.

2. Please include a detailed and accurate manifest with the shipment using the Central Lab Specimen Shipping Log (CSLB). Double check the ID# and verify that the ID# on the cryovials matches that on the shipment manifest(s).

3. Place the specimens in an appropriate shipping bag or box.

4. Fill the shipping container about half full of dry ice. Reminder: dry ice is very cold and should be handled with insulated gloves.

5. Place the bags or boxes containing the specimens on the dry ice.

6. Fill the remaining space of the container with dry ice. Do not tape the Styrofoam shipper closed, as this can cause pressure to build up inside the shipper.

7. Place the shipment manifest(s) on top of the closed Styrofoam shipper.

8. The outer container must have the "A 2" x 2" marking or label with UN3373 in the middle of the label. It is oriented in a diamond shape *adjacent to* the Proper Shipping Name label.

   Also, write your name and address in the "diamond" shaped label as the "Shipper's Name and Address" and fill in the "Consignee Name and Address" with:

   Paula Maier
   University of Rochester Medical Center
   601 Elmwood Avenue, Box 777
   Rochester, NY 14642

Phone: (585) 275-2434

9. Place the shippers air bill on the outer shipping box and schedule the pick-up according to the shipper's specifications.

*Shipments to the CBL should be shipped on a Monday – Thursday (NO FRIDAY SHIPMENTS, please). Notify the lab via email (*paula_maier@urmc.rochester.edu) *including information on the number of boxes in the shipment, the tracking number of the shipment, and your RIVUR site code.*

5.5.3.3 Blood for Genetics Repository

Blood is collected at Baseline for DNA analysis (through cell line immortalization), and will be stored at the National Institutes of Health Genetics Initiative at the Rutgers University Cell and DNA Repository. If a sample for the Genetics Repository cannot be obtained at the baseline visit, it may be collected at a later clinic visit.

The repository will provide sample collection kits including the necessary ACD blood collection tubes, packing and shipping materials, and Federal Express labels for collection and shipping of the samples. Collection tubes should be labeled using the participant ID label provided by the DCC, bar-coded and noting specimen type 'B'.

Each collection kit should contain two 3 mL ACD tubes. One full tube should be collected on participants ≤ 20 lbs. Two tubes filled $^{2}/_{3}$ full should be collected from participants > 20 lbs (providing a total of 4 mL since ACD tubes do not come in 4mL sizes).

Shipping instructions for the Repository are provided in the document 'NIDDK Genetics Initiative Phlebotomy Form – RIVUR Study', study form code NIDDK-BSL. The NIDDK-BSL will also function as the shipping log, and must be completed and included in the shipped package. This form is not date entered into the study DMS.

The sample ID requested is the specimen ID from the specimen label, the alternate ID# is this same ID number.

Once collected, be sure to invert the tube gently 6 times to mix blood with additives and keep them at room temperature.

A shipment notification to the Genetics Repository on the day the FedEx shipment is required by email or fax. For complete instructions on packing and shipping samples to the Genetics Repository, please review the documents located behind the "NIDDK-BSL" tab in your MOP. Shipments are to be made Monday through Friday; the lab will receive specimens on Saturday.

The Repository must be notified when blood is shipped with the tracking number and specimen ID number. This can be done through the Web Portal at

http://rucdr.rutgers.edu/shippingblood, by fax (1-732-445-1149), by phone (1-732-445-1498) or email witt@biology.rutgers.edu and peralta@biology.rutgers.edu. If Friday shipment, please indicate Saturday delivery.

5.5.3.4 Blood for Biosample Repository

Participants weighing more than 20 lbs, will also have 4mL blood collected for serum long-term storage at baseline and end-of-study. This blood is collected in a serum separator tube and shipped along with the urine specimen to the NIDDK Biosample Repository.

A 4mL serum separator (SS) tube will be included in the collection and shipping kit that Coordinator will receive from the Biosample Repository (also contains the urine specimen container mentioned in section 5.5.12). The SS tube should be labeled with the participant ID label provided by the DCC, bar-coded and indicating specimen type 'S'.

Each tube needs to be processed immediately following collection. The tube should be inverted 5 times to mix the clot activator with the blood. The blood should be allowed to clot vertically for 30 minutes, and then centrifuged at full speed for 10 minutes in swinghead units, or 15 minutes in fixed angle units. See Appendix 5.4 'How to Prepare a Quality Sample using vacutainer SST tubes'.

Packaging and shipping instructions for the Biosample Repository are provided in the document 'Instructions for Shipping Urine and Blood to the NIDDK Biosample Repository', study form code NIDDK-USL. The NIDDK-USL will also function as the shipping log, and must be completed and included in the shipped package. Coordinators should keep a copy of all shipping forms on site. Data recorded on this form is not data entered into the DMS.

Shipments are to be made Monday through Thursday only – do not ship on Fridays. Specimens collected on Friday will have to be refrigerated over the weekend and shipped on Monday.

Send a shipment notification to the repository via email at BIO-NIDDKRepository@thermofisher.com or fax (301-515-4049) on the day the package is picked up by FedEx. Include the 12-digit FedEx tracking number in the notification. Contact the NIDDK Repository via email or call Heather Higgins (240-793-0353) or Sandra Ke (240-686-4702) regarding questions about packaging and shipping.

5.5.3.5 Specimens for Quality Control

During the follow-up period of the study, sites will be asked and instructed on how to collect 'blind replicate' tubes/specimens for lab quality control monitoring. Such samples will be collected using the same collection and processing methods, but labeled with an alternate ID number (not the regular participant ID number). These replicates will be tested for quality control to check the precision of methods used by a laboratory analyzing blood, urine, and rectal swabs. No additional blood will be drawn on any one person, keeping the total volume collected within the limits specified in the protocol. Chapter 11, section 11.6.3 describes RIVUR's external laboratory QC procedures.

Appendix 5.1 - Packing and Shipping Instructions for NIDDK Genetics Repository, doubles as shipping log for genetics samples

NIDDK GENETICS INITIATIVE
PHLEBOTOMY FORM – RIVUR STUDY

SHIP AT ROOM TEMPERATURE IN SAFETY MAILER
ENCLOSE A COPY OF THIS FORM WITH BLOOD KIT

FOR RU LAB USE ONLY:

TO: DR. DOUGLAS FUJIMAN/GENETICS
RUTGERS UNIV./CELL & DNA REPOSITORY
DIV. LIFE SCIENCES – NELSON LABS
604 ALLISON ROAD (RM. C120A)
PISCATAWAY, NJ 08854-8082

FAX: (732) 445-1149
PHONE: (732) 445-1498

WEB FORM:
http://rucdr.rutgers.edu/shippingblood

INITIAL:

PURPLE M.: _____

ID#: _____

FROM (NIDDK-RIVUR SITE):

SHIPMENT TO INCLUDE BLOOD SAMPLES FOR DNA/PLASMA

PURPLE TOP TUBES: ____
FOR WB DNA/PLASMA

NIDDK STAFF: PLACE TUBE LABEL HERE OR COMPLETE BY HAND
(VERIFY INFO AGAINST INFO ON BLOOD TUBES!!!)

SEX: M___ F___ AGE: _____

SAMPLE ID#: _____

ALTERNATE ID#: _____

TO BE COMPLETED AT COLLECTION SITE (BE SURE TO KEEP A COPY FOR YOUR FILES FOR DATA ENTRY):

DATE BLOOD DRAWN: ___ - ___ - ___ (MONTH – DAY – YEAR)

TIME DRAWN: _____ (24 HOURS)

FORM COMPLETED BY: _____

CONTACT THE RUTGERS CELL & DNA REPOSITORY TO CONVEY PACKAGE TRACKING NO./DATE OF SHIPMENT (SEE BELOW). IF BLOOD IS SHIPPED ON A FRIDAY FOR SATURDAY DELIVERY, CHECK FEDEX FORM FOR SATURDAY DELIVERY.

EMAILED/FAXED/
CALLED IN BY*: _____ ___/___/___ _____
(SEE RUTGERS FAX/PHONE AS ABOVE) DATE TIME

PACKAGE TRACKING #: _____ (CHECK SATURDAY DELIVERY ON DELIVERY FORM IF APPLICABLE)

TO BE COMPLETED BY RUTGERS UNIVERSITY CELL & DNA REPOSITORY
PRIOR NOTIFICATION REC'D: YES ____ NO ____ - IF YES, DATE/TIME ___/___/___ _____ AM/PM
CONFIRMATION OF RECEIPT OF BLOOD SAMPLE TO NIDDK SITE SENT BY: _____ DATE/TIME ___/___/___

Revised AUG 2006

RIVUR STUDY
FLOW SHEET FOR BLOOD SAMPLE COLLECTION
Yellow TOP TUBE FOR NIDDK GENETICS INITIATIVE at RUTGERS UNIVERSITY

1) Complete and attach I.D. labels to the tubes. **DO NOT write the patient's name or any other personal identification information (e.g. SS#, DOB) on the tubes.**

2) Collect blood specimen in the 1 yellow top tube with ACD. **Be sure to invert the tube gently 6 times to mix blood with additives and keep them at room temperature.**

3) Double check NIDDK RIVUR ID #, verify that ID information on tube matches that on the enclosed NIDDK-RIVUR Phlebotomy Collection Form.

4) Date and sign the NIDDK-RIVUR Phlebotomy Collection Form in the TO BE COMPLETED BY PHLEBOTOMIST section.

5) Package the blood tube in the safety mailer following the enclosed instructions. Be sure to seal the Styrofoam container with the red tape (water resistant).

6) Place the collection form (NIDDK-RIVUR Phlebotomy Collection Form) in the mailer box outside of the plastic bag. Tape cardboard box closed when assembly is complete.

7) Use the enclosed Fed Ex shipping label to ship the sample to the Rutgers University Cell Repository. Be sure shipping label is marked for priority overnight delivery.

8) For routine shipments be sure the outside of the box is labeled "Diagnostic Specimen Packed in Compliance with IATA Packing Instruction 650."

9) **Call Federal Express, 1-800-GO-FEDEX (1-800-463-3339)**, and a courier will be dispatched to pick up the samples. **Be sure to give Fed Ex the Zip Code of the PICKUP address, not that of the destination.**

10) **Notify the Rutgers University Cell and DNA Repository** that blood is being shipped and provide the Federal Express tracking number(s) _____ and NIDDK-RIVUR ID #(s) _____. This can be done through the Web Portal at http://rucdr.rutgers.edu/shippingblood), by fax (1-732-445-1149),by phone (1-732-445-1498), or email witt@biology.rutgers.edu and peralta@biology.rutgers.edu

ThermoSafe®
DiagnosticShipper

Assembly Instructions for ThermoSafe® Diagnostic Shipper
Model 472 Transport Package for Diagnostic Specimens
(in Conformance with Title 49 CFR, Part 173.199 and IATA Packing Instruction 650)

Read all instructions thoroughly before starting assembly

Required Components*:

- 1 – 6 Vacutainer® brand 10 ml specimen tubes with red rubber stoppers (Becton Dickinson No. 6580) or equal
- Scotch® brand ¾-inch wide reinforced packing tape (3M No. 896 34) or equivalent (not supplied)
- One expanded polystyrene foam mailer (body and lid)
- One 4½-inch x 9-inch section of absorbent material
- Two 18-inch lengths of waterproof tape
- One press-lock plastic bag
- One corrugated mailing carton with locking tabs
- Two-inch wide package sealing tape (not supplied)

Assembly Procedure:

1. Cut two 5-inch long strips of ¾-inch wide reinforced packing tape (not supplied) to secure the rubber stopper of each filled specimen tube. Use the first strip of tape over the top of the rubber stopper and down along opposite sides of the tube. Use the second strip of tape to wrap around the specimen tube and also cover the cut ends of the first strip of tape (Fig. 1).
2. Place specimen tubes into the body of the foam mailer and cover the tubes with the absorbent material (Fig 2).
3. Place the lid of the foam mailer over the body and absorbent material (Fig. 2); and press the lid firmly until all sides of the lid meet the sides of the body.
4. Cut two 18-inch long strips of red, waterproof tape. Peel the white backing from the tape, and seal the foam mailer by completely covering the joint between the lid and the body (Fig. 3). The ends of the tape should overlap about an inch.
5. Place the sealed foam mailer into the press-lock bag, but do not seal the bag yet.
6. Slide the foam mailer and press lock bag into the corrugated mailing carton (Fig. 4). Use the space under the foam mailer to include the required itemized list of the mailer's contents.
7. Seal the press-lock bag, close the corrugated carton using the locking tabs, and use package sealing tape (not supplied) over the locking tabs.
8. The package must identify its contents as "Diagnostic Specimens" in type at least ½-inch high. It also must display the diagnostic specimen marking: "UN3373" in type at least ½-inch high inside a diamond measuring at least 2 inches by 2 inches whose line is at least 2 mm thick.

Fig. #1 **Fig. #2** **Fig. #3** **Fig. #4**

* Certification that this product meets United States and International Regulations governing the transport of diagnostic specimens is contingent on proper use of all "Required Components" as described in these instructions. Substitution or omission of supplied and required components, except as described here, is not permitted. Substitution of the supplied specimen tubes (primary receptacles) is permitted only when replacement primary receptacles have been shown to meet the requirements of Title 49 CFR, Section 173.199 and all applicable sections of the IATA Dangerous Goods Regulations, including but not limited to Packing Instruction 650; 5.0.2.9; 6.1.1; and 6.3.1.2.

SCA Packaging NA
ThermoSafe Brands
3930 Ventura Drive, Suite 450
Arlington Heights, IL 60004
www.thermosafe.com
800 323 7442 ◆ Fax 847-398-0883
LIT127-04/06

SCA

Appendix 5.2 – Packing and Shipping Instructions for NIDDK BioSample Repository, doubles as shipping log for repository urine and serum samples

Instructions For Shipping RIVUR Urine and Blood to the NIDDK BioSample Repository

Sample ID: _____ - _____

Urine collection date: _____/_____/_____ (mm/dd/yyyy)

Blood collection date: _____/_____/_____ (mm/dd/yyyy)

This package contains 10 ml of human urine and 4 ml of human blood (or less) for diagnostic purposes.

---

1. Freeze the gel pack included in the shipping kit prior to sample collection.
2. Enter the sample ID and date of collection for the urine and blood on the top of this form, on the urine cup and on the Vacutainer label. The sample ID is the participating site's three-digit NIDDK site ID, followed by the seven-digit participant ID. Please do not write any personal information on this form, the specimen containers, or anywhere on the box (e.g., patient name, SSN, address, phone number, etc.).
3. Collect the urine in the specimen cup and screw the lid on the cup. Verify that the lid is secured tightly, and wipe any urine off the outside of the container.
4. Place the urine cup and the white absorbent strip into the zip-lock bag. Seal the bag.
5. Insert the Vacutainer into the bubble wrap pouch. Place the pouch and the white absorbent strip into the zip-lock bag. Seal the bag.
6. Place the frozen ice pack in the bottom of the foam cooler.
7. Place the zip-lock bags containing the urine and blood on top of the ice pack. Make sure the urine container is in an upright position. Place bubble wrap around the urine to hold it in place.
8. Place the lid on the foam cooler. Fold and place this document on top of the foam lid (but under the cardboard box flaps). Close and seal the box with packing tape.
9. Affix the "UN 3373 Biological Substance Category B" label to the top of the box in the upper right corner. Affix the repository address label to the top of the box in the upper left corner.
10. Use the pre-printed FedEx air bill to ship specimens to the NIDDK Repository:
    a. Section 1, From: Fill in your name, return address, phone number and the date. Leave "Sender's FedEx Account Number" blank.
    b. Section 5, Packaging: Place a check mark in the "Other" box.
    c. Section 6, Special Handling: Place a check mark in the "No" box, indicating no dangerous goods are in the shipment.
    d. Section 7, Payment: Enter "1" under "Total Packages" and the total weight of the package.
    e. Follow the peel-and-stick instructions on the back of the air bill. As shown, affix the air bill to the side of the box.
11. Call Federal Express, 1-800-GO-FEDEX (1-800-463-3339). Give them the account number (in Section 7, Payment) on the preprinted FedEx air bill and your pickup address. FedEx will dispatch a courier to pick up the package. Please schedule shipments Monday through Thursday. **The repository is closed on weekends, so do not ship specimens on Fridays.** Specimens may be refrigerated and shipped on the following Monday.
12. Send a shipment notification to the repository via email at BIO-NIDDKRepository@thermofisher.com or fax (301-515-4049) on the day the package is picked up by FedEx. Include the 12-digit FedEx tracking number in the notification.
13. Contact the NIDDK Repository via email or call Heather Higgins (240-793-0353) or Sandra Ke (240-686-4702) regarding questions about packaging and shipping.

Revision date: 16 Apr 2007

Appendix 5.3 – Pointers on Shipping Clinical Specimens for Central Lab Shipping (FedEx)

At FedEx Express, we understand the importance of ensuring the safe shipping of clinical samples such as human or animal materials, including excreta, secreta, blood (including FDA-approved pharmaceuticals that are blood products), tissue and tissue fluids, as well as environmental test samples of soil and water. Our objective is to deliver these special shipments safely to their destinations in the same good condition as we receive them from you.

This brochure provides essential pointers to help you meet FedEx Express requirements on the proper packaging of these materials. In addition, all shipments must comply with all applicable local, state and federal laws governing packing, marking and labeling. Blood, urine, fluids and other specimens containing or suspected of containing infectious substances must be shipped according to applicable government and International Air Transport Association (IATA) regulations. For more information, call 1.800.GoFedEx 1.800.463.3339 and press "81" to reach the Dangerous Goods/Hazardous Materials Hotline.

The illustrations depict sample packaging that is acceptable for shipping clinical samples such as human or animal materials, including excreta, secreta, blood (including FDA-approved pharmaceuticals that are blood products), tissue and tissue fluids, as well as environmental test samples of soil and water. All of the packaging illustrated here are acceptable and may be used in any combination as long as the four basic requirements for acceptable packaging are met.

NOTE: Specific requirements for Diagnostic Specimens are highlighted and underlined below.*

GENERAL ACCEPTABLE PACKAGING

Proper packaging of clinical samples and environmental test samples includes four basic requirements:

1. Watertight Primary Receptacles
2. Watertight Secondary Receptacles
3. Absorbent Material
4. Sturdy Outer Packaging

NOTE: Internal filler or cushioning is recommended to protect fragile contents and limit movement.

For Diagnostic Specimens containing liquids, absorbent material is required between the primary and secondary receptacles. For both liquids and solids, cushioning material is required.

*Dangerous-goods regulations can be reviewed in the IATA Packing Instruction 650.

1. Watertight Primary Receptacles

All primary receptacles must have positive closures (such as screw-on, snap-on or push-on lids) that must be taped.

For Diagnostic Specimens, primary receptacles may be glass, metal or plastic. Positive means of ensuring a leak-proof seal, skirted stopper or metal crimp seal must be provided. Reinforce screw caps with adhesive tape.

For liquid specimens, the primary receptacle(s) must be leak-proof and must not contain more than 1 L.

The primary or secondary receptacle(s) must be able to withstand, without leakage, an internal pressure producing a pressure differential of not less than 95 kPa in the range of -40 C to 55 C (-40 F to 130 F).

For solid specimens, the primary receptacle(s) must be siftproof and not contain more than 500 g.

Plastic Canister

Glass/Plastic Jar

Glass/Plastic Vial

2. Watertight Secondary Receptacles

To prevent contact between multiple fragile primary receptacles, individually wrap or separate each and place inside a leak-proof secondary receptacle.

For Diagnostic Specimens, enclose an itemized list of contents between the secondary packaging and the outer packaging. For solids, the secondary packaging must be siftproof. These illustrations below are not intended to represent secondary containers for Diagnostic Specimens. Secondary containers for Diagnostic Specimens must be certified by the manufacturer prior to use.

Sealed Styrofoam® Container (1-inch-thick minimum)

Sealed Plastic Bag

Plastic Canister

Screw-Cap Can

3. Absorbent Material

Place absorbent material between the primary and secondary receptacle, making sure that multiple primary receptacles are individually wrapped to prevent contact. Use enough absorbent material to absorb the entire contents of all primary receptacles.

Cellulose Wadding

Cotton Balls

Super-Absorbent Packet

Paper Towels

4. Sturdy Outer Packaging

Sturdy outer packaging must be rigid, consisting of corrugated fiberboard, wood, metal or rigid plastic and be appropriately sized for content.

For liquids, the outer packaging must not contain more than 4 L.

For solids, the outer packaging must not contain more than 4 kg.

When using an airbill pouch on outer packaging, the minimum package size that FedEx Express will accept is 7" x 4" x 2". For outer packaging smaller than these dimensions, use a plastic FedEx® Clinical Pak as an overwrap. As long as the final package meets the four basic packaging requirements, you may insert your package into the FedEx Clinical Pak to comply with the minimum acceptable size. (See "FedEx Clinical Pak" on the following page.)

For Diagnostic Specimens, the minimum outer-container size in the smallest overall external dimension is 4 inches.

Each completed package must be capable of withstanding a 4-foot (1.2-meter) drop test outlined in IATA 6.6.1. The outer package must be rigid.

Corrugated Fiberboard

Wood

Rigid Cooler

Rigid Plastic Container

MARKINGS: Patient specimens for which there is minimal likelihood that pathogens are present are marked by the shipper "Exempt human specimen" or "Exempt animal specimen" as appropriate to comply with current IATA regulations. Each UN3373 shipment must show the text: "BIOLOGICAL SUBSTANCE CATEGORY B," "DIAGNOSTIC SPECIMENS" or "CLINICAL SPECIMENS" at least 6 mm high, marked on the outer package adjacent to the following diamond-shaped mark.

The UN mark must be in the form of a square set at an angle of 45 degrees with each side having a length of at least 50 mm (2 inches). The width of the line must be at least 2 mm and the letters and numbers must be at least 6 mm high.

The name, address and telephone number of a responsible person must be marked on the package **OR** provided on the airbill.

Finally, if more than one properly prepared Diagnostic Specimen shipment is placed into another outer package, this constitutes an overpack. The word "OVERPACK" must be marked on the outer package and all other required package markings must be reproduced on the outside of the overpack.

Specific requirements:

Please consult the current ICAO/IATA regulations handbook for specific requirements for the following:

a. Diagnostic Specimens shipped refrigerated or frozen.

b. Diagnostic Specimens shipped in liquid nitrogen.

AIRBILL ENTRIES

If a paper airbill is used, the following text must be included: "Biological Substance Category B," "Diagnostic Specimens" or "Clinical Specimens" and "UN 3373." If not marked on the outer package, the name, address and telephone number of a responsible person must be marked on the airbill.

Don't Forget ...

- Infectious substances or probable infectious substances require additional specifications and must be shipped according to applicable government and IATA requirements.
- Shipments marked or labeled 6.2 (infectious materials) and/or containing dry ice cannot be shipped inside the FedEx® Clinical Pak.
- Consult the Occupational Safety and Health Administration (OSHA) regulations to determine if your commodity requires the biohazard label.
- FedEx Express will not accept clinical samples, Diagnostic Specimens or environmental test samples packaged in the FedEx® Envelope, FedEx® Tube, FedEx® Pak or any FedEx box.
- Don't place clinical samples, Diagnostic Specimens (UN3373) or environmental test samples in a FedEx Express® Drop Box. Please call FedEx for pickup, or you can drop off the shipment at any staffed FedEx location or FedEx Authorized ShipCenter.® FedEx Kinko's Office and Print Centers may accept FedEx Clinical Pak shipments provided they do not contain UN3373. For further assistance call 1.800.GoFedEx 1.800.463.3339.

- Mark and weigh packages correctly.
- Have packages ready when you call for pickup.

NOTICE

FedEx Express will refuse to accept packages not meeting FedEx Express, government or IATA requirements.

This brochure is in no way intended to replace requirements mandated by 49CFR and IATA. This is for informational purposes only.

This packaging brochure is provided free to FedEx Express customers to reduce the possibility of loss or damage during transit. It is NOT intended to be a comprehensive guide for packaging items we accept for transit. We make no warranties, expressed or implied, regarding this information. Proper packaging is the sole responsibility of the shipper. For more information and comprehensive guidelines, contact the FedEx Dangerous Goods/Hazardous Materials Hotline at 1.800.GoFedEx 1.800.463.3339, and press "81." Refer to the current FedEx Service Guide for terms, conditions and limitations applicable to FedEx® delivery services.

BD Indispensable to human health

How to Prepare a Quality Sample

Using BD Vacutainer™ SST™ Tubes

Invert
5
Times

- *Gently* Invert 5 times to mix clot activator with blood.

Clot
30
Minutes

- Allow blood to clot for a minimum of 30 minutes in a vertical position.
- Observe a dense clot.

Spin
10
Minutes

- Centrifuge at FULL SPEED (between 1100 and 1300g) for 10 minutes for swing-head units or 15 minutes for fixed angle units (balance tube in centrifuge).
- Barrier will form, separating serum specimen from clot.
- Transport spun tube to laboratory.

BD Vacutainer Technical Services
1.800.631.0174

Chapter 6: Study Medication

Table of Contents

Chapter 6. Study Medication

6.1 General Description

RIVUR study medication, both active drug and placebo will be prepared and distributed to each clinical center for the 600 participants, approximately 300 receiving placebo and 300 receiving sulfamethoxazole and trimethoprim (TMP-SMZ) oral suspension USP prophylaxis.

Study medication will be distributed to participants 4 times over the course of the trial, at each of the protocol specified clinic visits at randomization, and the 6, 12, and 18 month clinic follow-up visits. At distribution, each participant will receive a 7-month supply of study medication, a dosing syringe, and dosing cup, and instructions on use and storage.

6.2 Drug Procurement

6.2.1 Description of Study Medication

There will be two formulations of study medication, active and placebo. The active medication is a generic form of trimethoprim-sulfamethoxazole (TMP-SMZ) in liquid-suspension, containing 200 mg sulfamethoxazole and 40 mg trimethoprim per 5 mL of suspension. The active medication is bottled at UPM Pharmaceuticals (UPM). The generic drug is pink and cherry-flavored.

UPM will also manufacturer the placebo formulation. The placebo will be formulated to be indistinguishable from the active with respect to smell, taste, appearance, color, and viscosity. Table 6.1 on the following page lists the ingredients of the active and the study placebo.

6.2.2 Bottling and Labeling

The study medication will be bottled in 500 mL opaque bottles with a child resistant cap. Each bottle of RIVUR study medication will have a unique bottle code number which will be generated by the DCC.

Figure 1.0 below shows an example of the label that will be affixed to the front of the medication bottle. Labels will indicate the name and sponsor of the study, bottle code number (example shows ‘000000’), instructions, storage instructions, expiration date (shown as format mm/yyyy under the bottle code number), and any other information required by law.

Participant ID and bottle distribution information will be recorded and entered at each site at the time of participant medication distribution (see Section 6.4.2.5).

Table 6.1 RIVUR Study Medication Components

Components of RIVUR Placebo	Components of RIVUR Active
Microcrystalline Cellulose/Carboxymethylcellulose Sodium (Avicel® CL-611)	Sulfamethoxazole
NEOSORB 70/20B	Trimethoprim
Ethyl Alcohol, 190 Proof USP/NF	Alcohol (less than 0.5%)
Methylparaben, NF	Methylparaben
Glycerin, USP/NF	Sodium Benzoate
Sodium Benzoate NF	Carboxymethylcellulose Sodium
Saccharin Sodium, Dihydrate, Powder, USP	Citric Acid
Polysorbate 80, NF	Glycerin
Denatonium Benzoate, NF	Microcrystalline Cellulose
Titanium Dioxide, USP/NF	Polysorbate 80
FD & C Red No. 40 Powder	Purified Water
FD & C Yellow NO.6 Powder	Saccharin Sodium
Citric Acid Anhydrous USP	Sorbitol
Flavor, Cherry Extract, Natural and Artificial	FD&C Red #40
USP Purified Water	FD&C Yellow #6
	Artificial Cherry Flavor

6.2.3 Shelf Life and Temperature Limitations

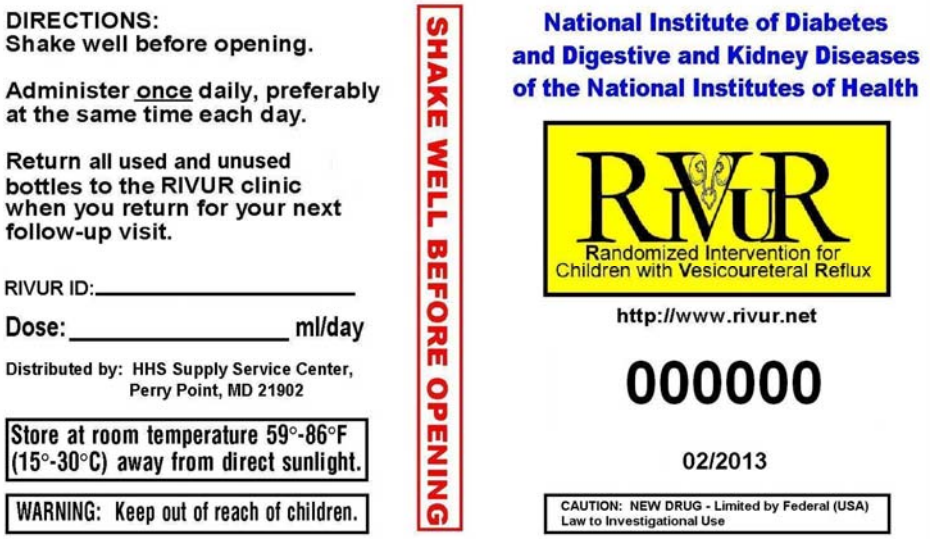
The expiration date of each batch of medication will be determined by the drug manufacturer. The placebo has a matching expiry date for individual batches of study medication. The study medication from a particular batch will not be distributed 7 months prior to the expiry date of a batch. The shelf life of a particular batch will depend upon usage and/or expiry date. The DCC closely monitors the inventory of the study medication through the data management system.

The medication label will have special instructions for RIVUR study medication with regard to temperature control. The medication should remain in a climate-controlled area away from direct sunlight in the temperature range between 59-86°F.

6.2.4 Stability Testing

The active study medication, TMP-SMZ, will be purchased from a generic manufacturer. It will then be re-bottled by UPM Pharmaceuticals into 500cc amber round wide-mouth HDPE bottles with 45 mm white ribbed child-resistant polypropylene caps and heat seal inner foil liners. Stability data will be collected. The placebo will be formulated, manufactured and bottled by UPM Pharmaceuticals into the same type of containers as the active study drug.

Figure 6.1 Example Label for RIVUR Study Medication



6.3 Distribution to Clinical Centers

6.3.1 Packaging of Bottles

UNC DCC will contract with HHS Supply Service Center (HHS SSC), Perry Point, MD, to serve as the storage facility and distribution center for study medication. UPM will ship bottled and labeled study medication to HHS SSC. HHS SSC will then distribute medication via overnight shipping to the clinical sites in accordance with a schedule provided by the DCC.

6.3.2 Shipment of Study Medication to the Clinical Sites

Study medication bottles will be packed in boxes for shipping, with a label affixed to the outside of the box that includes a box/shipment identifier and the words, 'DO NOT REFRIGERATE.' Also included in the shipment will be a dosing syringe and dosing cup per bottle to be distributed to the participants by either the coordinator or the pharmacist.

6.3.2.1 Initial Shipment

The RIVUR clinics will receive an initial shipment of study medication from HHS SSC that will be expected to last for the first 6 months after recruitment has begun. The number of bottles distributed to each site in the initial shipment will be based on the assumption that recruitment will proceed uniformly. Each core site is responsible for recruiting approximately 60 participants per year for the first two years. Those satellite sites affiliated with core sites will contribute equally to their core site's expected 60 participants. The recruitment at the core sites is estimated to be 5 participants per month for 24 months while the satellite sites' recruitment is estimated to be ~1 participant per month for 24 months.

The number of bottles of medication to be sent in the initial shipment will be approximately 3 bottles per expected recruited participant. The satellite sites will receive 24 bottles of study medication and the core sites will receive 90 bottles of study medication.

6.3.2.2 Subsequent Shipments

Subsequent batches of study medication will be manufactured and packaged by UPM as needed, based on recruitment patterns, weight distributions of participants, and the relative closeness of the study medication's expiration date, as monitored by the DCC. Packaged medication will be sent to HHS SSC for subsequent storage and distribution. The DCC will order shipments from HHS SSC as needed. Each site can expect to have a sufficient amount of drug inventory available for all randomized participants.

6.3.3 Receipt of Shipment at the Clinic – Clinic Medication Distributor

Shipments will be addressed to each site's Clinic Medication Distributor (CMD). This should be a pharmacist, Project Coordinator, or a responsible person with knowledge of receiving, dispensing and inventory of drugs. For some sites the CMD is the Project Coordinator, and for others, the CMD is the site's research pharmacist.

The CMD is responsible for receiving the medication shipment, verifying the contents of the shipment against the packing list, storing the medications, and monitoring the distribution of the study medication. The CMD will be notified via email that a drug shipment will be arriving. The DCC and the site's Project Coordinator will be copied on the notification of shipment email. Upon receiving the study medication, the CMD will inventory the contents of the shipment for accuracy by checking off the bottles received and fax a copy of the checked packing list to the DCC (fax number: 919-962-3265, attention RIVUR Staff). The CMD will also periodically, at the request of the DCC, provide a current inventory of the bottles of medications available for distribution.

Project Coordinators are responsible for providing the DCC with current contact information of the CMD. The Project Coordinator will notify the DCC of any changes to the Clinic Medication Distributor (personnel, address, phone, etc.), or to medication storage, distribution, record-keeping, or disposal procedures. The listing of RIVUR clinic CMDs is stored on the study website.

The Project Coordinator will brief the CMD regarding RIVUR procedures surrounding drug distribution. The Project Coordinator will track all bottles of medications dispensed using the Medication Distribution Log (see Section 6.4.2.5). If the CMD is not the Project Coordinator, and study medication is being distributed other than in the RIVUR clinic, then study medication tracking will also be done by the CMD. The CMD and Project Coordinator should maintain regular contact in order to assure both parties have an accurate inventory of their site's study medication.

6.3.4 Medication Storage at the Clinic

Initially, each core clinic will be required to provide space for approximately 90-120 bottles of study medication. The satellite sites will need to store 15-25 bottles, depending on the core site

affiliation. The round 500 mL bottles will be approximately 6 inches high and 3 inches wide. The study medication should be stored in a secure, climate-controlled location (59-86°F), away from direct sunlight. The storage location will vary depending on the policies of the institution. In some clinics the study medication will be maintained in the hospital pharmacy and requisitioned by study personnel as needed. In other clinics the study medication may be stored in a secure locker or cabinet within the research facility.

6.4 Clinic Procedures

Protocol scheduled distribution of study medication to participants will occur at the randomization visit (contact occasion 01) and every 6 months at protocol scheduled clinic follow-up contacts (contact occasions 04, 07, and 10). The medication dose and number of bottles distributed will be determined based on the child's measured weight. Each bottle of study medication will have an accompanying dosing syringe and dosing cup.

Weight-dependent dosing and bottle assignment for medication distribution will be done through the RIVUR DMS. Medication compliance will be assessed by parent report, and by weighing returned bottles (both opened and unopened) of study medication at the subsequent protocol scheduled clinic visit. Procedures related to medication distribution, return, and discontinuations are detailed below.

6.4.1 Data Collection Forms

Forms documenting medication distribution, return, and discontinuation include:

- Medication Dosing and Distribution Form (MDD)
- Medication Return Form (MRF)
- Drug Discontinuation Form (DDF)
- Medication Distribution Log (MDL)
- Medication Distribution Log – Pharmacy (MDL-P)

Item specific instructions for the forms listed above are documented in each form's corresponding QxQ.

6.4.2 Participant Medication Distribution

Medication dosing and dispensing will depend on the treatment assignment and the child's weight. At the randomization visit, the ERF and the PEF must be entered into the DMS before entering the Medication Dosing and Distribution Form (MDD). Upon completion of the MDD, the child will be assigned bottle codes from the site's medication inventory. Subsequent scheduled dispensing will require the PEF to be data entered before the MDD form. There will be procedures for Project Coordinators to follow in situations where drug must be dispensed in the time between clinic visits (see Section 6.4.2.6).

Refer to Chapter 4: Randomization and Baseline, and Chapter 7: Follow-up Contacts for details on overall data collection at these visits.

The process of calculating dose, number of bottles, and the bottle code number assignments for study medication distribution will be performed through data entry of the Medication Dosing and Distribution form (MDD).

6.4.2.1 Dosing

The number of bottles dispensed to the subject will depend upon the prophylactic dose of 3 mg trimethoprim per participant weight in kg taken once daily, as specified in the manufacturer's instructions. Since the active was bottled with 40 mg of trimethoprim per 5 mL of suspension, the formula for dosing becomes (((child's weight in kg*3)*5)/40) rounded to the nearest 0.5 mL. Every 6 months, at each protocol scheduled clinic visit, sites will dispense enough study medication to last for 7 months. Thus, the formula for the number of bottles to distribute becomes the (daily dose in mL/day*213 days)/500 mL rounded up to the nearest 500 mL.

The dosing instructions will remain constant during the time between the 6 month protocol scheduled clinic visits. If a missed visit occurs and the child cannot be seen again for another 6 months, the coordinator should make a telephone contact, following the instructions for unscheduled dosing and dispensing so that the child's dose may be appropriately adjusted. Refer to section 6.4.2.6 for details on unscheduled dosing and dispensing.

6.4.2.2 Drug Dosing Procedure Using the Data Management System

Data entry of the MDD form will provide the DMS system with the information required to calculate dose, number of bottles, and the bottle codes to be dispensed. As a QC check for dosing, the DMS will validate the weight measures in the MDD against the weights measured on the Physical Exam Form (PEF). Entry of a "Y" to the question "Are you ready for medication bottle numbers and dosing?" will trigger the data management system (DMS) to populate the fields for dose and bottle codes. A successful DMS dosing procedure will also automatically send a notification email to the DCC containing bottle assignment information.

The completed MDD form can be printed for study records. For sites where drug dispensation occurs at a pharmacy or location outside of the research clinic, a DMS report entitled 'Prescription' can be run and printed by the Project Coordinator to be used as a prescription for the CMD. Participant ID labels (provided by the DCC, used for data collection forms) should be included with the 'Prescription' for the CMD to apply to the bottle labels. The participant ID label should be placed on the 'Name' field of the bottle label, in order to protect participant privacy.

In the event that the DMS dosing program aborts or cannot run, you will be prompted with an error message explaining the reason for the program failure. This will likely be the result of edit failures or attempting to run the dosing program prior to entering the required DMS validated weights. When this occurs, correct the MDD and begin the dosing procedure again.

6.4.2.3 Drug Dosing Procedure when System is not Functional

Since the dosing procedure requires entry through an internet connection, a backup procedure is necessary for cases in which the clinic's computer system is not functional, or the WEB is inaccessible or not operating appropriately.

This will impact randomization visits as well as follow-up visits where drug dispensing is needed. As soon as it is realized that the DMS is nonfunctional, the coordinator should contact the DCC to arrange a remote randomization or drug dosing (whichever is needed). Emergency randomization and/or dosing procedures will be done by telephone with the DCC. Refer to Chapter 4, Section 4.4.3.2 for the specific procedures.

6.4.2.4 Instruction to Participants

The Project Coordinator will instruct the participant's parent/guardian on the dosing instructions for the medication, how to store the medication, and how to dispense the liquid medication. Parent/Guardians must also be instructed to keep all used and unused medication bottles and to bring them to the next clinic follow-up visit.

The participant's parent/guardian will be given the study medications with dosing instruments (syringe and dosing cup) and will be instructed as follows.

a. Medication is for the participant's use only.
b. Keep the bottles of medication out of the reach of children.
c. Shake the bottle of study medication prior to giving the child the daily dose.
d. Take the prescribed dose of medication one time daily, preferably at the same time each day. However, if the regular time is missed, it should be taken later in the same day.
e. Take any other medications on their regular schedule.
f. Medication should be stored at room temperature away from direct sunlight or heat.
g. If participant does not take study medication and parent realizes it the next day, do not administer two doses in the same day.
h. If planning a trip or staying away overnight, remember to take the RIVUR medication along.
i. If medication has been lost, the clinic should be notified as soon as possible to schedule a time for re-dispensing.
j. If any unusual symptoms flare after the onset of taking the daily medication, then call the RIVUR clinic as soon as possible. The Project Coordinator will fill out an Adverse Events Form (AEF) if the participant experiences any problem with the study medication.

In general, coordinators should emphasize the importance of taking **one dose every day and returning all bottles, including empty, partially used, and unopened ones, at the next clinic visit.** Returning the bottles is important for collection of compliance data.

6.4.2.5 Distributing Bottles to Participant

The DMS Prescription Report lists the daily dose of study medication, the bottle codes to be distributed to the participant, and the expiration of each medication bottle. The Clinic Medication Distributors (CMDs) or Project Coordinator will log the medication bottles assigned

to each participant onto the Medication Distribution Log-Pharmacy or the Medication Distribution Log. Prior to dispensing, all medication bottles must have participant ID label applied to the bottle label, and medication dose must be recorded on the bottle.

Careful identification of the proper bottle codes and checking of the bottle expiration dates before distribution will be essential in avoiding errors related to this procedure. CMDs will need to be particularly careful in checking the expiration date before distribution to a participant. The expiration date must be at least 7 months after the date of distribution to a participant. In addition, the DCC will notify the clinics when remaining medications in a batch must be discarded due to impending expiration. (See section 6.4.7 for information on medication disposal.)

In the case where the Project Coordinator is not the functioning as the CMD, the Coordinator must confirm that the parent/guardian has received the assigned bottles of medication, and verify the expiration date of the medication by contacting the pharmacy.

Clinic pharmacies that are dispensing RIVUR medication, must maintain their own inventories that address their center's IRB and other regulatory requirements, as well as maintain the RIVUR Medication Distribution Log-Pharmacy.

6.4.2.6 Unscheduled Dispensing

Unscheduled medication dispensing may occur in the event that medication bottles are lost, or in the event a follow-up clinic visit is missed or changed to a later date. The participant will either need to return to the clinic to replace lost medication or study medication will be mailed to the participant if the sites have permission to dispense via mail.

The study medication dose shall remain constant for 6 months at most. This point is troublesome for unscheduled dispensing of study medication. If more than 6 months elapse between the last measured weight and the next clinic visit, then the Project Coordinator must update the child's weight for accurate dosing. If the child is able to come to the clinic for an unscheduled dispensing of study medication, the Project Coordinator will fill out the PEF form followed by the MDD form. However, if the child is unavailable to come to the clinic, the Project Coordinator will enter the MDD and will be instructed to ask the parents to provide a recent weight. If the parents don't know the child's weight, the Project Coordinator may estimate the child's weight from the 2000 CDC Growth Curves (Advance Data No. 314 Dec. 4, 2000) (see Figures 6.2-6.5 at the end of this chapter). Any weight supplied by the parents should be cross-checked against the growth curves.

In order to get an accurate estimate of the child's weight, use the most recent measured weight from the PEF of the most recent contact occasion. The RIVUR DMS report entitled "Measured Weight of Participant" will provide the most recently measured clinic weight. The child's weight for age percentile from the previous contact occasion may be read directly from the growth chart using the weight and age from the earlier clinic visit. Follow along the same percentile curve to the current age of the child to read their current estimated weight. Enter the estimated weight into the MDD for use in the dosing procedure. Note, the parents reported weight of the child may be checked using the growth curve. If large deviation occurs between the parents report and

the growth curve, use the estimated weight from the growth chart and encourage the parents to visit the clinic for accurate dosing.

6.4.3 Bottle Returns and Compliance

At each clinic follow-up, parents/guardians will have been reminded to return all study medication bottles dispensed from the previous visit. This includes bottles open and in-use, empty bottles, as well as unopened bottles. The return of the bottles will give RIVUR medication compliance information. Participant compliance information will also be collected during the follow-up interview using the FUP.

The Participant Follow-up Report on the DMS will include a listing of bottle code numbers previously dispensed and not returned. Regarding compliance, this report will summarize the status of the participant's medication use, indicate the dose and number of bottles given to the parent/guardian at the last clinic visit, and provide information about the participant's previous compliance. Coordinators can use the DMS follow-up visit report to verify that the number of bottles returned is correct. Monthly management reports will provide overall compliance rates for each clinical center.

More information on the importance of parents to comply with medication administration as well as methods of collecting compliance data may be found in Chapter 8: Compliance.

Upon return of bottles, the Project Coordinator will weigh each opened bottle, including empty bottles, and record the weight as well as the bottle code on the Medication Return Form (MRF). A Denver Instrument scale (model MMS-2001) will be provided to each site for use in weighing the returned (opened) bottles. Each balance comes with an operating manual and a 2 kilogram weight used for calibrating the scale. Instructions for calibration are on page 15 of the manual. The scale should be calibrated if the scale gets moved from place to place or if the scale goes unused for long periods of time.

If bottles are returned at times other than protocol scheduled follow-up contact visits, refer to Chapter 13: Administrative Procedures, for rules on assigning contact occasion and sequence number necessary for entry of the MRF.

6.4.4 Medication Side Effects and Drug Discontinuation

Medication side effects, serious or otherwise, are to be reported as an adverse event. Details on side effects and adverse event reporting are presented in Chapter 9. Participant Safety, Side Effects, and Adverse Events. Drug discontinuations as a result of adverse events are also covered in chapter 9.

6.4.5 Unmasking Policy

Refer to Chapter 9, Participant Safety, Side Effects and Adverse Events for unmasking procedures.

6.4.6 Record Keeping

6.4.6.1 Verifying Shipment of Medication

Each case of study medications that is received by the Clinic Medication Distributor will be accompanied by a packing list that indicates the number of bottles in the case. The Clinic Medication Distributor will verify that the case contains the items listed on the packing list by comparing the codes on the list with those in the case. Check off each bottle on the packing list as you locate it within the case. If all is satisfactory, sign and date the packing list. Make a copy of the verified packing list and fax it to the DCC (fax number: 919-962-3265, attention RIVUR Staff). If there is a discrepancy between the contents of the box and the packing list, notify the DCC immediately so that a correction can be made.

6.4.6.2 Maintaining the Medication Distribution Logs (MDL and MDL-P)

The Project Coordinator will maintain the MDL for all medications that are distributed. This form will document the details of distribution of each bottle to facilitate clinic inventory of study medication. The form will also be used during medication dosing and dispensing when the DMS is non-functional. As study medication is assigned to a participant, copy the required information from the Prescription Report for each bottle on the log without delay. For those sites that dispense medication outside of the RIVUR clinic, a pharmacy-specific medication distribution log (MDL-P) should be used by the Clinic Medication Distributor (CMD). The Project Coordinator is responsible for verifying that the medication bottles listed on the prescription report were actually distributed to the participant and that the MDL matches the MDL-P.

The MDL must be current as it will be the source of medication inventory in the event that the data management system is inoperable and randomization must occur via telephone. If a randomization occurs via telephone, the Coordinator must be able to provide the latest drug distribution information in order, to maintain the proper order of drug distribution. The MDL should be filed in a convenient location in the clinic for frequent updating.

6.4.7 Disposal of Excess or Expired Medication

Study medications should not be discarded or destroyed without approval from the DCC. In general, medications will be disposed of on a regular schedule before, but near, the time that a batch is expiring. Following authorization from the DCC, the coordinator will arrange for disposal according to the policy of the local institution. Disposal will include unused medications returned by a participant, medications unusable because of the expiration date, and drugs remaining at the conclusion of the study. Each Project Coordinator is requested to send a statement to the DCC briefly describing the disposal method to be used (incinerate, bury, flush down drain, etc.) at that site.

6.5 Data Coordinating Center

The primary tasks of the DCC with respect to drug distribution are to provide the list of codes for each dose group to the CMD, to monitor the storage, shipping, ordering, and disposal of medications, and to manage the quality control system.

6.5.1 Quality Control

The primary objectives of quality control with respect to RIVUR study medication are to insure:

A. participants are always given the correct doses,
B. bottles are not given out to be used beyond their expiration date,
C. active medication and placebo preparations remain indistinguishable to participants and RIVUR investigators.

Reports and procedures covering quality control and study medication are in progress.

Figure 6.2 Boys Weight for Age Percentiles – Birth to 3 years

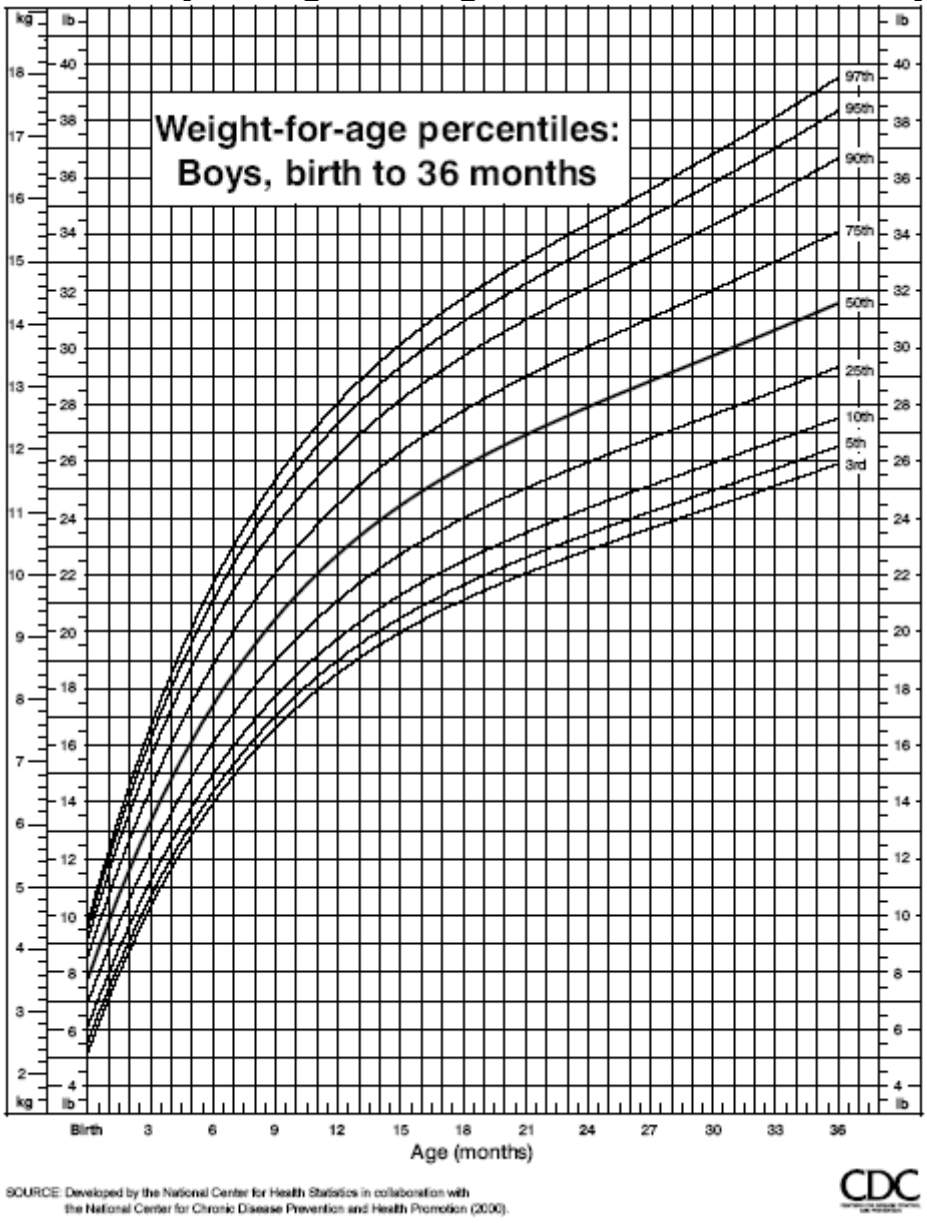


Figure 6.3 Girls Weight for Age Percentiles – Birth to 3 years

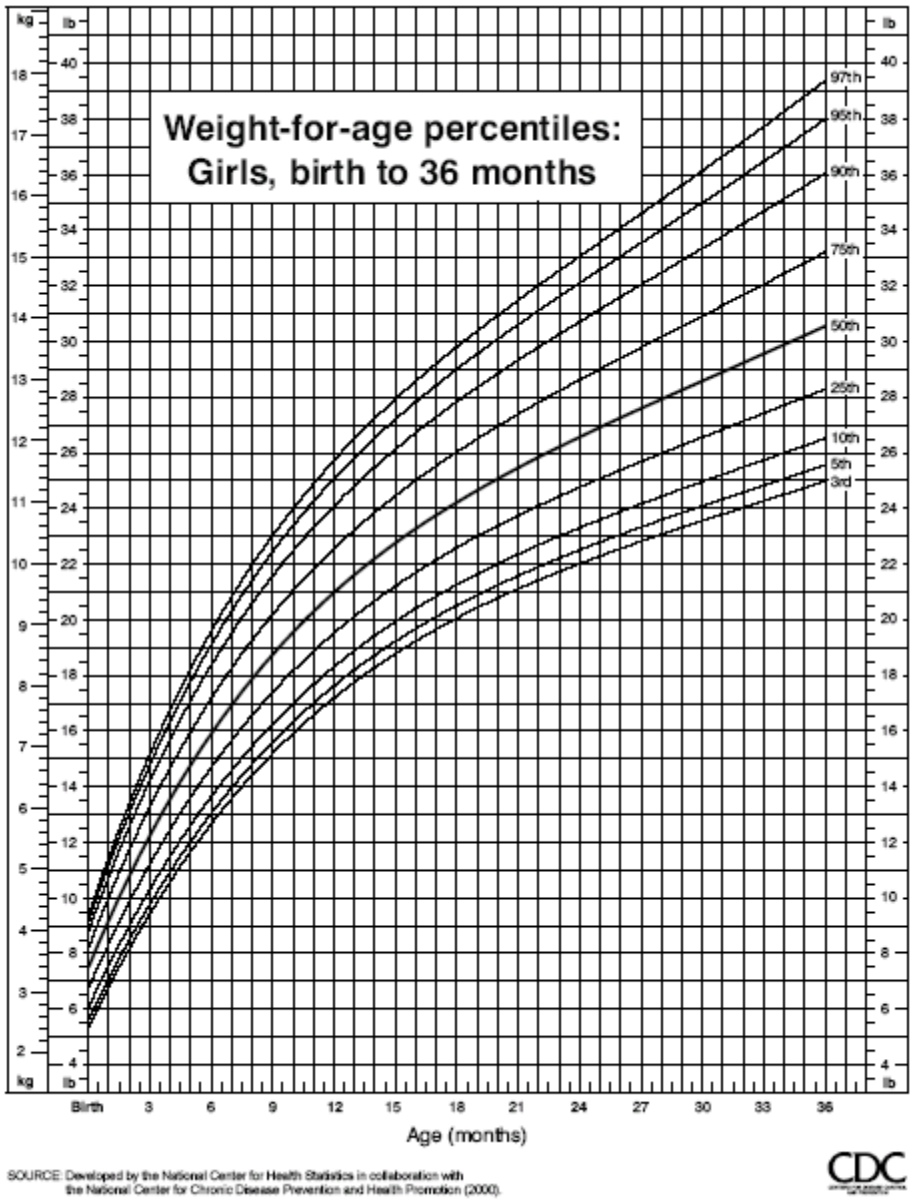


Figure 6.4 Boys Weight for Age Percentiles – 2-20 years

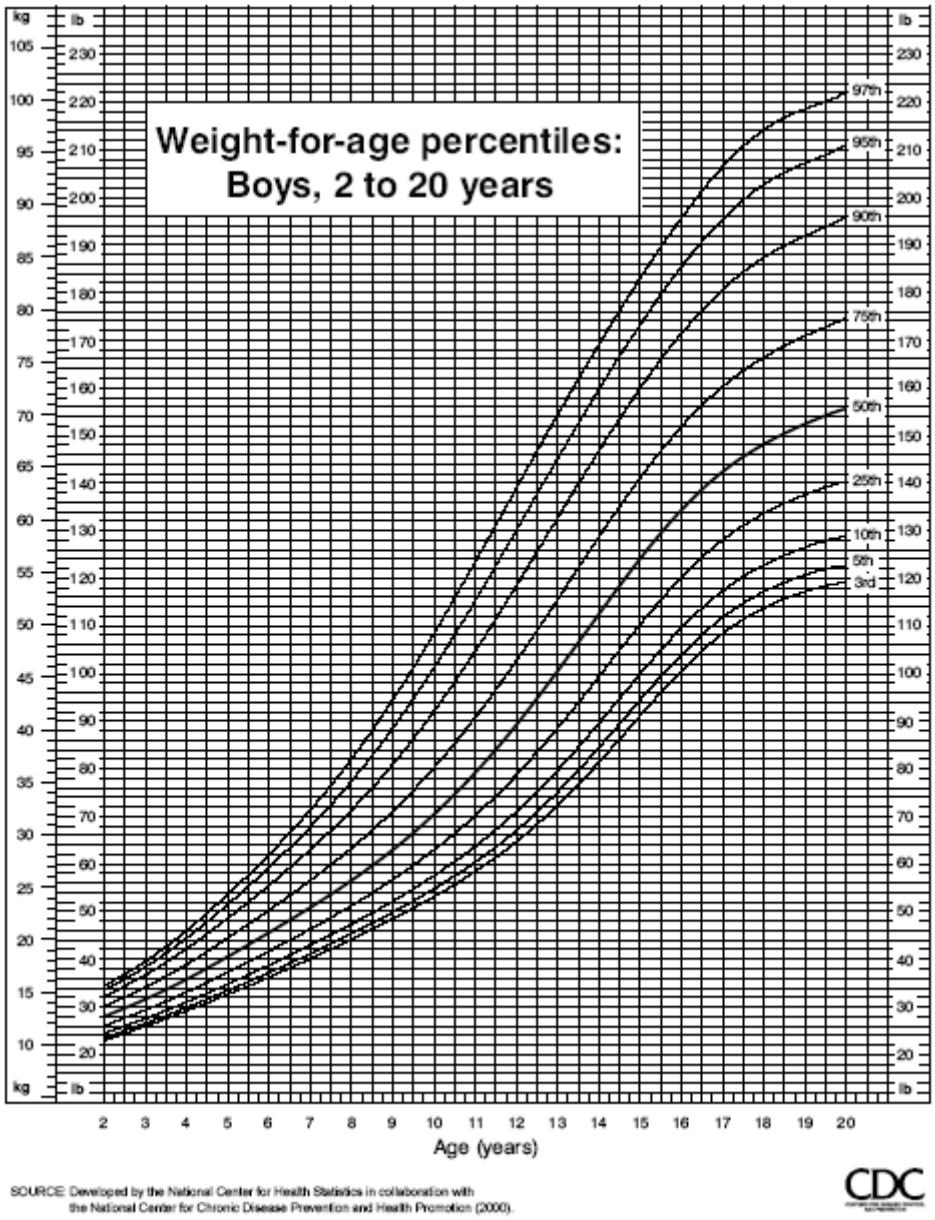
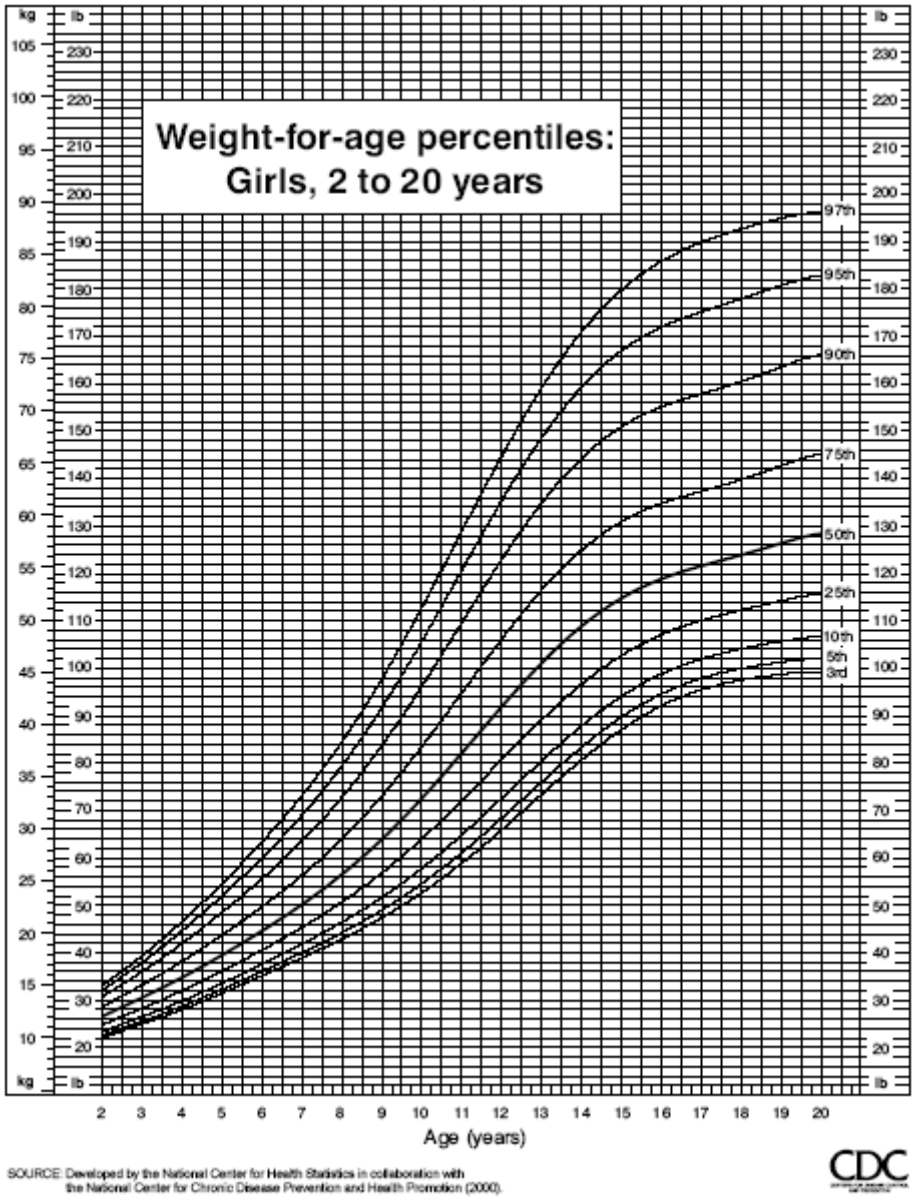


Figure 6.5 Girls Weight for Age Percentiles – 2-20 years



Chapter 7: Follow-Up Contacts

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Chapter 7: Follow-Up Contacts

7.1 Overview

During the two-year follow-up period, parents will be contacted by phone every 2 months and scheduled for clinic visits every six months. Follow-up contacts and visits will continue through 24 months, regardless of medication compliance.

In brief, the follow-up contacts will provide monitoring for participant safety, as well as data for endpoint ascertainment. They are designed to insure that the study captures data on all potential urinary tract infections (UTIs) that occur during the 24 months of study. At each follow up contact, Coordinators will collect data on the occurrence of any adverse events and medical care visits, review concomitant medication use, determine study medication compliance, and obtain the history of urine and bowel toilet training since the last study contact.

Parents/guardians will be asked to keep a patient diary recording occurrences of illness, medical care visits, and newly prescribed concomitant medications. This diary will be reviewed during all telephone and clinic visit follow-up contacts.

7.2 Scheduling of Follow-up Contacts

Follow-up procedures will continue for each participant until their end-of-study visit at 24 months after randomization, regardless of medication compliance, or a designation of treatment failure.

Project Coordinators should always remind parents/guardians that routine follow-up consists of both clinic visits and interim telephone interviews, which are scheduled every 2 months. At the randomization and baseline visit, the Coordinator should schedule the next two telephone contacts, at 2 and 4 months from randomization. At the end of every follow-up contact, the next 2 contacts should be confirmed or scheduled with the parent/guardian.

When scheduling clinic visits, the Coordinator will always need to verify that the principal investigator or his/her designee (which may be the Coordinator) is available to perform any necessary examinations during scheduled contacts.

7.2.1 Target Dates and Contact Windows

Target contact dates occur exactly every 2 calendar months from a participant's date of randomization, and continue through the end of the 24-month study period. All protocol scheduled follow-up contacts should be scheduled on, or within ± 10 days, of a target date. This allows a 21-day window for Coordinators and parents to work with when scheduling follow-up contacts.

Table 7.1 below shows the first three target dates and resulting contact windows for a patient randomized January 1, 2007.

Table 7.1
Target Dates and Contact Windows for a Patient Randomized January 1, 2007

Study Contact Occasion	Target Date	Window (± 10 of target date)
02 (2-mo phone contact)	March 1, 2007	Feb 19 – Mar 11
03 (4-mo phone contact)	May 1, 2007	Apr 21 – May 11
04 (6-mo clinic visit contact)	July 1, 2007	Jun 21 – Jul 11

It is important to remember that target dates are **always scheduled from the date of randomization,** regardless of the last contact date. The RIVUR DMS contains a RIVUR Participant Follow-up Schedule Report that can be run on each patient, listing the target contact date and the upper and lower dates of the window for the full 24 months of the participants study. A copy of this report should first be provided to the parent/guardian at the time of randomization, and the information may also be written into the patient handbook/diary.

7.2.2 How closely together can two contacts be scheduled?

The Coordinator should make every effort to schedule protocol contacts within the contact windows for the participant's target dates. However, there may be instances when this is not possible. Protocol contacts can be scheduled outside of the target date window if necessary. The RIVUR DCC would rather have data outside the time period than no data at all, but it would be a waste of resources to schedule two contacts too close together.

The general rule of thumb is that scheduled contacts for randomized participants must be at least 30 days apart. When a participant contact (clinic visit or phone) cannot be scheduled prior to 30 days before the next required contact, then it must be considered skipped (i.e., there will be no data collected for this contact occasion). If a contact is skipped, an FUP form for that expected visit must still be completed and entered in the DMS. Section A of the FUP form (Contact Information) will allow Coordinators to specify that the contact occasion was missed.

7.2.3 Follow-up Clinic Visits and Reminders

Since the clinic visits allow Coordinators to gather more information than the telephone contacts, and are the occasions when study medication dose is assessed and distributed, it is especially important that study clinic visits not be skipped. If a study clinic visit is skipped, the next contact, which would normally be a follow-up phone contact, should be scheduled as a clinic visit replacing the scheduled telephone contact. See Chapter 6: Study Medication regarding study medication distribution when clinic visits are missed.

Postcard Reminders

Two to three weeks before a follow-up clinic visit, the Coordinator should send a postcard reminder to the participant and his/her parents. On the postcard, the Coordinator should

remind the parent/guardian to bring in the Participant Handbook/Diary, all study medication bottles (used and unused), as well as any current medicines the child is taking.

Phone Call Reminders

Coordinators should also follow-up with a phone call reminder two to three days before each follow-up clinic visit. Again, the Coordinator should remind the parent/guardian to bring in the handbook/diary, all study medication bottles (used and unused), as well as any current medicines the child is taking.

7.3 Follow-up Data Collection Forms

The Tables below summarize the data collection forms used during participant follow-up in the RIVUR study. Some forms must be completed at specific clinic contacts. Others are completed or updated on an 'as needed' basis. These forms are often triggered by data collected or responses given during the required data collection, or are based on the participant's status in the study at a particular time. Table 7.2 lists both the administrative forms that Coordinators must maintain and keep updated, as well as the forms that are to be completed on an as-needed basis throughout the duration of the study. Table 7.3 lists the forms that are required at specific study contacts. Scheduled follow-up contacts in clinic or by telephone require certain forms such as the Follow-up Contact Form (FUP), and verification of contact information on the Participant Contact Form (PCF).

There are forms which are completed on an as-needed basis, in addition to being required at specific study contacts. For example, in the event that medication is lost, or additional medication is needed between clinic contact visits, the Medication Dispensing and Dosing Form (MDD) for study drug distribution and the Medication Return Form (MRF), both of which are completed at every clinic contact, will need to be completed at the time of re-distribution.

Table 7.2 Data Collection Forms completed or updated on an as-needed basis

Forms updated throughout study	Forms completed as needed throughout study
Informed Consent Tracking Form (ICT) Participant Contact Form (PCF) Record of Contacts Form (RCF)	Adverse Events Form (AEF) Medwatch FDA 3500A (FDA3500A) Medical Care Notification From (MCN) Medical Care Abstraction Form (MCA) Urine Specimen Results Form (USR) Medication Return Form (MRF) Medication Dispensing and Dosing Form (MDD) Drug Discontinuation Form (DDF) DMSA Sedation Form (DSF) DMSA Scan Shipping Form (DSS) VCUG/Ultrasound Scans Shipping Form (VUS) VCUG Sedation Form (VSF)

Table 7.3 Summary of Data Collection during Scheduled Follow-up Contacts

DATA COLLECTION FORMS	2-mo Tele	4-mo Tele	6-mo Clinic	8-mo Tele	10-mo Tele	12-mo Clinic	14-mo Tele	16-mo Tele	18-mo Clinic	20-mo Tele	22-mo Tele	24-mo Clinic
Contact Occasion	02	03	04	05	06	07	08	09	10	11	12	13
Follow-Up Contact Form (FUP)	X	X	X	X	X	X	X	X	X	X	X	X
Participant Contact Form (PCF)	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Form (CMF)	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam Form (PEF)			X			X			X			X
Medication Dispensing and Dosing Form (MDD)*			X			X			X			X
Medication Return Form (MRF)*			X			X			X			X
Medication Distribution Log (MDL)*			X			X			X			X
LIA Questionnaire (LIQ)						X						X
DV Questionnaire (DVQ)						X						X
DES Treatment Form (DTF)*						X						X
DMSA Results Form (DMF)*						X						X
DMSA Sedation Form (DSF)*						X						X
DMSA Scans Shipping Log (DSS)*						X						X
VCUG Sedation Form (VSF)*												X
VCUG/Ultrasound Scans Shipping Log (VUS)*												X
Urine Specimen Results Form (USR)*												X
Specimen Collection Form (SCF)			X			X			X			X
Blood Results Form (BSR)			X			X			X			X
Central Lab Shipping Log (CSL)												X
NIDDK Urine and Blood Shipping Log (NIDDK-USL)												X
NIDDK Genetics Blood Shipping Log (NIDDK-BSL)												X
Rectal Swab Shipping Log (RSL)												X
Exit Form (EXF)												X

*also completed as need throughout the study

7.4 Detailed Follow-up Procedures

7.4.1 DMS Participant Follow-up Summary Report

The DMS will include a report that the Coordinator can run prior to a participant's follow-up contact. This report will summarize data collected during previous contacts that will be helpful to the Coordinator during the contact interview. Reported information will include such things as the status of the participant in regards to study medication, whether the participant is classified as a treatment failure, a summary of previous follow-up contact compliance, medication compliance, previous adverse event reporting, and concomitant medication. It is important to note, that a patient's Follow-up Summary Report will only be current if all previous data entry and query resolutions have been completed for that patient.

7.4.2 Participant Handbook/Diary

At baseline, each participant's parent/guardian will be given a participant handbook/diary, and a follow-up schedule. The handbook provides a summary of procedures associated with the follow-up contacts. The handbook also functions as a diary for recording any fever or illnesses, medical care visits, and changes in concomitant medications that need to be reported to the Coordinator at each follow-up contact. Other important information and instructions are also documented in the handbook.

7.4.3 Participant Record of Contacts Form (RCF)

The RCF is used to document every attempt to contact a participant's parent/guardian in order to schedule a study contact. In addition, contacts made to the clinics initiated by the parent/guardian to reschedule contacts, or to report illness or medical care visits should also be documented in the RCF. Protocol scheduled contacts should not be reported on the RCF.

Refer to the RCF QxQ's for specific item-by-item instructions.

7.4.4 Protocol Scheduled Clinic Follow-up Visits Data Collection

A summary of required data collected during the protocol scheduled follow-up contacts is provided in Table 7.3 above. The follow-up clinic visits focus on collecting potential side effects and adverse events, assessing study medication compliance, concomitant medication use, the status of the child's toilet training, and include a CBC local lab blood assessment.

7.4.4.1 Modification of Informed Consent

A participant may modify their Informed Consent at any time during the follow-up period. If a participant indicates a change in their consent to participate in the study, complete an Informed Consent Tracking Form (ICT).

7.4.4.2 Physical Exam (PEF)

Each protocol scheduled clinic visit includes a brief physical exam. The exam includes temperature, blood pressure, and height and weight measures, as well as a brief abdominal exam. The physical exam should be performed at the beginning of the clinic visit, prior to completion of the FUP and MDD forms. Measured weight is used for dosing of study medication distributed at the end of the visit. Any abdominal tenderness, or other medical conditions or complaints discovered during the physical exam are collected according to instructions on the FUP.

7.4.4.3 Protocol Scheduled Follow-Up Form (FUP)

The FUP is the primary instrument used during a follow-up contact. The form will provide instruction about additional data collection and forms if needed, based on responses to specific questions. The FUP form is only used during protocol scheduled contacts with participants.

Questions related to side effects, adverse events, and medical care received since the last contact will trigger the AEF and the endpoint data collection forms MCN and MCA. Refer to Chapter 9: Participant Safety and Adverse Event Reporting for data collection procedures, and the AEF QxQ for question by question instructions. Refer to Chapter 10: Medical Care Abstraction and Endpoints for data collection procedures on the MCN and MCA forms, as well as the QxQ for each form.

Participant compliance to study medication based on interview is documented on the FUP. Concomitant medication use is also queried on the FUP, but details should be collected on the CMF.

The FUP also includes questions related to interim voiding and bowel history, and age at toilet training.

Refer to the FUP QxQ for additional information.

7.4.4.4 Medication Dispensing and Dosing (MDD, MDL)

Medication dispensing is done through data entry of the MDD form, using the participant's weight measured during the physical exam. This weight provides the dosing necessary for the participant. A DMS report will provide a prescription with dose, number of bottles to be dispensed, and the bottle numbers to be dispensed for the next 6 month until the next clinic visit. The Medication Distribution Log (MDL) is also completed at the time of medication dispensing. See sections 7.61 and 7.6.2 for contacts that are out of protocol order.

Refer to Chapter 6: Distribution of Study Medication for detailed instructions on study medication distribution procedures, and the MDD QxQ for form specific information. Chapter 6 addresses unusual situations (i.e. lost medication bottles need to be replaced, or drug bottles need to be mailed because of a missed clinic visit, etc…).

7.4.4.5 Medication Return (MRF)

At each clinic visit, previous study medication bottles are returned, whether used or unused. It is also possible that bottles are returned to the clinic off schedule (i.e. forgotten at the time of the visit). Returned bottle numbers are documented on the MRF form, along with their weight, to be used as a measure of compliance.

7.4.4.6 Specimen Collection at Clinic Visits (SCF, BSR)

Each protocol scheduled follow-up clinic visit requires a CBC blood analysis at the site's local lab. The Specimen Collection Form (SCF) should be completed to document the collection of blood, and the Blood Specimen Results Form (BSR) is completed at the time the lab results are known.

7.4.5 The 12 Month Clinic Follow-up Visit

The only differences between the 12 month follow-up clinic visit and other follow-up clinic visits (not including the end-of-study visit Section 7.4.6) are:

- An interim DMSA scan is to be scheduled and collected. Refer to Chapter 3: Radiology.
- The self administered questionnaires, LIA Questionnaire (LIQ) and DV Questionnaire (DVQ) are administered. Refer to chapter 4: Randomization and Baseline, section 4.5.3.

Participants who have a study endpoint (as determined by the UTI Classification Committee), or who have been determined to be a treatment failure prior to the 12 month follow-visit, will have different scheduling criteria for their repeat DMSA. In this situation, the DCC will provide important information regarding any scheduling of repeat DMSA scans. All other data collection procedures for the 12 month clinic follow-up visit should proceed as documented above.

7.4.5.1 Scheduling the 12 month DMSA

The 12 month DMSA scan, if not scheduled at the clinic on the same day as the 12 month visit, should be scheduled within the 21 day window of the 12 month visit. If the image is done at the clinic, and on the same day, the physical exam and follow-up interview should occur prior to the imaging.

Refer to Chapter 3: Radiology for detailed instructions on study procedures for data collection.

7.4.6.2 Specimen Collection

Blood for local CBC measures will be collected at every follow-up clinic visit as long as the participant remains on study medication. If participant is taken off of study medication, either formally by the PI or by the parent, a CBC should be collected at the clinic visit following the drug discontinuation, but is not necessary at subsequent clinic visits. Specimen collection procedures at the end-of-study clinic visit are similar to collection at baseline,

including urine, blood, and rectal swabs. The only specimen that is only collected one time during the study is the NIDDK Genetics Repository specimen (see section 7.12.4). If the genetics specimen is not collected at the randomization visit, it should be collected at a follow-up visit. It is also expected that most of the participants who were less than 20lbs at baseline will now be over 20 lbs, doubling their blood collection to 10mL total.

For detailed procedures on specimen collection, processing, and shipping, refer to Chapter 5: Specimen Collection.

7.4.7 Telephone Follow-up Contacts

Parents will be scheduled for a telephone interview every 2 months after their child's randomization, between the clinic follow-up visits, until the conclusion of the study. The Study Coordinator will send a reminder postcard to the participant two weeks before the scheduled telephone interview. If that scheduled date and time is not convenient, the Coordinator requests a phone call from the participant to reschedule the telephone interview.

Prior to making the telephone call, the DMS follow-up report should be reviewed. At the prearranged time, the Study Coordinator calls the participant and conducts the interview. During the interview, the Coordinator should ask the parent if they have any information recorded on the patient handbook/diary that is important. The interview consists of administering the Follow-up Contact Form and associated forms (FUP, Section 7.4.4.3) and updating the participant information on the PCF. Refer to Section 7.4.4.3 regarding administration of the FUP and associated forms.

Upon completion of the telephone follow-up contact, the date of the next follow-up contact should be confirmed, and a date for the second following contact should be scheduled.

7.5 Alert Notifications

Clinically significant findings (laboratory, or examination) in a participant during the study follow-up would require reporting on the Adverse Event Form (AEF), regardless of whether this is reported on data collection forms as study data or not. An example would include: laboratory analysis that may be done locally as clinical care, or even because requesting a panel from the lab is more efficient.

In addition, clinical sites have a responsibility to report these finding to a participant's primary care providers. This reporting is handled by each site's Investigator.

7.6 Non-Protocol Sick Child Clinic Telephone Calls and Visits

In the event of inter-current illness involving fever or symptoms related to a urinary tract infection, parents/guardians will be instructed to (1) contact primary care providers and study personnel, (2) have their child evaluated within 24-48 hours, and (3) have a urine specimen obtained to evaluate for the presence of UTI.

Sick child clinic calls and visits that are outside of a patient's target date contact window are not considered protocol follow-up contacts, and do not include the standard follow-up data collection (i.e. FUP). Telephone calls reporting an illness are to be documented on the PCF.

If a sick participant is scheduled and seen in clinic for a sick visit, all the appropriate AEF, MCN and MCA data collection should occur. If the participant is referred elsewhere for medical care, the parent should be instructed to update the participant handbook/diary to document fever and symptoms, the medical care visit, and any new medication prescriptions. The Coordinator should also make arrangements with the parent to follow-up on the event, and to complete the required study data collection and reporting.

Refer to Chapter 9: Participant Safety and Adverse Event Reporting and the AEF QxQ for data collection procedures on adverse events. Refer to Chapter 10: Medical Care Abstraction and Endpoints and the MCN and MCA QxQ's for data collection procedures of a sick medical care visit or a medical care visit reported.

If an on-site sick visit (that is, a sick visit to a RIVUR Study clinic) occurs within a patient's target date contact window, then the Coordinator should try to go ahead and collect the follow-up contact data as specified in section 7.4 of this chapter. This would replace any previously-scheduled protocol contact within that contact window, and prevent the patient's family from having to come back to clinic for a study protocol visit.

7.7 Use of Proxy

During the course of the study, it may be necessary to use a 'proxy' instead of the participant's parent/guardian who typically responds to the study interviews. For example, if the participant's parent or guardian that normally provides the study data becomes extremely ill, incompetent, dies, or is no longer the participant's caregiver or living in the home, rendering them unable to respond to interview questions, a proxy should be used. A "proxy" would be someone who responds on behalf of the participant's parent/guardian who typically has provided the study data. The proxy must be someone very close to the participant, such as a relative, caretaker, or friend, who is in frequent (e.g., daily) direct contact with the participant.

The Participant Contact Form completed at the baseline visit, and updated throughout the study should include proxy (or next of kin) contact information. This contact information may also be helpful when it is difficult to reach the parent or guardian in general.

7.8 Changes in Clinic Follow-up Procedures

The FUP form begins with a short section for documenting contact information related to the specific follow-up contact, and any change in protocol procedures for this contact.

7.8.1 Telephone Contact Replaces Clinic Visit

If a participant and their parent/guardian is unable to attend clinic visits due to severe health problems, geographical relocation, or another reason, but agrees to respond to the RIVUR telephone interview, this information must be indicated on the FUP. This will inform the DCC that follow-up is continuing, but data forms relating to a clinic visit will not be forthcoming for this contact occasion.

The participant should continue to receive his/her study medication every 6 months. If at a later point in time the participant is able to resume clinic visits, record this appropriately on the FUP completed at the clinic visit either by indicating a regularly scheduled clinic visit or a clinic visit replacing a telephone contact.

7.8.2 Clinic Visit Replaces Telephone Contact

Occasionally, it may be appropriate to replace a telephone contact with a clinic visit, for example if a participant has missed a previous clinic visit but is now available for a visit. However, each protocol scheduled clinic visit (6, 12, 18, and 24 months) should still be expected, even if clinic visit occurred two months prior. Drug distribution should still occur on the protocol scheduled clinic visit, dosing should not change for earlier clinic visits.

All scheduled follow-up clinic visits follow the same data collection procedures for the clinic visit in this situation, the usual follow-up clinic visit forms should be administered. Indicate that a clinic visit is replacing the telephone contact on the FUP so the DCC will know what forms are expected for this contact occasion.

7.9 Changes in Participants Follow-up Status

7.9.1 Participant Stops Taking Study Medication

If a participant refuses to continue taking the study medication, or the parent/guardian decides the child will stop taking the study medication, they can and should continue to remain in the study. Study personnel should always try to convince the participant to resume taking study medication, but continue collecting clinic and telephone visit data on participants not taking the study medication. If the parent discontinues study medication without the PI's approval, the child is still considered to have an 'ON STUDY MEDICATION' status recorded in the Study Medication Status section of the FUP. The site will not be responsible for distributing drug in the case where the parent has discontinued medication compliance.

7.9.2 Participant or Parent/Guardian Refuses to Come to Clinic

If a participant and parent/guardian are not willing to come to the clinic then the Coordinator should only conduct telephone follow-up contacts. If the parent/guardian who typically provides interview responses is not willing or unable to continue in telephone contacts then the Coordinator should arrange to contact another family member or caregiver who can supply reliable data. This would need to be a person who has regular contact with the participant and is continually aware of their medical status.

7.9.3 Treatment Failure Participants

Participants who have had a study endpoint assessed by the UTI Classification Committee, or have been categorized as a treatment failure (Chapter 10: Medical Records Abstraction and Endpoints) will follow a different schedule for repeat DMSA imaging. The DCC will provide a report that notifies the Coordinator and Investigator of any endpoint determinations of treatment failure, and will provide instruction on the DMSA scheduling as specified in the protocol.

If treatment failure criteria are met, a rectal swab specimen will be collected at next scheduled clinic follow-up contact.

7.9.4 Participant is Deceased

This is a serious adverse event and data must be collected on an AEF as well as any other study forms that may be required or triggered, (i.e. FDA3500A, SAE, MCN, and MCA).

When the clinical center staff becomes aware that a participant is deceased, an FUP for the next contact occasion should be completed, even if the target window for that contact is not yet open. The type of contact is "missed" with the reason being that the participant is deceased. Adverse event reporting and corresponding medical care forms need to be completed.

Refer to Chapter 9: Participant Safety and Adverse Event Reporting and the AEF QxQ for data collection procedures on adverse events. Refer to Chapter 10: Medical Care Abstraction and Endpoints and the MCN and MCA QxQs for data collection procedures.

7.9.5 Participant has Moved Away

The participant has moved away and the participant and parent/guardian cannot or will not return for follow-up appointments and any scheduled follow-up visits. If the participant has moved close to another RIVUR clinical center area, the participant may be transferred to the other RIVUR clinic. The DCC should be contacted for instructions on how to transfer participant from one center to another. The Transfer of Participant Form (TRN) will be used to formally transfer a participant from one RIVUR clinic to another.

7.9.6 Participant/Parent Dropout

A participant is a dropout if the participant is living, but the child and family are not completing follow-up contacts. Examples of a dropout include a participant whose parent refuses telephone contacts as well as clinic visits, a participant who has moved and cannot be located, or a participant or parent/guardian with a long-term illness preventing their participation in a clinic visit or telephone interview and who has no proxy available.

When participant dropout occurs, Coordinators should determine the willingness of the parent/guardian to work on solutions to overcome barriers to participation. If participant has

dropped out of active treatment and the parent/guardian is absolutely unwilling to return to clinic visits, negotiate continued participation in telephone follow-up assessment and data collection on inter-current illnesses and medical care visits. To the fullest degree possible, Coordinators should document possible UTI events and medical care visits per protocol instructions. If the parent/guardian cannot be converted to continue telephone contact at a minimum, record participant reasons for withdrawal and date of withdrawal on an Informed Consent Tracking Form (ICT).

7.9.7 Participant is Lost to Follow-up

If all efforts to locate a participant and his/her family have failed, then the participant is considered Lost to Follow-up. The Coordinator will record on the RCF whether the participant's vital status is known or unknown, and record the last date of known contact with RIVUR. To the fullest degree possible, Coordinators should document all possible events and medical care visits per protocol instructions. Because parents have already signed a consent form and a medical release form, medical care records should be obtainable as long as the consent has not been rescinded. The Coordinator will continue to complete the FUP and the CMF for each missed contact.

7.9.8 Change in Parent/Guardian During Study Follow-Up

If there has been a change in a participants parent/guardian during the follow-up, or a parent/guardian is unable to communicate clearly during the interview, another family member or proxy may be used during study follow-up provided they can provide accurate data and are willing to assist the parent/guardian (see section 7.7).

7.9.9 Consent is Revoked or Altered

Participation in RIVUR is voluntary. At any time a parent/guardian can decide to change their mind and refuse continued consent. In this event, Coordinators and Investigators should attempt to discuss the reasons behind the parent decision, and try and negotiate levels of participation that can continue. However, if consent is refused, there can be no continued data collection.

7.9.10 Recurrent Event

If participant or parent/guardian is temporarily hospitalized, or otherwise unable to continue follow-up visits because of a recurrent event or other health condition, discuss importance of returning to follow-up after recovery. Conduct weekly follow-up phone calls to determine status of participant.

7.10 Attempted Recovery of Dropouts

When applied systematically, dropout recovery methods have been demonstrated in clinical trials to re-engage participants who have become inactive. While not originally conceptualized in this manner, this approach incorporates the use of good reflective-listening

and directive skills that can elicit barriers to participation from subjects and their family. This information is then used to problem-solve with the parents/guardians about methods to overcome the identified participation barriers. Finally, an essential component of dropout recovery is the application of motivational interviewing methods in an attempt to further elicit and clarify the participant or parent/guardian's reasons for discontinued participation.

The approach to dropout recovery will involve the following steps:

1) contact the participant's parent/guardian
2) identify and discuss reasons for withdrawal
3) negotiate solutions to overcome barriers
4) apply motivational interview methods

If the Coordinator is not successful in re-engaging the parent/guardian, then the principal investigator should initiate contact. Contact by a new member of the staff results in new perspectives and is encouraged in dropout recovery.

7.10.1 Contact the Participant's Parent/Guardian

Attempt to contact the participant's parent/guardian. When a follow-up clinic visit or phone contact has been missed without advance warning, the Study Coordinator should first attempt to make contact directly by phone. If the Coordinator finds the telephone number is no longer correct or operational, then an attempt should be made to contact the proxy for the participant. Proxy contact information will have been previously supplied and updated by the parent/guardian and is documented on the Participant Contact Form (PCF). The proxy may be asked to have the family contact the study staff or to find out whether the participant is still in the area and his/her status. The Study Coordinator may also send a letter by certified mail, asking the family to contact the study staff. Record the results of all attempts to contact the participant either by phone or by mail on the participant's Record of Contact Log (RCF).

Attempt to contact the participant's physician, by letter or by phone, for the participant's current address and/or vital status. Record the result of the attempt to contact the participant's personal physician on the RCF. Other staff in the physician's office, such as the nurse, may also be asked to provide this information.

Other sources to investigate the participant's whereabouts include parent/guardians' employers, internet directories, Social Service agencies, the Department of Motor Vehicles, the Police Department, etc. In each instance record the results of the inquiry on the RCF.

7.10.2 Identify and Discuss Reasons for Missed Contacts

Continued follow-up data collection on all participants is critical for successful completion of the study. Identifying the reasons behind the missed contacts may result in required data documentation (i.e. adverse event reporting), and will also provide the Coordinator with

information to work out solutions that can be negotiated with the parent/guardian to continue the follow-up data collection.

In some cases, discussing the reasons for withdrawal will reveal that the barriers to participation are solvable. It is important to use good reflective-listening and directive skills to elicit barriers to participation from participant. When engaging in reflective-listening, your tone is empathetic, accepting and open.

Here are some general guidelines for reflective-listening:

- Do more listening than talking
- Respond to what is personal rather than to what is impersonal, distant, or abstract.
- Restate and clarify what the other has said, without asking questions or communicating what you, the listener, feels, believes, or wants.
- Try to understand the feelings contained in what the other is saying, not just the facts or ideas.
- Work to develop the best possible sense of the other's frame of reference while avoiding the temptation to respond from your frame of reference.
- Responding with acceptance and empathy, not with indifference, cold objectivity, or fake concern.

7.10.3 Negotiate Solutions to Overcome Barriers

When major barriers to participation involve logistical obstacles, first try to identify alternative strategies that the participant's family may use to overcome these obstacles. If these alternative strategies fall short or are not available, then offer reasonable logistical assistance provided by study resources. For example, we already mentioned that if a patient's parent/guardian absolutely refuses to come back to clinic, Coordinators can offer to continue follow-up over the phone.

7.10.4 Apply Motivational Interview Techniques

Motivational interviewing can help patients identify and change behaviors that may be preventing them from optimal management of a particular condition. Coordinators can use motivational interviewing techniques to encourage participant's parent/guardian's to reconsider their decision to withdraw, and explore possible compromises. As with reflective-listening, your tone should be empathetic and non-judgmental. However, with this approach you actively help the participant steer themselves toward a compromise or common goal.

Here are some general guidelines for Motivational Interviewing:

- Express empathy – convey an informed understanding of the other person's predicament

- Avoid argument – arguments only cause the other person to become defensive
- Support self-efficacy – encouraging and reinforcing the other person to say self-affirming statements can help the him/her believe in his/her ability to make a change
- Roll with resistance – instead of falling into the argument trap, find ways redirect and build on the other person's negative statements. Questioning, asking for clarification, elaborating on a point, or humor are all good ways to roll with statements of resistance.

7.11 Locating Difficult-to-Follow Participants

If the initial call to the number provided by the participant at last contact is unsuccessful, the first telephone tracing step is to contact Directory Assistance in an attempt to verify the address provided and to obtain a new telephone listing. If the address is verified and the phone number is unlisted, send a letter to the participant requesting that the participant telephone the Study Coordinator. If attempts to obtain a listing or verify the address are unsuccessful, secondary sources will be used. Identifying the order of tracing sources for all cases is difficult, though the typical tracing will follow the procedures described below.

The first step is to obtain from the participant's record the contact person (proxy) listed by the participant at enrollment and during follow-up contacts. A Proxy is contacted to determine if they can provide the current address or telephone number of the participant. If successful, the Study Coordinator enters the updated location information on the PCF and attempts to contact the participant.

If this is not successful, depending on the participant's last residence, a decision is made whether to consult the city directory information or to contact the local post office. If the address is rural, the postmaster is called, since, in rural areas, the postal carrier or postmaster typically knows individuals in their service area. Since address corrections should have been obtained from the mailing of the advance letter, calls are not made to urban post offices.

7.11.1 Hard-to-reach participant form

If a participant has missed two consecutive visits the study coordinator should mail the parent/guardian the RIVUR follow-up form (RFF). This form is designed to capture information regarding medical care and compliance. This form should be mailed to the parent/guardian after a participant has missed two consecutive visits. The Study Coordinator should attempt to contact the parent/guardian at least twice during the morning, twice during the afternoon, twice at night and at least once on the weekend before deeming the visit as a missed visit.

7.12 Participant Exit from the Study

7.12.1 Overview

Follow-up procedures continue until study contact occasion 13 (the 24-month clinic visit), regardless of medication compliance or classification of treatment failure. The final (exit)

study contact should take place at a clinic visit if possible. It is similar to a regularly scheduled follow-up clinic visit, with the exception that study drug is not dispensed. If the participant has been on telephone-contact-only, special efforts should be made to get the participant in for this last clinic visit. If the participant is a dropout but his/her location is known, a final effort should be made to have the participant come in for this exit clinic visit or complete a phone follow-up to capture events that may have occurred since the last study contact.

Table 7.4 Summary of Data Collection During the Exit Visit

Forms Collected During Exit Visit:

- Physical Exam Form (PEF)
- Concomitant Medication Listing/Coding Form (CMF)
- LIA (Life Impact Assessment) Questionnaire (LIQ)
- Dysfunctional Voiding Questionnaire (DVQ) – if toilet trained
- DES Treatment Form (DTF), if DVQ score ≥6 for females or ≥9 for males
- Medication Return Form (MRF)
- Participant Exit Form (EXF)

Specimen Collection forms for Exit Visit:

- Specimen Collection Form (SCF)
- Participant Contact Form (PCF) *****
- Biospecimen Repository Shipping Log (NIDDK-USL) *****
- Rectal Specimen Shipping Log (RSL) * †
- Central Blood Lab Shipping Log (CSL) *****
- Blood Specimen Results Form (BSR)
- Urine Specimen Results Form (USR)

Radiology forms for Exit Visit

- DMSA Sedation Form (DSF) †
- DMSA Imaging Inventory and Shipping Log (DSS) †
- VCUG Sedation Form (VSF)
- VCUG / Ultrasound Inventory and Shipping Log (VUS)

***** Not data entered

† Not required for participants already classified as treatment failure

7.12.2 Completeness of Exit Visit

Every RIVUR participant should have a final exit visit. Concerted effort should be made to obtain the required clinic data on those participants who are on telephone-contact only, and participants who have dropped out of the study. Without complete assessment of study endpoints, the scientific validity of the entire study may be compromised.

7.12.3 Exit Radiology Procedures

All participants are required to have exit VCUG. An exit DMSA scan is also required for

participants who have *not* been classified as treatment failure. All exit radiology procedures should be performed within 10 days of the final exit visit. For participants completing the full study, coordinators should schedule exit procedures at the time of the 22-month telephone contact (contact occasion 12).

7.12.4 Exit Visit Specimen Collection

Specimen collection at the exit visit is similar to the randomization specimen collection (see Baseline Specimen Collection Scheme laminated MOP insert). In patients who have already been classified as treatment failure, blood for CBC is not required. Rectal swab is required for participants classified as treatment failures.

7.12.4 Recognition of Participant in the Study

At the final Exit Contact the participant will be given a certificate of appreciation or a commemorative for his or her commitment gift to the RIVUR study. If the Exit Contact is completed by telephone, the certificate is to be mailed to the participant.

Appendix 7.1 Exit Visit Checklist of Procedures and Forms

Exit Visit Forms Checklist

Task / Procedure		Associated Forms
Data to be collected at any time during the visit	Participant Contact Form	PCF (paper only)
	Protocol Scheduled Follow-Up Form	FUP
	Physical Exam Form	PEF
	LIA Questionnaire	LIQ
	DV Questionnaire (if toilet-trained)	DVQ/DTF
	Concomitant Medications	CMF
	Exit Form	EXF
Study Medication	Collect used and unused study medication bottles	MRF
Specimen Collection (see reverse)	Urine Collection	SCF, USR, BSR, RSL, CSL, NIDDK-USL, NIDDK-BSL
	Peri-rectal Swab Collection	
	Blood Collection (exit blood collection may be collected at the exit DMSA)	
Exit Imaging	Exit DMSA scan (performed within 4 weeks of exit visit if permitted; treatment failures may already have had exit DMSA)	DSF, DSS
	Exit VCUG scan shipping	VUS, VSF

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Appendix 7.2 Exit Visit Specimen Collection Scheme

RMuR
Randomized Intervention for Children with Vesicoureteral Reflux

END OF STUDY Specimen Collection Scheme

Urine Collection - Collect at END OF STUDY visit

A. **Dipstick** to screen for leukocyte esterase
If trace or positive, send urine for culture.

B. Order local **microalbumin** & **creatinine** on collected urine using the volume required by local lab

C. Send collected urine (1-10 ml) in orange-top cup, unfrozen
⇨ Ship to **Biosample Repository** (U label)

Peri-rectal Swab* - Collect at END OF STUDY visit

⇨ Ship to **Central Lab in Pittsburgh, PA** (R label)
(If shipping delayed for more than 20 minutes, then refrigerate prior to shipping)

* If off study medication for > 6 months, then swab is not required, however it is required for Treatment Failures

Blood Collection - Collect at END OF STUDY visit

1) 

0.5ml in purple EDTA tube for **CBC**† ⇨ Send to **Local Lab** (no pre-printed label)

† If Treatment Failure or off study medication for > 6 months, then CBC is not required

2) 

1.5ml in yellow SS tube, aliquot serum

Priority 1: 0.5ml for **Cystatin C, Creatinine and C Reactive Protein**
⇨ Batched & FROZEN at -70 , ship every 3 months to
Central Blood Lab in Rochester, NY (C label)

Priority 2 (collect if enough in *this* SS tube): 0.1ml serum for **Electrolytes**
⇨ Send to **Local Lab** (no pre-printed label)

3) 

*Collect **ONLY** from kids >20lb*
4.0ml in yellow SS tube ⇨ ***Spin*** and Ship unfrozen (with frozen gel pack) to
Biosample Repository (S label)

NOTE: If ACD tube(s) for Genetics Repository not previously collected, then collect at exit visit.

Central Swab Lab in Pittsburgh: Karen.Barbadora@chp.edu
Central Blood Lab in Rochester: paula_maier@urmc.rochester.edu
Genetics Repository: Dana Witt witt@biology.rutgers.edu
Biosample Repository: BIO-NIDDKRepository@thermofisher.com
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Chapter 8: Compliance

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Chapter 8: Compliance

8.1 Overview Adherence and Compliance

Ensuring adherence to the RIVUR study protocol and to the study medication may be a challenge for the clinic staff, requiring as much or more effort than that put into recruitment. Enrollment is only the beginning. Once patients are enrolled in the study, participant compliance to study protocol is crucial to the study's success.

The power of the study to show an effect of treatment (if one exists) is contingent upon the participants taking their prescribed study medication according to protocol. To ensure that the resources spent and the efforts of the Project Coordinators (PC) are not wasted, it is necessary to put an effort toward minimizing non-compliance. Compliance will be monitored throughout the trial. Adherence to study protocol and follow-up procedures will be examined through data reports and monitoring visits. Participant compliance with taking study medication will be assessed by weighing returned medication bottles, and by using data from participant diaries and interviews collected at the scheduled follow-up contacts.

8.2 Follow-up Visits and Telephone Contacts

Reports describing adherence to the study contact schedule as well as to the study medication, clinic-specific and overall, will be distributed to the Principal Investigators (PIs), Project Coordinators, Operations Committee, Executive Committee, and the Data and Safety Monitoring Board.

Steps will be taken within the trial to assist a clinic with lagging performance. Reasons for missed visits and telephone calls should be noted on the Record of Contacts Form (REC) at each site. This information will be important in assessing adherence to protocol during clinic monitoring visits.

Each contact is to be scheduled within 10 days of the target date for that contact, and all attempts should be made to complete a contact within the protocol specified 20-day window. However, to avoid missing data altogether, a contact can be conducted outside of this window, provided that it does not fall too close to next regularly scheduled contact. For a detailed discussion of visit scheduling, refer to MOP Chapter 7: Follow-up Contacts.

8.3 Medication Compliance

Parents will be reminded about the importance of daily administration of study medication at each scheduled telephone contact and every 6 months at routine follow-up visits. Participant follow-up visit reports will be available on the study DMS to assist the PCs prior to their patient contacts. Regarding compliance, this report will summarize the status of the participant's medication use, indicate the dose and number of bottles given to the parent/guardian at the last clinic visit, and provide information about the

participant's previous compliance. Monthly management reports will provide overall compliance rates for each clinical center.

Encouraging non-compliant participants to take their study medication should be a team effort. Project Coordinators should encourage non-compliant participants to improve their compliance by reminding them of the instructions regarding dose and administration. If a consistent pattern of non-adherence develops, the coordinator should alert the study physician, who should then also use this information at a future clinic visit to discuss the reasons for non-compliance.

Specific information on data collection related to medication distribution and return are detailed in Chapter 6: Medication Distribution.

8.3.1 Weighing Medication Bottles

Every 6 months at each clinic visit, the parent/guardian will bring in all medication bottles dispensed during or since the previous clinic visit. The Project Coordinator will record the number of bottles, and the weight of each bottle on the Medication Dispensing and Dosing Form (MDD). Coordinators can use the DMS follow-up visit report to verify that the number of bottles returned is correct.

All returned bottles; including bottles containing study medication will be retained by the Project Coordinator, and will be handled according to directions provided by the Data Coordinating Center (DCC).

Specific instructions on weighing medication bottles and recording the data needed for measuring medication compliance are detailed in Chapter 6: Medication Distribution.

8.3.2 Participant Self Report

Another measure of medication compliance will be based on participant self report. During each participant contact, telephone or visits, the PC will review the participant diary with the parent/guardian and then ask the set of self report compliance questions on the protocol specified Follow-Up Form (FUP)

8.4 Setting the Scene for Good Adherence and Compliance

Setting the stage for good adherence and compliance can be facilitated in a number of ways:

- Discussion of the Informed consent
- Clinic atmosphere and staff attitude
- Discussing perceptions of personal benefit
- Having the endorsement of others

8.4.1 Discussion of the Informed Consent

Much of the potential for poor compliance can be negated from the start by excellent explanations of the role of the participants and their families in meeting the goals of the study. The explanation should be simple enough to be understood and remembered, and not so detailed that it is overwhelming and alienating.

The participant handbook outlining the phases of the study and the procedures involved with other important information such as phone numbers, contact persons and even transportation and parking information will be very helpful. All written and printed materials, however, should be an adjunct to friendly face-to-face communication, where the parents/guardian and participant are encouraged to ask questions.

If the parent/guardian does not ask questions and seems to be too willing to enroll without adequate thought, the Coordinator/Investigator should review a list of basic information. Such a list would cover the length of commitment to the study, the requirements to take medication, the fact that some patients will get active medication and some will get placebo, the requirement to have the study images performed, and the assurance that their response to medication will be monitored regularly.

When parents/guardians give consent for their child to participate in a research study, those that are truly informed will be the best compliers.

8.4.2 Clinic Atmosphere and Staff Attitude

The clinic should be a pleasant place for the participants and their family to come to. The staff should have a warm, welcoming and supportive attitude. Even if the physical setting is a standard out-patient clinic, the participants and their families should have a very positive experience when they come for their RIVUR study visits. Never forget that they are volunteers. Waiting should be minimal and staff should greet each participant in a personal manner and develop a relationship with each one. At each visit the participant and their family should be told sincerely how much the staff values their participation and how important they are to this research effort.

8.4.3 Discussing Perceptions of Personal Benefit

Most study participants enter a study because they perceive some personal benefits to be gained. These should be emphasized; they include:

- Close medical surveillance
- Benefits of study medication (both active and placebo)
- Standard testing providing information about VUR
- Status of being an important part of a study to advance medical knowledge

8.4.4 Having the Endorsement of Others

Consensual validation of the study by other health care professionals may be a key feature both in recruitment and in adherence. Clinical trial literature has more than one example of studies that have been virtually derailed due to opposition voiced in the media or by health care providers. Without know the rationale for the trial, RIVUR may appear

as a controversial study. It is always good policy to inform your medical colleagues in the target community of the rationale and goals of the study, and ask them to endorse it.

8.5 Maintaining Good Adherence and Compliance

There are also many approaches to maintaining good adherence and compliance, including:

- Providing Regular feedback
- Memory "joggers"
- Convenience
- Attention Side Effects and Adverse Events
- Attention to Concomitant illness or treatments

8.5.1 Providing Regular Feedback

Feedback is an effective reinforcer. Parents/guardians and participants should be given regular feedback on their progress related to medication adherence and on the progress of the study in general. Emphasize the important role each person is playing in the success of the study and praise them for their commitment. Other things to consider are a study newsletter, birthday cards or other holiday cards maintaining contact even outside regular protocol contacts.

8.5.2 Memory

In order to be compliant, parents/guardians have to remember what to do. Most of them will appreciate memory "joggers" whether they have poor memories or simply very busy lives. Some suggested techniques are:

- give all instructions in writing as well as verbally
- use reminder postcards or telephone calls prior to clinic visits
- use appointment cards with important information on the reverse (for example, contact person and phone numbers in case of adverse events, reminders of procedures)

8.5.3 Convenience

The ease of traveling to the clinic can affect visit adherence. Illness, disability, bad weather, parking difficulties, expense or inconvenience of public transportation, home/social problems can all cause cancellations and no-shows. A cancellation or no-show should flag a participant as someone who needs extra support to adhere to the visit schedule.

The families should not feel judged or censured for missing a visit. Staff should contact the parent/guardian immediately and be very supportive in finding a way to complete the visit. There should be a simple assumption that the visit will be made-up, and practical assistance provided to ensure adherence.

8.5.4 Attention to Side Effects Adverse Events

Perceived or actual adverse events of the study medication may be a reason for drop-out from the study. Most reported side-effects occur early in the study (within the first 6-8 weeks). Staff must show that they take every report very seriously, however unlikely it is to be related to the medication, so that the families feel that their concerns are being recorded and acted on. Conversely, unless there is good reason to take action, complaints of minor problems should be dealt with in a practical and supportive manner and the parent/guardian should be told to continue their child on study medication. If the medication has been stopped, it should be resumed as soon as possible. Consider having clinic staff telephoning, or asking the parent/guardian to telephone within the week to check on the progress of symptom(s) and to check on compliance. For more information, refer to MOP Chapter 9: Participant Safety, Side Effects and Adverse Event Reporting.

8.5.5 Attention to Concomitant Illness or Treatments

In a study of this length, many participants will have an illness at some time, even if only a cold, which will cause them (perhaps even their physicians) to want to stop the study medication while the child is being treated. Staff should emphasize the importance of reporting all illnesses to the clinic staff and the importance to the study of not stopping medication unilaterally.

The study investigator must be available at all times to talk to the participant's primary care (or other) physician about the composition of the study medication and its physiological impact.

8.6 Undue Pressure to Comply

Although staff is expected to initiate measures to prevent and combat poor adherence, they must be sensitive to the potential for crossing the line and exerting undue pressure on the participants and their family. Participants are volunteers who are free to quite at any time and their adherence must be voluntary, not forced. At each clinic there will be a few "difficult" participants who will test your skills, patience and good humor; the challenge is to have them remain in the study because they want to, not because they were persuade against their will to remain.

Any individual staff person who is having problems with a parent/guardian and child or who feels that a personality conflict has developed, should initiate discussion among the center's study staff to receive input on developing a resolution. Recognizing when, in spite of your best efforts, you do not have the answer to the problem is a sign of experience and professionalism.

Chapter 9: Participant Safety and Adverse Events

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Chapter 9: Participant Safety and Adverse Events

9.1 Participant Safety

Participant safety always takes priority over all else. The International Conference on Harmonization's general principles of Good Clinical Practice will be followed. These principles dictate, first and foremost, that we have weighed and will continue throughout the study to weigh the anticipated benefits versus the foreseeable risks to all participants. Participants will be fully informed of these risks before they are enrolled. The study's leadership will continually review the medical literature to determine any new findings that might substantially affect the study's rationale or justification, and for new or previously unforeseen risks that must be conveyed to participants. Any significant new findings will be reported to the Data and Safety Monitoring Board (DSMB) and the NIDDK Project Officer in a timely manner.

A Data and Safety Monitoring Board (DSMB) has been established by the NIDDK to provide appropriate oversight and monitoring of the conduct of the trial and to ensure the safety of participants and the validity and integrity of the data. The DSMB's monitoring functions and oversight of such activities are distinct from the requirements for study review and approval by an Institutional Review Board (IRB).

Responsibility for monitoring patient safety during the study is shared by each clinical center's IRB, the study's Data and Safety Monitoring Board (DSMB), and the FDA. In order to ensure appropriate monitoring can occur, clinics are responsible for following informed consent procedures, taking measures to ensure participant confidentiality, adhering to HIPAA regulations, and closely monitoring and reporting adverse events. Timely reporting of all untoward events occurring during the study is the only way to ensure that these groups can conduct appropriate monitoring of patient and study safety. Study procedures for monitoring and reporting of events are detailed below. Study monitoring of compliance to these procedures is described in the Quality Assurance and Quality Control Chapter 12 of the RIVUR MOP.

9.2 Monitoring Events at the Clinical Sites

Data collection of side effects and adverse events allows appropriate safety monitoring of subjects. In RIVUR, in addition to safety monitoring, data collection on adverse events is necessary for endpoint ascertainment. For both of these reasons, complete, accurate, and timely information is crucial. Detecting and reporting a serious adverse event is the responsibility of the Principal Investigator, although the actual data collection and reporting is often delegated to the site's Project Coordinator.

During the informed consent process, the parent or guardian will have been asked to report all fevers and illnesses to the clinic. Appropriate contact information will be provided. A patient handbook containing a record diary will be provided to allow simple recording of fevers, illnesses, and new concomitant medications, to insure good recall at follow-up contacts.

At each follow-up telephone and clinic visits, parents will be asked to report on all untoward medical occurrences since the last study contact. Data collection on side effects and adverse events monitoring is triggered by the question "Has your child had any health problems since the last study contact?" on the Protocol-Scheduled Follow-Up form (FUP). Additional questions querying about any medical care visits, or newly prescribed medications all provide mechanisms for monitoring of side effects and adverse events.

The study will collect information on all reported side effects and adverse events, medical care visits, emergency room (ER) visits, hospitalizations, and deaths.

9.3 Definitions related to Adverse Experiences

9.3.1 Adverse Events

An **adverse experience or adverse event** (AE) is **any** untoward medical occurrence in a patient or a clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. This includes any untoward signs or symptoms experienced by the patient or subject from the time of first administration of study medication.
Adverse events may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the patient or subject and/or observed by the physician or medical staff.
- Laboratory abnormalities of clinical significance.

Disease signs, symptoms and/or laboratory abnormalities already existing prior to the use of the product are not considered adverse experiences unless they re-occur after the patient has recovered from the pre-existing condition, or represent an exacerbation in intensity or frequency.

9.3.2 Serious Adverse Events

A **serious adverse experience or adverse event (SAE)** is any adverse event that results in any of the following outcomes:

- Death
- A life-threatening experience
- Inpatient hospitalization or prolongation of existing hospitalization
- An ER visit
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The distinction between an adverse event and a serious adverse event is based on the definition for serious adverse events, and not on the severity of an event, i.e. serious vomiting

is not considered a serious adverse event except if it requires hospitalization. Adverse events are reported regardless of the supposed relationship to study medication.

9.3.3 What Adverse Events are RIVUR Reportable Events

1) **All** serious adverse events regardless of any relationship to study drug are reportable.

2) Non-serious adverse events that are:
   - Known study medication side effects
   - Considered potential study medication side effects
   - Other events/experiences that were not expected in a patient on prophylaxis antibiotics (regardless of medication compliance)

Some sites IRB's may require IRB reporting of other adverse events or experiences that do not fit the description above. This additional reporting would be the site's responsibility (as are all IRB reporting), and not part of study data collection.

9.3.4 FDA Adverse Event Definition for IND reporting

The code of federal regulations (21CFR312.32) offers the following definitions for IND safety reporting: Any adverse experience **associated with the use of the drug** that is both **serious and unexpected**. These events are a subset of the RIVUR reportable events described below.

A **serious adverse drug experience** is defined as "Any adverse drug experience occurring at any dose that results in any of the following outcomes:
- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- An ER visit
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect.

Associated with the use of the drug is defined as "there is a reasonable possibility that the experience may have been caused by the drug."

A **life-threatening adverse drug experience** is defined as "any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death."

An **unexpected adverse drug experience** is defined as "any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. Unexpected refers to an adverse drug reaction that has not been previously observed.

9.4 Adverse Event Data Collection

There are two study forms required for adverse event reporting from the clinical sites, the Adverse Events Form (AEF) and the FDA-required Medwatch Form 3500A. The AEF is used to report both adverse events and adverse drug events. The Medwatch 3500A is the data collection form used to report an adverse drug experience to the FDA.

9.4.1 The Adverse Events Data Collection Form (AEF)

All RIVUR adverse events are recorded onto the AEF form. One AEF is completed for each individual diagnosis or complaint. The AEF form is designed to collect both non-serious and serious adverse events data, including adverse drug experiences. In addition to documenting all reported adverse events, the AEF form includes a very short interview administered to the parent/guardian regarding the illness.

The AEF form is triggered by responses to questions on the Protocol Scheduled Follow-up Form (FUP), as well as questions on the Medical Care Notification Form (MCN). Conversely, the AEF form has a question that could trigger the need to collect an MCN form.

Not every AEF will have an associated MCN form, if no medical care was sought for the event. Nor will every MCN form have an associated AEF, as some medical care visits may be associated with a well-child routine physical exam, or other reasons that are not adverse experiences.

9.4.1.1 MCID Number on the AEF

When there is an association between an AEF and MCN form, the linkage between adverse events and endpoint forms is critical to study data management. This link is done through the Medical Care ID Number, or MCID#. The MCID is assigned and associated with each medical care visit, not necessarily each adverse event. This is an important distinction to understand. Each adverse event corresponding with a medical care visit (this is the first medical care visit associated with the event), must have the MCID number associated with that first medical are visit recorded on the AEF in the space provided. The process of assigning MCID #'s is described in detail in Chapter 10: Medical Care Abstraction and Endpoints.

It is possible that there are multiple symptoms that define a single adverse event. The AEF is a multi-line form which enables the user to record multiple symptoms within one adverse event on the same data collection form. See Chapter 14 Data Management to review data entry for a multi-line form. When multiple symptoms occur for one event, the MCID recorded on each of the lines within the AEF form will match to the MCN/MCA associated with the medical care received for the event. There will not be multiple MCNs associated with any one AEF since the link is only to the first medical care visit related to an event.

9.4.1.2 Adverse Event Coding

Coding of adverse events is done at the time of data entry on the AEF. During data entry of the AEF form, item 2a is the parent reported event or symptoms. The following field in the DMS includes a feature that provides a search and lookup table of COSTART coding terms. This feature has been added to make the process very user friendly for the sites. Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART), is a terminology developed and used by the Food and Drug Administration (FDA) for the coding, filing and retrieving post marketing adverse reaction reports. COSTART contains unique code-able events that provide a variation in vocabulary commonly used by those who submit adverse event reports. A listing of all COSTART code-able terms is provided in Appendix 4 of this manual.

9.4.2 Adverse Drug Reaction Report - FDA Medwatch Form 3500A

The FDA required reporting form is the Medwatch 3500A. Detailed instructions written by the FDA on how to complete the Medwatch Form are included as the QxQ's for this form.

9.5 Reporting Processes for Adverse Events

9.5.1 IND Reporting of Serious Adverse Events

Appropriate monitoring of patient and study safety can only be made with timely reporting of all untoward events occurring during the study. Any adverse experience **associated with the use of the RIVUR study drug** that is both serious **and** unexpected must be reported immediately to the Data Coordinating Center DCC, within one working day of identifying the SAE. Notification includes an email to the DCC (Barbara Brown email address uccbwb@mail.cscc.unc.edu) with the subject heading "SAE – ID# CO# and SEQ#" where ID# is the subject ID, CO# is the contact occasion number and SEQ# is the sequence number associated with the event. The email should indicate a brief description or diagnosis of the event. A faxed copy of FDA Form 3500A should follow. An acknowledgement from the DCC will be provided within one working day of receipt. If acknowledgement is not received, contact the DCC by phone. In addition, all AEF forms associated with an IND reportable event should be completed and data entered within the reporting deadlines of the IND, 1 working day.

Within two working days of receipt at the DCC of FDA form 3500A, a letter revealing the participant's study medication assignment will be attached, and the reporting packet (FDA Form 3500A plus unmasking letter) will be submitted to Dr. Marva Moxey-Mims at NIDDK. As the IND sponsor, Dr. Moxey-Mims will decide whether to forward the information to the FDA (through submitting an IND safety report), the RIVUR DSMB, and all study Investigators.

Although the FDA and DSMB will be notified of the study drug assignment, study investigators will **not** be unblinded to the study medication assignment. NIDDK and/or the DSMB will have three working days to contact the DCC staff with any recommendations. These recommendations will be acted upon by the DCC the same or next working day.

The timetable for reporting experiences that will be submitted to the FDA is as follows:

- As soon as possible and within at most one working day of identifying a possible serious adverse event, the Principal Investigator will submit an FDA Form 3500A to the DCC by fax, and complete the data entry of the corresponding AEF forms (with email notification of fax).
- Upon receipt of faxed form, DCC will send acknowledgement to the form originator.
- Within two working days of receipt of the faxed form, the DCC will submit an SAE packet to the NIDDK IND sponsor.
- As soon as possible and within 7 calendar days after the IND Sponsor's initial receipt of information regarding unexpected fatal or life-threatening adverse experience associated with the use of the study drug, the Sponsor will submit a telephone or fax notification to the FDA, RIVUR DSMB, and study investigators.
- As soon as possible and within 15 calendar days after the IND Sponsor's initial receipt of information regarding any adverse experience associated with the study medication that is both serious and unexpected, the Sponsor will submit a written IND safety report to the FDA, RIVUR DSMB, and study investigators.
- NIDDK and the RIVUR DSMB will have 3 working days to notify the DCC with any recommendations. These recommendations will be acted upon at the DCC by the next working day following receipt.

9.5.2 Other Adverse Event Reporting to the DCC

All other adverse event reporting needs of the clinical sites (not falling under the IND reporting requirements) are completed by the prompt data entry of the AEF form into the study DMS. All AEF forms (not associated with an IND report) should have data entry completed within 5 working days upon hearing of an event. AEF forms associated with an IND report are to be data entered within 1 working days of having the knowledge that an event occurred.

9.5.3 Reporting to Site IRBs

Each clinical site is responsible for any IRB or regulatory reporting of adverse events as required by their institution. Notification of SAEs reported by other sites falling under an IND report, will be acted on by the IND Sponsor as required by NIDDK, or by the DCC based on a DSMB recommendation.

9.5.4 Reporting to Data and Safety Monitoring Board

In addition to the serious adverse event reporting based on a required IND report, the DCC will provide aggregate reporting of safety data and adverse events to the independent Data Safety Monitoring Board (DSMB) according to the guidelines and schedule established by that group.

9.6 Management of Medication Side Effects

9.6.1 Common Side Effects

Medication side effects will have been reported on an AEF. Per protocol, patients, who develop common side effects of the study drug, will have the study medication discontinued temporarily for 24-48 hours or until after the side effects resolve. If the same side effect recurs within 24-72 hours of restarting the medication, and is unacceptable to the treating physician, patient, or parents, study medication will be discontinued at the discretion of the Study Investigator. Common side effects include nausea, vomiting, or diarrhea, mild rash and/or urticaria, and headache. Refer to the Protocol Appendix A, Sulfamethoxazole and Trimethoprim Oral Suspension package insert for more detailed listing of potential side effects and adverse reactions.

Any prescribed discontinuation of study medication from the Study Investigator, temporary or permanent, requires that the Drug Discontinuation Form (DDF) be completed, see Section 9.6.3.

Medication discontinuations decided upon by parents/guardians, or other non study physicians are considered non-compliance until the Study Investigator makes a determination for study discontinuation.

9.6.2 Serious Side Effects

Medication side effects will have been reported on the AEF. Patients who develop serious side effects, i.e. Stevens-Johnson Syndrome, toxic epidermal necrolysis or blood dyscrasias, will be taken off study medication and offered an alternative long-term antimicrobial prophylaxis as part of routine clinical care. Refer to the Protocol Appendix A, Sulfamethoxazole and Trimethoprim Oral Suspension package insert for more detailed listing of potential side effects and adverse reactions.

Any prescribed discontinuation of study medication from the Study Investigator, temporary or permanent, requires that the Drug Discontinuation Form (DDF) be completed, see Section 9.6.3.

9.6.3 Drug Discontinuation Form

The Drug Distribution Form (DDF) is to be completed for any Study Investigator prescribed study medication discontinuation temporary or permanent. Refer to the DDF QxQ for item specific instructions related to the form.

9.7 Unmasking Policy

Given the expectation that there will be low occurrences of serious side effects associated with the use of study medications, unmasking should rarely be required. Therefore, the first action to take if suspected symptoms are related to study medication will be to temporarily discontinue drug. Investigators should later attempt to reinstitute the study medication in

participants who discontinue it. It is expected that study investigators will be aware of and adhere to this principle.

However, private physicians and emergency room physicians will not be aware of the nature of the study and may require some explanation if an adverse event occurs. The principal investigator of the clinical center should always be contacted when requests for unmasking are made. Frequently, a conversation with the physician managing the adverse event will help avoid the perceived need for unmasking.

Chapter 10: Medical Care Abstraction and Endpoints

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Chapter 10: Medical Care Abstraction and Endpoints

10.1 Overview

The primary endpoint to evaluate treatment efficacy is recurrence of febrile or symptomatic urinary tract infections ($_{F/S}$UTI). The proportion of participants who have at least one such recurrent $_{F/S}$UTI will serve as the primary analysis variable. Efficacy with respect to UTI will also be assessed based on analysis of time to recurrent $_{F/S}$UTI.

Renal scarring is a secondary outcome measure. The proportion of participants who have any renal scars assessed on the outcome DMSA scan will serve as the principal analysis variable for scarring. The proportion with *severe* scarring will also be evaluated. Treatment failures and the development of antimicrobial resistance will also be measured as secondary outcomes. Data collection procedures related to renal scarring is described in Chapter 3: Radiology.

This Chapter will focus primarily on data collection and procedures related to data collection and subsequent assessments of recurrent UTIs. Chapter 3: Radiology provides data collection and adjudication procedures related to radiographic images at baseline, 12 months, and end of study. The occurrence of recurrent UTIs in RIVUR participants may require the scheduling and collecting of additional DMSA scans during the study. The process of determining the need for additional DMSAs is covered at the end of this chapter.

10.2 Definition of UTI Primary Endpoint

The definition of recurrent $_{F/S}$UTI (the RIVUR primary study endpoint) requires the presence of:

1. Fever or urinary tract symptoms, and …
2. Pyuria based on urinalysis, and …
3. A culture-proven infection with a single organism

A UTI will be defined as recurrent only if its onset occurs more than 2 weeks from the last day of appropriate treatment for the preceding UTI or following a negative urine culture, or it is an infection with a new organism.

Suspected recurrent UTI events will be reviewed and adjudicated by the UTI Classification Committee (UCC) to determine if they meet the RIVUR criteria for a primary endpoint.

It is important to note that if a potential endpoint is determined not to meet the pre-specified criteria for an $_{F/S}$UTI event, it does not mean that the event did not occur. Rather, it means the event did not meet the RIVUR criteria for a study endpoint.

10.3 Data Collection Forms required for assessing a UTI Endpoint

The following data collection forms are required to document a potential UTI endpoint:

Medical Care Notification form (MCN)
Medical Care Abstraction Form (MCA)
Urine Specimen Results Form (USR)

In addition to providing the data and information about potential UTI events on the required data collection forms (MCN, MCA, USR), sites may need to provide additional essential source documents needed in the endpoints review process.

10.4 Clinical Site Procedures for Data Collection

Each site contributes to the endpoint classification process by promptly identifying and reporting any potential study endpoints. The process begins with the data collection at the clinical sites.

10.4.1 Identification of Potential UTIs

In order to assure that the study captures every potential endpoint. Data are expected on **all** participant medical care visits where the child had urine collected for analysis **OR** received medical care for symptoms that include fever, rash, abdominal or flank pain, diarrhea or loose stools, urinary urgency, painful urination, foul-smelling urine, or for children less than 4 months old, failure to thrive, dehydration, or hypothermia. A medical visit includes any doctor visit, clinic visit, ER visit, or hospital admission. This includes sick visits made to a RIVUR clinic at a non-protocol scheduled follow-up visit, as well as a protocol scheduled follow-up clinic visit when the Investigator suspects there are symptoms to indicate the participant is sick.

Parents/guardians will be asked to document all medical care visits the participant makes in the participant handbook/diary. They will also be asked to call and report any illnesses. These calls (if received) will be recorded onto the Participant Records of Contact Log (RCL) and will trigger the documentation process prior to recording on data collection forms.

Coordinators must collect sick visit data from wherever the participant sought care. Some sick visits may occur at the RIVUR clinics, so sick visit data will be readily available. Other sick visits will occur at non-study clinics, ERs, or hospitals. In these cases, Coordinators will have to collect data on the reported visits from the participant's primary care physician or other provider. For most participants, a combination of both will be required to capture all non-study medical care throughout the trial.

In addition to calls from parents/guardians reporting illnesses, the Protocol Scheduled Follow-up Form (FUP) includes questions that trigger the need for endpoints data collection including 'Has your child visited a doctor?' Other data collection, such as a change in concomitant medication use also provides a flag to the coordinator that a medical care visit occurred. A review of the participant handbook/diary will also allow recall of previous care visits since the last contact.

All medical care visits, including a doctor visit for an expected well child visit or physical exam where urine was collected or symptoms related to UTI were documented, will require some data collection on an MCN and MCA form in order for the UTI Classification Committee to determine whether or not a study endpoint has occurred.

10.4.2 Medical Care Notification Form (MCN)

The MCN form is based on an interview with the parents, and begins the official process of data collection for UTI endpoints. This form is used to document all medical care visits, including protocol scheduled follow-up visits where the child is noted to be ill or the clinic provides non-study sick child care (beyond standard follow-up data collection). One form should be collected for **every** medical visit where the child had urine collected for analysis **OR** received medical care for symptoms that include fever, rash, abdominal or flank pain, diarrhea or loose stools, urinary urgency, painful urination, foul-smelling urine, or for children less than 4 months old, failure to thrive, dehydration, or hypothermia.. A separate MCN form is completed for each subsequent visit (follow-up visit) on the same event. If a participant is hospitalized, and during the hospitalization is transferred to a second hospital, the second hospitalization should be treated as a separate medical visit. There are questions on the MCN that allow coordinators to fully describe the situation and link the two hospitalizations together.

The MCN serves two main functions:

1. It captures the information the coordinator needs to request medical records.
2. It alerts the DCC of potential endpoints.

The MCN form may trigger adverse event data collection as well. As such, timely entry of this form is extremely important. Coordinators should complete an MCN as soon as possible after being notified that a medical visit occurred.

The MCN also includes a short parent/guardian interview on the child's history of fever and possible UTI symptoms, as well as resource allocation data on events. Since the parent/guardian's ability to recall events is important to this data collection, it is important to begin the data collection process as soon as the Coordinator is aware that a medical care visit occurred. The participant handbook/diary, will also help with parent recall of events.

As soon as you have enough information about where/when the medical care visit occurred, immediately begin the process of requesting medical records and completing the MCA form. This can often be a timely process and is critical for participant safety monitoring.

Refer to the MCN QxQ for item specific instructions.

10.4.3 Assignment of Medical Care ID Numbers (MCID)

Medical Care ID numbers (MCID NUMBER) are the way in which multiple data collection forms are linked to non-protocol medical visits. The MCID number format

consists of 5 numbers, followed by a two-character site code. Coordinators will receive pre-printed MCID Labels which they will use as needed. MCID numbers should be used/assigned sequentially starting from the lowest number. MCID number labels should be affixed to all source documentation of medical visits (copies of external medical records, urinalysis reports, etc.)

An MCID NUMBER is assigned by the coordinator at the time that the MCN is completed. For every MCID NUMBER there will be an associated MCN form. This same MCID number will be used/entered to link together all forms associated with a medical visit, including the Medical Care Abstraction Form (MCA), and potentially the Urine Specimen Results Form (USR), Adverse Event Forms (AEF), and/or DMSA radiology forms.

Every clinic or doctor visit requires an associated MCN form, and therefore a unique MCID NUMBER. This means that even follow-up visits to previously reported events will require new MCN forms and new MCID numbers. There are questions on both the MCN and MCA forms that allow coordinators to reference the MCID numbers of related previous medical visits. For example on the MCA form coordinators must answer the following:

3. Is this a follow-up visit to a previously reported medical visit? ..... Y N → **Go to Item 6**

4. Date of previously reported medical visit? ..... ☐☐/☐☐/☐☐☐☐

5. MCID Number associated with the previously reported visit: ..... ☐☐☐☐☐☐☐

MCID numbers and labels will be provided to the clinics by the DCC. If more MCID numbers and labels are needed, coordinators should contact the DCC at 1-866-257-7242.

10.4.3.1 Clinic Tracking of MCID Numbers

The DMS system is equipped with a number of reports that will help coordinators track and correctly assign MCID NUMBERs.

The 'MCID Number Inventory' is provided as a tool for sites to track which MCID NUMBERs have been assigned. This report will present a listing of all MCID NUMBER currently listed on MCN forms in the DMS, sorted by MCID NUMBER. This is an easy way for coordinators to see which MCID NUMBER was assigned last, and will help him or her determine which MCID should be assigned next. An example of the report is presented in Table 10.1 below.

Table 10.1 MCID Number Inventory (by MCID)

MCID	Participant ID	Form Version	Contact Occasion	Sequence Number
00024BF	BF00389	MCNA	02	02
10016BF	BF12345	MCNB	03	01
10057BF	BF00389	MCNB	02	03

Another report is the 'MCID Form Inventory'. For this report, the coordinator is prompted to enter an MCID NUMBER, then the DMS generates a list of all forms associated with that MCID. And example of this report is presented in table 10.2 below.

Table 10.2 MCID Form Inventory

Form Inventory for MCID: 00024BF

Participant ID	Form Code	Contact Occasion	Sequence Number
BF00389	MCNA	02	02
BF00389	MCAA	02	02
BF00389	USRB	02	02
BF00389	AEFA	02	02

A third report called the 'Participant MCID Report' prompts the coordinator to enter a participant ID. The DMS then generates a list of alll MCID numbers used for a particular participant, as well as all other forms linked to each MCID. See table 10.3 below for an example.

Table 10.3 Participant MCID Report

Participant ID	MCID	Form Code	Contact Occasion	Sequence Number
BF00389	00024BF	MCN	02	01
		MCA	02	01
		USR	02	01
	00032BF	MCN	02	02
		MCA	02	02
		USR	02	02
		AEF	02	02

A final report available in the DMS is the 'MCID Tracking Report.' This is a more comprehensive version of the MCID Number Inventory. It lists all MCIDs used in the DMS, along with all participant IDs and all forms associated with each MCID, sorted by MCID.

Table 10.4 MCID Tracking Report (Listing of all MCID's and Associated Forms)

MCID	Participant ID	Form Code	Contact Occasion	Sequence Number
00012BF	BF00125	MCN	02	01
		MCA	02	01
00024BF	BF00389	MCN	02	01
		MCA	02	01
		USR	02	01
00032BF	BF00389	MCN	02	02
		MCA	02	02
		USR	02	02
		AEF	02	02

10.4.4 Contact Occasion and Sequence Numbers for Source Documentation

Procedures for assigning contact occasions and sequence numbers are covered in Chapter 13: Administrative Procedures. The challenges of these assignments is felt most often during endpoint and adverse event data collection, which most commonly occurs between contact occasions.

It is important to note that the forms associated with a medical visit may not all have the same seq#. For example, let's say that participant BF00389 had two medical visits between the 02 and 03 contact occasions. The first medical visit (MCID 00024BF) was a visit for a broken arm and no urine was collected. The second medical visit (MCID 00032BF) was a sick visit for a suspected UTI, so urine was collected. Although the urine collection occurred at the second medical visit where the MCN contact occasion and seq# are both 02, the USR form should be labeled with contact occasion 02 and **seq# 01**, because it is the first time since the last study contact that a USR form was completed. See table 10.5 below:

Table 10.5

Participant ID	MCID	Form Code	Contact Occasion	Sequence Number
BF00389	00024BF	MCN	02	01
		MCA	02	01
	00032BF	MCN	02	02
		MCA	02	02
		USR	**02**	**01**

Although the seq#s differ for the forms associated with the second medical visit, they are linked by the MCID NUMBER 00032BF, which is specified on each form.

10.4.5 Medical Care Abstraction Form (MCA)

For each medical care visit reported on an MCN form, an associated Medical Care Abstraction Form (MCA) is required. The MCA form has been designed to collect medical care visit data from primary care physicians, clinics, ER's and hospital admissions. Even if the coordinator cannot obtain access to outside medical records, he or she must complete an MCA form and indicate on the MCA that access to medical records was not granted.

10.4.6 Notification of Potential Endpoints to the DCC

The DCC is notified of potential study endpoints through the completion of the Medical Care Notification form. The DCC monitors daily the completion of MCN forms and tracks the completion of data forms linked to each MCN.

10.4.7 Additional Source Documentation

In addition to the RIVUR case report forms, supporting source documentation may be requested from the clinical site. The UTI Classification Committee (UCC) relies mainly on DMS data in order to determine whether endpoint criteria were met for a particular event. However, the committee does reserve the right to request additional source documentation if needed.

All source documentation requested and submitted to the DCC must include the MCID number, participant ID number, contact occasion and sequence number corresponding to the associated MCN and MCA entered into the DMS. Source documentation must be filed locally in the participant's study binder/file.

An Endpoint Source Documentation Cover Sheet, (ESD) should accompany all source documentation being sent to the DCC. Use a separate cover sheet for each MCID number.

All source documentation sent to the DCC must have personal identifiers masked. Participant name, social security number, physician and other individual names, medical record numbers, and other identifiers deemed confidential by local regulations must be masked or adequately blacked out prior to submission to the DCC.

Masked and labeled supporting documentation and cover sheet can be faxed to:

RIVUR DCC
919-962-3265

or mailed to:

RIVUR DCC
CSCC-UNC Biostatistics Dept.
137 E. Franklin Street, Suite 203, CB# 8030
Chapel Hill, NC 27514-4145

10.5 UTI Classification Committee (UCC)

10.5.1 Introduction

Given the wide range of RIVUR clinical sites, there will be differences in how participants are treated and how certain diagnoses are made. The RIVUR UTI endpoint has a very specific definition, and all criteria must be met in order to classify a UTI as a RIVUR endpoint.

In order to eliminate any site-to-site differences and remove all possibilities of endpoints being determined subjectively, all reported medical care visits (clinic, primary physician, hospitalization, etc…) will require data collection. Those visits where a potential UTI is identified will be reviewed and classified by UCC, who will use standardized criteria to adjudicate each event according to the study definitions. At the end of the trial, when reports are generated on the study data and a comparison is made between the number of events in one treatment group versus the other treatment group, investigators can be confident the events reviewed by the UCC all met the same criteria and were supported by source documentation.

10.5.2 Role and Responsibilities

The Clinical Endpoints Committee at UNC serves as an independent committee responsible for defining, reviewing and classifying RIVUR endpoints. Every potential study endpoint will eventually be sent to the UCC. The UCC will then review each event through data review by computer algorithm or UCC adjudication, and determine whether each meets the pre-specified endpoint criteria.

10.5.3 Review and Adjudication of UTIs

The DCC monitors entry of the MCN forms for every medical visit. When an MCN form entered into the DMS indicates a potential study endpoint, the DCC compiles the data from all DMS forms referencing that MCID# for that visit. This compiled data is sent to two randomly selected members of the UCC. Each of the two UCC members is considered a reviewer for that event. Based on the compiled data report received from the DCC, each reviewer must classify the event and complete the UTI Endpoint Classification and Adjudication Form (ADJ) in the DMS.

Once the two reviewers from the UCC have classified a UTI through entry of the ADJ into the Data Management System, the DMS will compare the two records. The DCC will monitor all UCC data entry daily. If adjudication is necessary for a medical visit, the DCC will alert the UCC, and the UCC will meet or set up a call as soon as possible to come to a final decision on items that need adjudication.

Timeliness of the review, classification, and adjudication processes is essential to prompt determination of study endpoints and potential treatment failures.

10.6 Clinical Procedures for UTIs

It is important to remember that all suspected UTIs should be treated according to standard clinical care, regardless of whether study endpoint criteria are met. If a potential UTI is determined not to meet the pre-specified criteria for an $_{F/S}$UTI or $_{F}$UTI, and is determined not to be a study endpoint, it does not mean that the UTI event did not occur. It only means that the event did not meet the RIVUR criteria for a study endpoint. This is where clinical care vs. study procedures may appear to conflict.

In addition, the occurrence of a UTI or an endpoint does not mean that study medication is discontinued. Discontinuation of study medication is only mandated for participants defined as treatment failures (Section 10.7). Investigators are responsible for participant safety and decisions based on clinical care as needed.

10.7 Treatment Failure

The designation of treatment failure is based on frequency and rate of $_{F/S}$UTI recurrence, or identification of new or worsening renal scarring found in subsequent follow-up DMSAs.

10.7.1 Definitions of Treatment Failure

Treatment failure in the RIVUR study is defined as either of the following:

1. In any participant, treatment failure is defined by:
    - Occurrence of 2 recurrent $_{F}$UTIs OR
    - Total of 4 recurrent $_{F/S}$UTIs within the study period, OR
    - An interim 12-month scan showing new scarring at a site different from the index APN or worsening scarring evidenced by extension of a preexistent scar seen on the baseline DMSA scan.

2. Among children whose baseline DMSA scan shows grade 3 or higher scarring in either kidney, a repeat DMSA will be performed at the time of any recurrent $_{F}$UTI. If additional renal segment involvement is observed in comparison with the baseline scan, these children will also be categorized as treatment failure.

10.7.2 Identification of Treatment Failure

The recurrence of a RIVUR study UTI is determined by either matching UCC classification records or the UCC adjudication process, and is based on data collected at the sites. The DCC will monitor daily the classification of UTIs and the number of recurrent UTIs for each randomized participant. The classification of UTIs must be very timely, as a determination of RIVUR UTI may result in a determination of treatment failure, the need for DMSA scheduling (for participant safety), and/or the need to discontinue study medication. Prompt completion of data entry forms and submission of

source documentation to the DCC (if requested) will assure that such determinations can be made in timely manner.

10.7.3 Notification of Treatment Failures from DCC to the Sites

UTIs determined by the UCC to be study endpoints will only be reported back to the clinical sites if the UTI now classifies the participant as a treatment failure, necessitating the discontinuation of study medication and/or scheduling of additional radiographic scans.

Once a UTI has been classified and it is determined that treatment failure criteria have been met, the DCC will send within 24 hours a memo via email to the site Principal Investigator (PI) notifying the PI that the participant has met treatment failure criteria, instructing the PI to discontinue study medication and refer the participant to standard care, and giving further instruction as necessary. The DCC will also mail a paper copy of the memo to the PI. PIs will be asked to notify the DCC when the memo is received.

10.7.4 Study Procedures for Treatment Failure Participants

All children categorized as treatment failure (Section 10.7.1) will discontinue study medication, be offered or referred to usual clinical care, undergo a DMSA scan 4 months post failure unless the interim 12-month scan is appropriate for use as the outcome scan, and continue follow-up until the 24-month exit.

An outcome rectal swab must be collected from treatment failure participants at the time study medication is discontinued. Another one will be collected, at the 24 month exit visit.

10.7.4.1. Procedures for Participants with ≥Grade 3 Scarring on Baseline DMSA

For participants whose baseline DMSA scan shows grade 3 or higher scarring in either kidney, the study procedures for treatment failure are triggered at the first recurrence of a febrile UTI. The flow charts below illustrate the procedures for treatment failure among these participants. Figure 10.1 outlines procedures for these participants who have a febrile UTI in the first year of the study. Figure 10.2 outlines procedures for these participants who have a febrile UTI in the second year of the study.

Figure 10.1

Grade 3 or Higher Photopenia at Baseline
Patients **with** a febrile UTI in the first year of the study

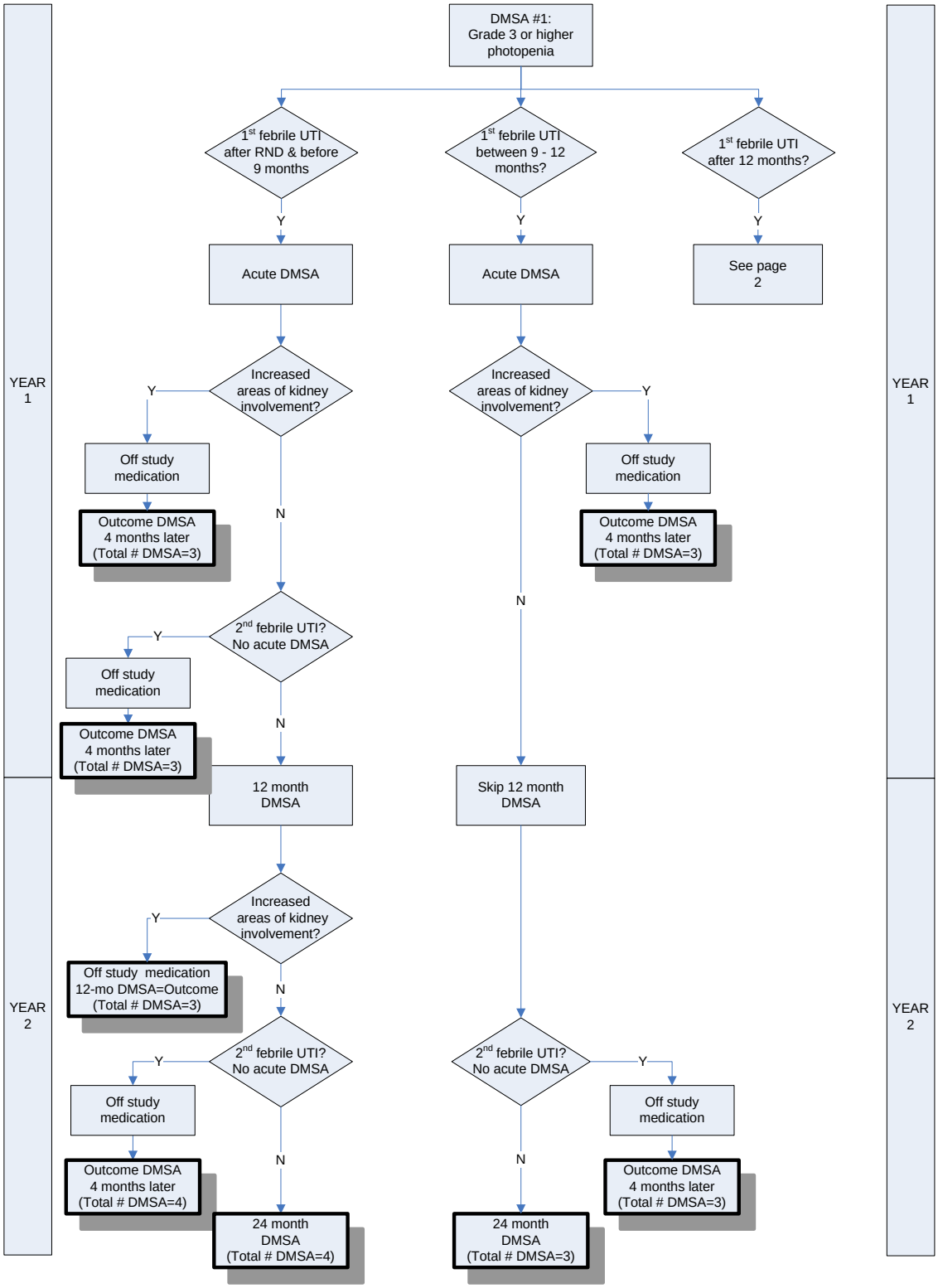
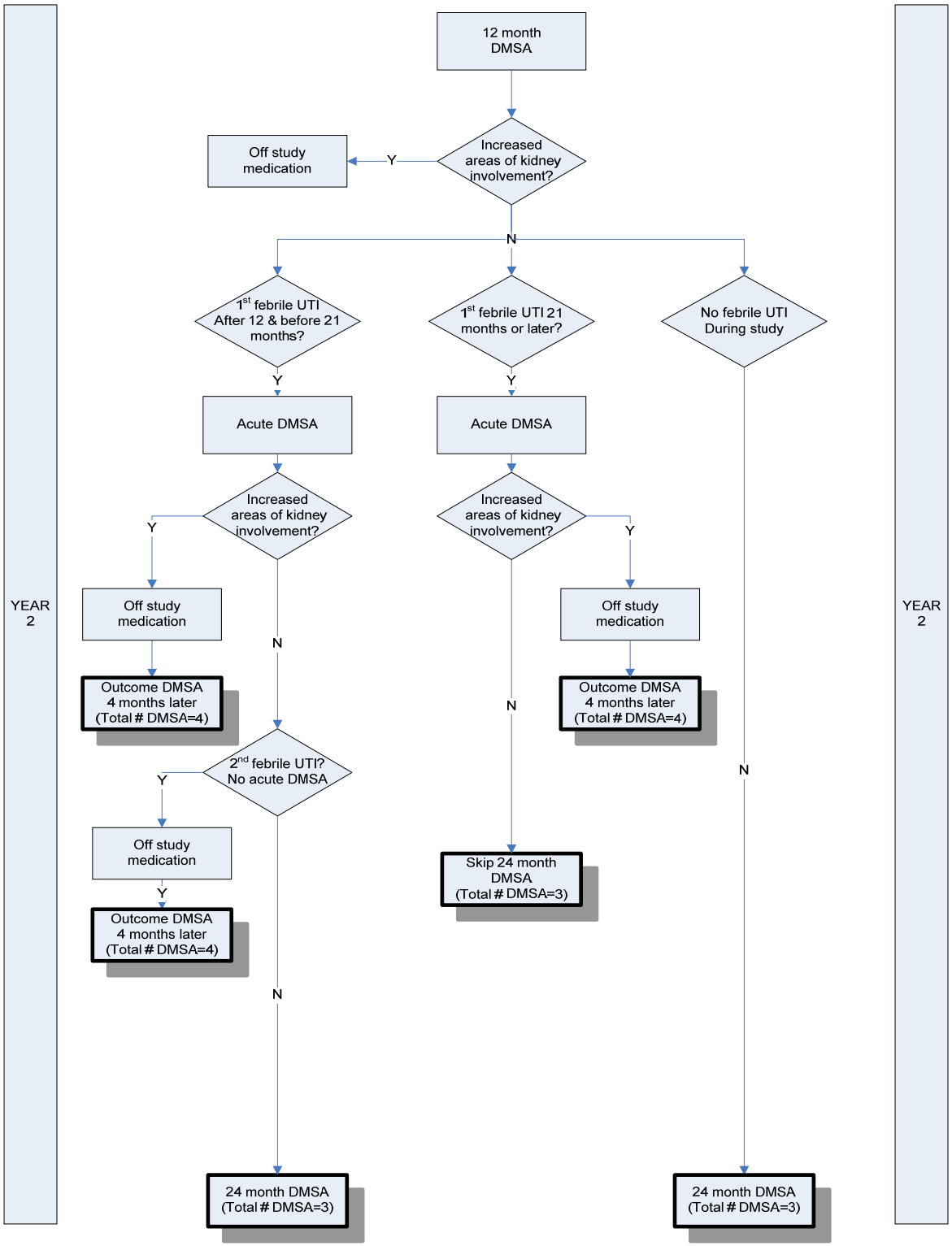


Figure 10.2

Grade 3 or Higher Photopenia at Baseline
Patients **without** a febrile UTI in the first year of the study



Chapter 11: Quality Assurance and Control

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Chapter 11: Quality Assurance and Control

11.1 Overview

The integrity and ultimate credibility of the study depend on such factors as ensuring adherence to the protocol and study procedures, completion of follow-up information on all participants enrolled, and using quality control measures to establish and maintain high standards for data quality.

Procedures designed to enhance adherence to the protocol and study procedures begin with the training and certification of clinic personnel before participants are enrolled. Once enrollment begins these same measures will continue along with monitoring clinics, operating suitable quality control systems, checking the quality of data collection and the timeliness with which data are received from the clinics, Central Laboratories, Reference Radiology Committee (RRC), and the UTI Classification Committee (UCC).

11.2 Quality Assurance and Control

Quality assurance is considered here as relating to activities to assure quality of data which take place prior to collection of data, while quality control relates more to efforts during the study to monitor the quality of data at identified points in the collection and processing stages.

Quality assurance is the essence of the entire Manual of Procedures (MOP) and includes the following activities:

- Detailed procedures. A clear description of the study design, training, certification, and the various data collection activities provides the blueprint for the study. The MOP is a written reference for study coordinators, and provides documentation of the standard procedures for the study. Procedures for handling the routine, as well as the unexpected, are given.
- Training and updating training. Training is the transfer of the study plans in the Manual of Procedures to the study coordinators and other staff members. Special materials for this purpose will be developed for RIVUR and will be the basis for initial training and for continuing education during the study.
- Certification. Criteria to examine the adequacy of an individual's training will be established. Individuals meeting these criteria will then be qualified to execute a procedure. The Data Coordinating Center (DCC) will monitor the study to ensure that staff performs only those functions for which they are certified.

For quality control purposes, RIVUR data collection and transmission will be monitored by observation and by quantitative assessment using both specific quality control procedures (e.g., repeated samples for laboratory assays) and statistical analysis of study data. Monitoring will be performed by the DCC via periodic site visits. A summary of selected aspects of RIVUR quality control follows:

- **Protocol adherence:** Periodic monitoring visits will be made to each site to review adherence to RIVUR recruitment and data collection procedures. Feedback and general recommendations for improvements will be provided. These visits also provide an opportunity for clinical staff to discuss questions, concerns, and suggestions with the DCC.

- **Quantitative monitoring, clinical sites:** A sample of data collected will be audited to assure that reported trial data are accurate, complete, and verifiable from source documents.

- **Quantitative monitoring, laboratory:** Random repeat measurements will be used to evaluate laboratory blood samples. Duplicate blood samples will be obtained in tandem with approximately 5% of the specimens collected for the study. These samples will be processed, shipped and stored in the same way as regular samples. The laboratory will be blinded to the identity of the duplicate samples and will run assays on them in the same way as for other samples. The DCC will then produce statistical analyses of the repeatability of the results.

- **Quantitative monitoring, radiology image readings:** All ultrasound, VCUG and DMSA scans used in the study are read by at least two reference radiologists. Results will be compared at the DCC and discrepancies will be adjudicated by the reference radiologists. For inter-reader QC, The DCC will select randomly selected scans for repeat readings by the reference radiologists.

- **Quantitative monitoring, UTI Classification Committee:** Study endpoints will be ascertained by at least two members of the UCC independently. Results will be compared by the DCC and discrepancies will be adjudicated by the UCC.

- **Reporting results:** Two aspects of reporting quality control monitoring should be emphasized. First, the results must be timely. When remedial action is required, reporting must be prompt so that a return to an acceptable level of performance is not delayed. Second, the reporting format must be easily understood.

- **Action on results:** With conscientious and trained staff, quality control reports provide an opportunity to praise a job well done. On the other hand, a poor performance is the basis for remedial action. Depending upon past performance, the amount of error, and, taking due account of personal circumstance, the

appropriate action may be a simple discussion to encourage a better performance. Re-training may also be appropriate at times.

11.3 Training

11.3.1 Training of Clinical Center Staff

Each new coordinator will attend central training at the DCC soon after starting with the RIVUR study. Continued investment in quality data during the study will be made by periodic refresher training sessions which review the protocol and update personnel on any changes which may have occurred.

Certification of study personnel is an essential aspect of effective quality assurance in RIVUR. After attending a central training or being trained at the local clinic by another centrally-trained coordinator, and meeting all certification requirements, the coordinator is considered certified. Areas of training essential for certification include randomization procedures, drug handling and accountability, specimen collection and processing, adverse event reporting, endpoints ascertainment and learning the data management system. The DCC will monitor the study data collection to ensure that staff performs only those functions for which they are certified . To protect the quality of the study results, data will not be collected by non-certified personnel.

In order to maintain proper collection of data despite potential for personnel changes over the long term follow-up period, the DCC is responsible for establishing and providing the requisite minimum criteria and training and ensuring continued adherence to standards.

11.3.2 Training of Reference Radiology Committee (RRC)

Each reference radiologist will participate in telephone training with the DCC to familiarize themselves with the study radiology MOP chapter, associated forms, and the Data Management System (DMS) for radiology forms and adjudication data entry. A pilot study will be conducted by the sites prior to their initiating study randomization, to ensure uniformity in reading and technique of radiographic images. This study will also have an MOP and telephone training.

11.3.3 Training of UTI Classification Committee (UCC)

The UTI Classification Committee will participate in a training session with the DCC to familiarize themselves with the study MOP, endpoints adjudication process, data collection forms, and the Data Management System (DMS).

11.4 Clinic Monitoring

There are three major concepts in the RIVUR approach to clinic monitoring:

Firstly, clinic staff is encouraged to contact the DCC for an immediate answer to an operational question or for help in obtaining clarification of a particular situation. For questions of a clinical nature, and those the DCC is unable to answer, the DCC will consult the Executive Committee. For each clinic, a primary Study Coordinator is identified. Each site has a Principal Investigator who has the overall responsibility for the recruitment of participants and management of the study at the clinic.

Secondly, site visits are made to individual participating centers by a clinic monitor from the DCC. Monitors will compare data sent to the DCC to that in the clinic and other medical or hospital records, and verify adherence to protocol. There may also be times when a particular clinic demonstrates a need for assistance in following protocol, filling out forms, or documenting events beyond what can be done through telephone conversations

Thirdly, the DCC will closely monitor clinic recruitment numbers. If recruitment falls below a certain level, appropriate personnel designated by the Executive Committee, such as a team consisting of a urologist or nephrologist, and coordinator from a highly productive center, will be sent to advise on recruitment strategies.

11.4.1 Site Visits at the Clinical Sites

The DCC is responsible for assuring that throughout the clinical investigation, the Investigators obligations are fulfilled and that the facilities used in the clinical investigation are acceptable. The most effective way to achieve this assurance is to maintain personal contacts between the DCC and the Project Coordinators, Principal Investigators, and clinic staff. The DCC will initiate monitoring visits at least annually at each clinical site in order to assure that:

- the study protocol is followed and implemented in compliance with Good Clinical Practices
- the facilities used by the investigator are acceptable for the purposes of the study.
- changes to the protocol have been approved by the local IRB
- changes to the Manual of Procedures are documented at the site and incorporated into the site procedures
- accurate and complete records are maintained
- the appropriate staff, trained and certified are performing the agreed-upon activities and not delegated to other unspecified staff

11.4.2 Conducting the Monitoring Visit

One month prior to the visit, email the Study Coordinator(s) and the PI a memo to arrange a convenient date for a monitoring visit. Prior to the visit, the site PI and Coordinator will be sent an agenda and a list of participant IDs for data auditing.

Particular issues covered during monitoring visits include:

- adherence to study schedule
- protocol violations and deviations
- enrollment rate
- drop-out rate
- questions or problems experienced by the staff since last visit
- changes in the study staff
- adverse event reporting
- shipment of laboratory specimens
- drug accountability, quantities and storage
- data management issues
- audit of source data
- acceptability of study site facilities and staff

Each monitoring visit will end with a debriefing meeting with the Project Coordinator and Principal Investigator.

11.4.3 Monitoring Visit Reporting

Monitoring visits are completed with a formal written report, distributed to the PI, Coordinator, and the Executive Committee within one month of the visit. The report will summarize the findings during the visit, and highlight all recommendations and action items for both the DCC and the clinical center.

11.5 Data Quality Monitoring

The DCC helps reduce the frequency of errors as much as possible through discussion and training of study procedures and use of data collection instruments before recruitment begins, and through continued review and clarification of the protocol during the study as necessary. The study DMS includes features designed to identify data entry errors at the sites with automated error checks and correction processes. Monthly data management reports of data quality and participant follow-up are prepared and circulated by the DCC. These reports are reviewed to determine which clinics may need to be visited.

11.5.1 Data Check Reports

The DMS includes an automated query system reporting data checks at entry for use in investigating and correcting specific problem items in collected data. The DMS reports provide listings of missing forms, unexpected, and inconsistent data. Additional data quality

reports will be run and sent to the sites monthly by the DCC. Follow-up is provided by the DCC to help sites resolve identified problems.

11.5.2 Data Management Reports

Data management reports are compiled and distributed monthly for use in identifying general problem areas in data collection. The standard reports include data on:

- Current study and site recruitment, and recruitment over time

- Screening, randomization and follow-up contacts
    - Timeliness of randomization and follow-up contacts
    - Timeliness of specimen processing and shipping
    - Timeliness of radiographic scan collection and processing
    - Timeliness of endpoints data collection
    - Completeness of forms

- Participant Withdrawal Rate
    - Number of participants who have withdrawn from the study

- Participant Medication Adherence Rate
    - Number of participants whose adherence is less than 75%

11.5.3 Data and Safety Monitoring Reports

Twice yearly DSMB reports (or as required by the DSMB) will be generated by the DCC. While the content of these reports will ultimately be determined by the DSMB requests, the reports will likely consist of four major sections; recruitment and follow-up, side effects and adverse events, efficacy, and data quality. The section on recruitment and follow-up will provide the status of recruitment by clinical centers, including graphs comparing performance goals. It will also detail reasons for withdrawals and non-compliance. The data quality section will aid the committee in evaluating the data collected. It will include information on data completeness and timeliness, rates of questionable data, and protocol violations.

11.6 Laboratory Quality Monitoring

11.6.1 Blood Central Lab QC – Cystatin C and Creatinine

Quality control procedures at the RIVUR Blood Central Laboratory at are overseen by the director of the laboratory. Their internal quality control program ensures that test results, which are generated by the lab, are accurate, reliable, and reproducible. The goal is accomplished by evaluating the quality of specimens submitted for testing, assessing test performance using appropriate controls, performing instrument function tests and temperature records daily, maintaining written procedures, reviewing personnel performance and technical procedures.

Additional quality control of reagents and media used in testing include:

a. Date all media and reagents upon receipt into the lab, and also specify "date opened".
b. Observe manufacturer's expiration dates and discard materials when outdated.
c. Examine each new batch of media for clarity and color. Media showing signs of dehydration must be discarded.
d. Examine each batch of media for sterility.
e. Perform procedures as described in the technical procedure manual.
f. Assess test performance by testing the appropriate positive and negative control specimens as delineated in the specific procedure.
g. Reference strains are available in the lab.

11.6.2 Anti-microbial Resistance (Rectal Swab) Central Lab QC

1. Quality Oversight and Program Administration:
   The Pathologist-in-Chief has been designated as the Medical Director of the Microbiology program and will be responsible for quality oversight, and the Infectious Diseases Research Lab is under the umbrella of CHP Pathology/Microbiology Department for CAP certification.

2. The purpose of the quality control program is to ensure that test results, which are generated by the lab, are accurate, reliable, and reproducible. The goal is accomplished by evaluating the quality of specimens submitted for testing, assessing test performance using appropriate controls, reviewing personnel performance and technical procedures.

3. Responsibility for the program is as follows:
   Ronald Jaffe, MBBCH , Pathologist-in-Chief
   Jayne Rasmussen, MT(ASCP) MPM, Exec. Director

4. Testing Personnel
   All Infectious Diseases Research personnel will receive training for all testing during their initial orientation. Competencies will be assessed annually thereafter. The Laboratory is responsible for planning and implementing orientation and competency assessment programs in conjunction with nursing education. Records of orientation and competency will be maintained on file in the employee's personnel records and/ or with each respective department's training records. Quality Control is performed by ID Chief Technologist and testing personnel according to procedure unless otherwise noted as performed by laboratory personnel.

5. The Chief Tech reviews records of controls of routine procedures, instrument function tests, and temperature records on a daily basis. Any problems with compliance are

addressed immediately, and the Infectious Diseases Lab Director is notified of all problems.

6. The Chief Tech ensures that technical procedures are written in a manner easily understood by technical staff by preparing the written procedures in accordance to the NCCLS document GPA-2.

7. Quality Control of reagents and media:
    - Date all media and reagents upon receipt into the lab, and also specify "date opened".
    - Observe manufacturer's expiration dates and discard materials when outdated.
    - Examine each new batch of media for clarity and color. Media showing signs of dehydration must be discarded.
    - Examine each batch of media fro sterility.
    - Perform procedures as described in the technical procedure manual.
    - Assess test performance by testing the appropriate positive and negative control specimens as delineated in the specific procedure.
    - Reference strains are available in the lab.

11.6.3 External Laboratory QC: Blind Replicate Matching

Blind Replicate Matching (BRM) for the RIVUR study is a method of quality control to check the precision of methods used by a laboratory analyzing blood and urine samples. This is a '**blind**' check as the lab does not know which samples are being used to test the quality of its work. Essentially, two '**replicate**' tubes/specimens from the same person are labeled with two different IDs so that the lab does not know they are from the same person. The DCC will '**match**' these two IDs from the one participant to compare the results from the analyses.

The study goal is to collect BRM QC on approximately 5% of all vial types for all clinic visits. The DCC will notify the clinical site when to begin collection the BRM specimens. As participants become randomized or visit the clinic for their biannual follow-up visits, the site will collect, process, and ship or store the replicate tubes as well as the regularly collected tubes for that specific visit type. The clinical site will continue to collect BRM specimens until the DCC notifies them to discontinue.

To minimize participant burden, no more than one BRM blood specimen is drawn per participant visit. Therefore, a complete set of BRM tubes for a contact occasion will be comprised of extra specimens collected from multiple participants. However, the same participant can donate an extra tube at different contact occasions (i.e., baseline AND 24 month end-of-study visits). This extra specimen must be the last specimen drawn from the participant, and should never require an additional 'stick'. If blood flow is insufficient to fill

the BRM specimen, a different participant should be selected for collection of the BRM specimen. Replicate blood draws will be completed only on participants > 20 lbs where overall blood draws are not to exceed 10 ml, and will only include QC specimens for the NIDDK repositories and central laboratories. BRM urine specimens and rectal swabs may be obtained on any participant, regardless of weight.

The link between a participants's ID and the blind replicate specimen ID is made through the Specimen Collection Form (SCF). These forms contain an indicator of whether the sample is a blind replicate duplicate. This is the only way in which quality control duplicates are distinguished from regular samples. In all other respects they are indistinguishable. The Q x Q's for the SCF provide detailed instruction for completing the BRM section of this form.

11.7 Data Management Quality Assurance

The data management system in RIVUR will provide all the capabilities required for research data management, including: data entry and validation, database updating, database closure, data retrieval, data inventory, security and confidentiality, and archiving.

Appendix 11.1 - Blind replicate matching instructions for sites

General Instructions to RIVUR Sites for Collection of Blind Replicate Matching (BRM) Specimens

1. The RIVUR protocol specifies that a 5% sample of replicate specimens will be collected to evaluate quality assurance on specimen collection. In order to begin replicate specimen collection, a set of blind replicate matching (BRM) ID labels (example in Table 1.) and specimen labels (example in Table 2.) will be sent to your site from the DCC. The ID labels will be used on the Specimen Collection Form (SCF) and the specimen shipping forms. The replicate specimen labels will be used on the replicate specimens as well as the shipping forms.

2. The DCC will send written notification via email to each site informing the site that BRM specimen collection should begin. The site coordinator will collect BRM specimens until the DCC has sent a written notification to stop collecting replicates.

3. When a child comes to the clinic for a protocol-scheduled clinic visit, the site coordinator should collect the normal specimens as detailed in the MOP. If the site has been notified to collect replicate specimens, then the site coordinator should attempt to collect matching specimens if possible. The replicates will be collected using the same techniques as the study specimens.

4. The site coordinator should plan to collect a BRM specimen for each of the specimen label types (S=biorepository serum, C=cystatin-C and creatinine, R=rectal swab, U=biorepository urine, and B= genetics repository) for each of the BRM ID's supplied to the site.

5. The complete set of specimens for one BRM ID will likely be collected from **multiple participants**. A single participant may contribute to more than one BRM ID. A single participant may also contribute to replicate specimens more than one time in the study.

6. Only collect a replicate specimen at a visit where the study specimen has been collected at the same visit. For example, the site may only submit a replicate rectal swab specimen from a participant on a baseline visit if the baseline RIVUR rectal swab has already been collected from the participant from the same visit.

7. Matching baseline specimens will be drawn at randomization visits where specimens are being collected and matching exit specimens will be drawn at exit visits where specimens are being collected. If a genetics repository specimen is drawn at a visit other than the baseline visit for a participant, a matching replicate for genetics repository may be drawn at the same time.

Appendix 11.1 - Blind replicate matching instructions for sites

8. The replicate blood specimens will only be collected on children ≥ 20 lbs. The total volume of blood collected for the protocol-defined RIVUR specimens at baseline on children ≥ 20 lbs is 10 mL. The volume of blood collected at the exit visit is 6 mL, assuming the participant's genetics repository specimen was collected at a prior clinic visit. If the genetics repository specimen is collected at the exit visit then the total volume of blood collected for the protocol-defined RIVUR exit specimens on children ≥ 20 lbs is 10 mL.

   The replicate specimens collected at the baseline and exit clinic visits will push the total volume of blood collected during a single clinic visit over the preset volumes of 10mL (baseline) and 6 mL (exit). The maximum amount of blood collected per participant including baseline specimens and BRM specimens should not exceed the maximum blood volumes specified at individual institutions mandated by that institution's Internal Review Board (IRB).

   The BRM blood specimen(s) should be the last blood specimen(s) collected at the visit and should never require an additional needle stick. If blood flow is insufficient to complete the BRM specimen(s), do not proceed with the replicate specimen collection, and instead, wait for another participant to continue with the BRM blood specimen(s).

9. Any clinic visit where replicate specimens are collected will require the completion of two Specimen Collection Forms (SCF). The data for a single participant detailing collection of regular RIVUR specimens will be collected on an SCF with the participant's RIVUR ID recorded in 'ID Number' field in the header as usual. The data for replicate specimen collection will be collected on a separate SCF where the BRM ID will be recorded in the 'ID Number' field in the SCF header and the participant's RIVUR ID will be recorded in Item #2 on the SCF Form.

   Refer to the partial SCF form displayed in Table 3. for an example of using the BRM ID (AK40116) and linking the replicate ID to the real RIVUR ID (AK40015). The SCF QxQ includes detailed instructions on completing the SCF for BRM specimens.

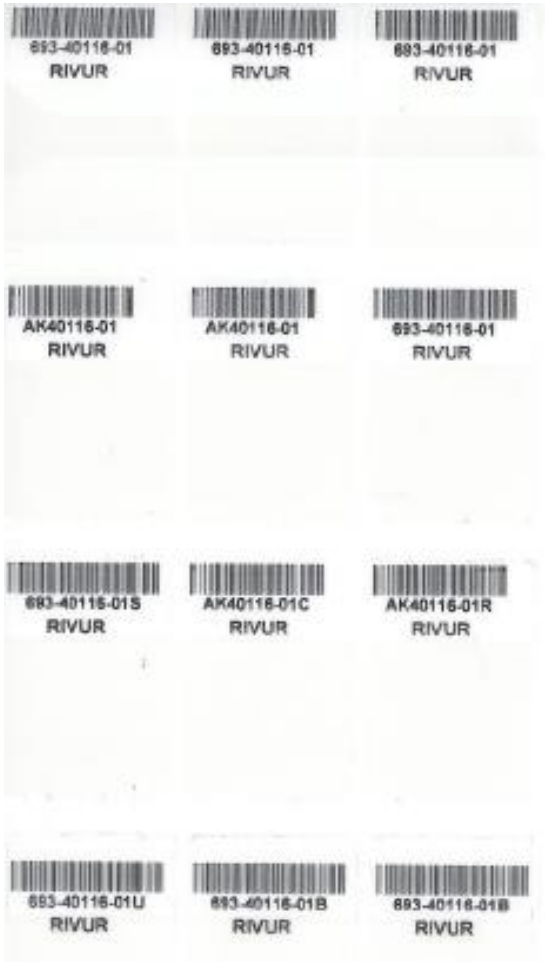
10. The Yes/No skips embedded in the SCF allow for recording data on only the replicate specimen types collected from one participant during a single visit. For example, if the 5 different baseline replicate specimens are collected from 5 different RIVUR participants, there will be 5 separate SCF forms detailing the replicate specimen collection.

Appendix 11.1 - Blind replicate matching instructions for sites

Table 1. Blind Replicate Matching (BRM) ID Labels Supplied to Site from DCC

Appendix 11.1 - Blind replicate matching instructions for sites

Table 2. Blind Replicate Matching (BRM) Specimen Labels Supplied to Site from DCC



Appendix 11.1 - Blind replicate matching instructions for sites

Table 3. How to Link Replicate ID to RIVUR ID on SCF for BRM

RIVUR
Randomized Intervention for Children with Vesicoureteral Reflux

Specimen Collection Form

ID NUMBER:	AK40116	FORM CODE: SCF VERSION: A 11/19/08	Contact Occasion		SEQ #	

Participant Name: _____

Instructions: *Complete this form for collection of all protocol specified specimens, including blood, urine, and rectal swabs. If collection is for a QC specimen, record the QC ID provided by the DCC in the form header above.*

A. QC SPECIMEN

1. Is this a QC specimen collection? ..... (Y) N → Go to Item 3
2. Record or attach the participant ID label **AK40015**

Chapter 12: Staffing and Training

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Chapter 12: Staffing and Training

12.1 Overview

Certification of study personnel is an essential aspect of effective quality assurance in RIVUR. In order to maintain proper collection of data despite potential for personnel changes over the long-term follow-up period, the Data Coordinating Center (DCC) and the Principal Investigators Committee are jointly responsible for establishing and providing the requisite minimum criteria and training and ensuring continued adherence to standards.

The complexity of the design requires that Project Coordinators be instructed and trained on specific tasks. To protect the quality of the study results, data are to be collected by trained personnel only.

12.2 Project Coordinators

Project Coordinators are responsible for providing the thread of continuity from participant recruitment, evaluation and treatment through follow-up, endpoint determination and ultimately trial closeout. Coordinators routinely initiate recruitment, conduct interviews and administer questionnaires. Coordinators serve as the liaison with the Steering Committee, the DCC, the Central Laboratories, and the clinical site. They familiarize their physicians and staff with study procedures and implement operational modifications. The Project Coordinator is ultimately responsible for accurate collection of data at the clinic and its transfer to the DCC. The Coordinator is also responsible for overseeing the collection, processing, and shipment of blood, urine, and rectal swab samples to the appropriate Central Laboratories and repositories. Therefore, an in-depth knowledge of all aspects of the protocol is required. As such, Project Coordinators attend a training session initially held before recruitment into RIVUR commences.

In general, successful completion of training will result in proficiency in all aspects of study procedures necessary for the collection of data on paper forms and the computerized data management system (DMS) to ensure the accuracy and integrity of the collaborative database. The Project Coordinator must demonstrate proficiency in the use of the DMS during the training to complete the training requirements to enter data and randomize participants on the DMS.

12.3 Training Procedures

Every Project Coordinator must be trained by the DCC. If a clinic has more than one Project Coordinator, then the DCC must train each Project Coordinator.

Once trained, a Project Coordinator can subsequently train additional personnel (auxiliary, back-up) who may perform any or all of specimen collection and processing, data entry, overall data collection or medical records abstraction for endpoint data collection, provided each person passes the training requirements specific to the activity.

In most clinics it is expected that the Project Coordinator will perform all duties relevant to screening and randomization.

Training of the initial group of Project Coordinators from each site is accomplished by participation in a central training session held by the DCC.

12.4. Training Requirements

At a minimum, training requires a complete reading and familiarization of the RIVUR Manual of Procedures. The central training of Project Coordinators will include presentations and examples of data collection that provide a thorough review of the MOP. In some cases Project Coordinators and auxiliary or back-up personnel may be required to complete a task-specific quiz to verify that all instruction in the Manual of Procedures are understood.

12.4.1 Specimen Collection and Processing Training

Initial training will be based on attendance at RIVUR central training, and demonstration of an acceptable level of proficiency, as indicated on a laboratory quiz of specimen collection and processing administered by the DCC. Clinics utilizing other lab personnel to collect, process and/or ship specimens will be required to give the lab personnel the quiz and submit it to the DCC for evaluation. Phlebotomists who perform the venipuncture **only** are not required to take the laboratory quiz, but are required to receive instructions in RIVUR protocol on the order of draw and handling of the vacutainer tubes. The RIVUR project coordinator is responsible for ensuring adherence to study procedures for specimen collection and processing even if external laboratory personnel are being utilized.

12.4.2 Radiographic Images Collection and Processing Training

Initial training will be based on attendance at RIVUR central training. Project Coordinators who have attended central training may train auxiliary or back-up personnel in proper procedures for collection, processing, and shipping of radiographic images.

12.4.3 Endpoints Ascertainment Training

Initial training will be based on attendance at RIVUR central training.

12.4.4 Data Management System (DMS) Training

Initial training is based on attendance at the central training session. Project Coordinators who have attended central training may train auxiliary or back-up personnel in study data entry procedures. It is expected that only centrally trained Project Coordinators or certified back-up coordinators will perform all data entry relevant to screening and randomization.

12.5 Coordinator Turnover

If the primary Project Coordinator leaves the study, trained and certified auxiliary back-up personnel (see Section 12.7) can continue to function in their roles. A back-up Coordinator who has completed a central training at the DCC may be designated as the new Project Coordinator with no interruption of study activities. Or, the back-up Coordinator who has been trained by the primary Coordinator may continue all study activities until a new primary Coordinator, or until they are centrally trained by the DCC.

If the site is a satellite site administered under a core site, the core site Project Coordinator can train backup personnel temporarily (if there are no previously trained back up personnel) so study activities can continue until the new Coordinator is trained by the DCC.

All data collection activities must cease at a site if a new Coordinator has not been trained at a DCC central training, or temporarily by the previous centrally trained Coordinator, and there is no backup or auxiliary trained personnel at that site. The DCC will make every effort to provide emergency training when necessary. Effort should be made to complete such training within 60 days of loss of the primary Project Coordinator.

For clinics with auxiliary personnel, it is recommended that the new Coordinator centrally train as quickly as possible in the areas the previous Coordinator handled exclusively. When the clinic has someone trained for every aspect of the study (combination of new, auxiliary, and back-up), then the clinic can continue study activities.

12.6 Recertification of Coordinators

The need for retraining may be triggered by monitoring visits, or upon recommendation of the Data and Safety Monitoring Board, or upon the Executive Committee's review of the data. This recertification may be study-wide or clinic-specific.

12.7 Additional Clinic Personnel

Once training and certification requirements for the Project Coordinators are met, additional personnel may be trained by the Project Coordinator or by the DCC to perform tasks related to the RIVUR study under certain conditions.

Local laboratory personnel may perform specimen collection and processing activities. In this case, the Project Coordinator is still responsible for study protocol and must be certified in specimen collection and processing. Lab technicians must be RIVUR-certified and their initials are entered on the specimen collection form as the person processing the blood.

Data entry personnel may enter data into the DMS from paper forms that have been completed by trained personnel, after training by a DMS-trained Project Coordinator, at a DCC central training, or training during a DCC monitoring visit. These technicians are

allowed to enter already collected data into the DMS only. It is expected that only centrally trained Project Coordinators or trained back-up coordinators will perform all data entry relevant to screening, randomization, and direct data collection and entry into the DMS.

12.8. Reference Radiology Committee (RRC)

The Reference Radiology Committee radiologists are responsible for independently reading, interpreting and adjudicating results of RIVUR renal/bladder ultrasound, VCUG, and DMSA scans. The study endpoints of renal scarring will be comprised from the results of these central readings. The RRC must be knowledgeable of all forms and procedures necessary to read and adjudicate study images, and the computerized data management system.

The RRC will be trained by the DCC by telephone conference call. Training is based on familiarization with the RIVUR Manual of Procedures and attendance at a training session.

12.9 Clinical Endpoints Committee (CEC)

The Clinical Endpoints Committee serves as an independent committee responsible for reviewing and classifying RIVUR UTI endpoints. The CEC must be familiar with the study endpoints definition, and the types of data collected to ascertain endpoints. In addition, the CEC must be knowledgeable of forms used to define and adjudicate the study endpoints and the computerized data management system.

The CEC will be trained by the DCC either by a training meeting or telephone conference call. Training is based on familiarization with the RIVUR Manual of Procedures and attendance at a training session.

Chapter 13: Data Management and Administrative Procedures

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Chapter 13: Data Management and Administrative Procedures

13.1 Overview

This chapter pertains to general guidelines for data collection and processing that will be used throughout the study. It covers topics such as identification of participants, correct usage of contact occasion and sequence numbers, instructions for recording and correcting data collection forms, general data entry guidelines, adding revisions to the Manual of Procedures and to the forms, and general data management guidelines to ensure participant confidentiality, data security accuracy, and accessibility

13.2 Confidentiality

Violating participant confidentiality is regarded as a serious problem. Each Clinical Center's Investigator is responsible for confidentiality of study documents, although this responsibility may be delegated to the Center's Study Coordinator. All study personnel are expected to maintain participant confidentiality.

All study documents should be treated as confidential. Of particular concern is any document that contains both the Study ID Number and the participants name or other personal identification. Clinical data is especially sensitive. No data containing participant personal information will be sent to the DCC. If certain participant data are required to be sent to the DCC, such as records containing details regarding an adverse event or endpoint, personal identifiers must be removed at the clinical center prior to sending to the DCC.

All research data forms and/or paper records must be in a locked cabinet maintained for this purpose when not in use by the study personnel. Records in use must be kept under the supervision of study staff that has been appropriately trained in HIPPA and site specific confidentiality procedures.

Data management procedures for RIVUR were designed with participant confidentiality in mind. All data collection forms are entered and stored at each Clinical Site. Participant name or any other personal identifier will not be entered in the data management system. Participants are identified only by study ID number on all data files at the DCC.

13.3 Participant ID Numbers

ID numbers for participants enrolled into RIVUR are generated at the DCC. Each participant is assigned a unique RIVUR ID number. This ID number is what is used in the studies database to discern participants, no participant names or other identifying information. The clinical center is the only location that maintains the link to any identifying information of the participant. Each site will be given an Excel Spreadsheet of valid Participant ID's for

their own data management purposes, and sheets of Participant ID labels for use on data collection forms, will be provided.

RIVUR ID's will follow the following format:

7 fields:

Field 1-2 Site Identifier
Field 3-6 Participant ID number
Field 7 Check Digit (based on arithmetic algorithm for QC)

The following site identifiers are used:

Site ID	Site Name
AL	University of Alabama
CO	Children's Hospital of Columbus
DC	Children's National Medical Center
GA	Emory University School of Medicine
MA	Children's Hospital of Boston
MD	Johns Hopkins School of Medicine
MI	Wayne Stat University School of Medicine
MO	Children's Mercy Hospital of Kansas City
NY	Women and Children's Hospital of Buffalo
OK	University of Oklahoma
PH	Children's Hospital of Philadelphia
PO	Oregon Health Sciences University
PT	Children's Hospital of Pittsburgh
TO	Hospital for Sick Children, Toronto
TX	Texas Childrens Hospital

RIVUR participant ID numbers are assigned at the time of participant consent.

13.4 ID Labels

The DCC will provide clinical sites with ID labels

13.4.1 Participant ID Labels

Participant ID labels will be provided by the DCC for use on consent forms, data collection forms, and any other source documents (i.e. medical records) to help the site with their data management tasks.

13.4.2 Laboratory Specimen ID Labels

Labels will be provided by the DCC for laboratory specimens shipped to central labs or repositories. These labels will have bar-coding necessary for inventory at the labs, and will also indicate the participant ID number and contact occasion, including sequence number and tube number where appropriate. Refer to Chapter 5: Specimen Collection and Processing for laboratory specimen collection procedures.

13.4.3 Radiographic Image ID Labels

Participant ID labels will be provided by the DCC for CDs and/or films containing study radiographic images. These labels will also indicate the participant ID number, contact occasion, and sequence number associated with the time of data collection. Refer to Chapter 3: Radiographic Images for data collection procedures related to radiographic image collection.

13.4.4 MCID Labels

Each medical care visit (sick visit), regardless of where it occurs (i.e. study clinic, primary physician, hospitalization), made by a participants during the study, is assigned a Medical Care ID Number (MCID) for use on some of the study data collection forms. Labels with these specific ID numbers will be provided by the DCC.

13.5 Paper Forms versus DMS

In RIVUR, the DMS screens are designed to mimic all paper forms. Coordinators can choose to collect study data on paper forms first followed by data entry, or by direct data entry. If paper forms are used, this becomes the original source document for interviews.

13.5.1 Recording Responses

Most of the questions in the RIVUR forms have pre-coded responses. There are a few questions, however, that you must write in a response to the question. Some questions have pre-coded responses as well as an "other" category. If the participant's answer does not fit into a pre-coded answer, you must specify the response. The recording practices below must be followed at all times to assure that the response recorded accurately reflects the participant's answers and to assure the questionnaire data can be converted to machine-readable form.

- You must listen to what the participant says and record/key the appropriate answer if the response satisfies the objective of the question.

- In recording answers to open-ended questions or "other" categories, print/key the response verbatim.
- Use a black ballpoint pen when recording on paper form.
- Record in the white space below the questions any responses "that don't quite fit" in one of the response categories. Your notes will help the analysts in understanding points of confusion, difficulty, etc. When using direct data entry, these notes can be entered as notelogs in the DMS.
- Always print or write legibly when using paper forms.
- If a participant refuses to answer a question, write "refused" in the left margin beside the question and enter equal signs in the response field on the form or on the entry screen.
- A single answer choice code must be circled/keyed in each question to represent the participant's answer, unless the item states you can circle all that apply.

Some of the questions in the RIVUR study ask about recall of events over time. You may assist the participant without violating probing rules by working with him/her on math or pinpointing dates or events. Another way to help pinpoint more accurate information is to ask the participant to think about time of year or season when an event occurred.

13.6 Data Collection Forms

All data collection in RIVUR is documented on data collection forms. RIVUR uses a combination of data collection methods: direct data entry, paper forms followed by data entry, and forms collected on paper only (no entry). All RIVUR data collection forms will also have associated QxQ (question by question) instructions to aid in the data collection process.

13.6.1 Form Structure

The paper forms in RIVUR are designed to correspond almost exactly to the computer screens used for data entry. All items will be listed in the same order on both the paper and screen versions. Most forms are structured as follows:

1. Form Title
2. Header Administrative Information
    - Form Code
    - Version Number and Date
    - Participant's ID Number
    - Contact Occasion
    - Sequence Number
    - Participant's Name (this is only an option on paper forms, is not data entered)
    - at the top of each additional page is a space to record the participant's ID, the contact occasion and the sequence number
3. Form Data Items

4. End of Form Administrative Information
    - Date of Examination or Data Collection
    - Method of Data Collection
    - Examiner or Recorder's initials

13.6.2 Header Administrative Data

The information that identifies each form as a unique record in the RIVUR DMS is the key field information contained in the "header" box at the top of all form pages. The following guidelines should be observed in filling out the "header" information located at the top of the each form page.

HEADER EXAMPLE:

RIVUR Randomized Intervention for Children with Vesicoureteral Reflux

BASELINE MEDICAL HISTORY FORM

ID NUMBER:							

FORM CODE: BMH Contact Occasion | | SEQ # | |
VERSION: A 9/29/06

Participant Name: _____

13.6.2.1 Participant ID

Preprinted Participant ID labels (Section 13.4.1) should be used in the header of paper forms whenever possible. If the 7-digit ID number is handwritten, care must be taken to make sure the number is very legible for data entry. The first two boxes contain the letters identifying the field center, followed by the 5-digit numeric portion of the ID number.

Example: ID NUMBER:

A	L	1	2	3	4	5

13.6.2.2 Form Code and Version

Form code will be unique for each data collection form in the RIVUR study. Form codes are a 3 character code make up from the forms title. Form versions begin with the letter A, then increment as revisions are made to the data collection forms. Form codes and version are preprinted on all forms.

Form codes and versions are part of the unique identifier of a data record along with ID, contact occasion and sequence number, and are used as part of each data items identifier. For example, question #2 on form Baseline Medical History, version A would be referred to as BMHA2. All data queries and communication from the DCC regarding data items will use this terminology.

It is the responsibility of the site to make certain they are using the appropriate version of each form at all times. For details of the documentation procedures that are designed to facilitate communication to sites about form changes, see Section 13.8.

13.6.2.3 Contact Occasion / Sequence Number / Line Number

13.6.2.3.1 Contact Occasion

The term "Contact Occasion" refers to any protocol specified study contact that occurs while a patient is enrolled in the study. There are 13 protocol scheduled participant contact occasions in RIVUR, and to facilitate data management, these are numbered 01-13. The Imaging Pilot is recorded as contact '00'. These numbers are used in the Data Management System (DMS) and on all paper forms and study documentation to identify and differentiate the various contacts.

Table 13.1: Contact Occasion Numbers

Description	Contact Occasion #
Imaging Pilot	00
Randomization / Baseline	01
2-mo. Phone Follow-up	02
4-mo. Phone Follow-up	03
6-mo. Clinic Follow-up Visit	04
8-mo. Phone Follow-up	05
10-mo. Phone Follow-up	06
12-mo. Clinic Follow-up Visit	07
14-mo. Phone Follow-up	08
16-mo. Phone Follow-up	09
18-mo. Clinic Follow-Up Visit	10
20-mo. Phone Follow-up	11
22-mo. Phone Follow-up	12
24-mo. Clinic Exit Visit	13

Following the first main study protocol contact the randomization and baseline visit (CO 01) there are scheduled study contacts every two months: clinic visit contacts every six months, as well as telephone contacts every two months between the clinic visits. This continues

through the 24-month clinic visit, which is CO 13. CO 13 will be the Exit Visit for the study for most of the participants.

When completing header information fill in the appropriate contact occasion for the form, using leading zeros where necessary. Note: This item may be pre-coded on some forms.

Example: For the Randomization visit the contact occasion should be recorded as:

CONTACT OCCASION: | 0 | 1 |

13.6.2.3.2 Sequence Number

In addition to contact occasion, the sequence number also provides data management information about the timing of data collection activities. Both the contact occasion and sequence number together indicate a contact. Protocol scheduled contacts, numbered in the table above, are always assigned sequence number '00'.

Some data collection forms will be collected independent of protocol scheduled follow-up telephone and clinic contacts, every 2 months. These include reporting of serious adverse events and study endpoints forms such as the Adverse Event Form (AEF), Medical Care Notification Form (MCN), and Medical Care Abstraction Form (MCA).

In situations when data are collected on events that occur between the scheduled study contacts, corresponding data should be labeled according to the most recent regularly scheduled contact occasion preceding the event, and the Seq # should be incremented. For example, if on the 2-month telephone call (CO 02) you discover that the participant was hospitalized once during the previous month, meaning the hospitalization occurred between the randomization visit (CO 01) and the 2-month phone call (CO 02), the corresponding Medical Care Abstraction Form for that hospitalization would be labeled with CO 01, Sequence Number 02 (See Table 13.2 below).

Table 13.2: Sequence Number Usage

Contact Description	Date of Contact	Contact Occasion #	Sequence #
Randomization	08/29/2006	01	00
→ Hospitalization	**9/5/2006**	**01**	**01**
2-month telephone call	10/30/2006	02	00
4-month telephone call	12/29/2006	03	00
6-month clinic visit	02/29/2006	04	00

Even if the coordinator is unable to complete the Medical Care Abstraction form for a hospitalization *or* wasn't informed about it until the 4 month telephone call, the contact

occasion would remain CO 01 because the hospitalization occurred between the 01 and 02 contact occasion dates.

Incrementing sequence numbers allows you to track multiple unscheduled events that occur between scheduled study contacts. For example, in Table 13.3 below there are two different medical care visits that occurred between COs 04 and 05; that is, between the 4-month telephone call and the 6-month clinic visit. The CO for both hospitalizations is 04, and the sequence numbers are 02 and 03 respectively, thereby giving each event its own unique identity.

Table 13.3: Sequence Number Increment Usage

Contact Description	Date of Contact	Contact Occasion #	Sequence #
Randomization	08/29/2006	01	00
2-month telephone call	10/30/2006	02	00
4-month telephone call	12/29/2006	03	00
→ Doctor Visit	**01/09/2006**	**03**	**01**
→ Doctor Visit	**02/11/2006**	**03**	**02**
6-month clinic visit	02/29/2006	04	00

When completing header information fill in the appropriate sequence number for the form, using leading zeros where necessary. Note: This item may be pre-coded on some forms.

Example: For the second Doctor Visit that occurred after CO 03, but before CO 04, the sequence number should be recorded as:

SEQUENCE NUMBER: | 0 | 2 |

13.6.2.3.3 Line Number

Together, both the contact and sequence number indicate a point in time. There are some forms that may be collected more than once at the same point in time. These are distinguished by line numbers. For example, there may be 3 AEF forms reporting different side effects or events all occurring at the same point in time (CO# and SEQ#). See header for AEF form below with space for Line Number.

These multiple forms are all entered into the DMS under the same CO# and SEQ# using the DMS feature referred to as 'Multi-Line'. The DMS assigns the actual Line Number in the order the forms are entered. If you are collecting data on paper forms, you must verify that the Line Number reported on the paper form is the same that is assigned in the DMS.

Refer to the DMS User's Guide for specific instructions on data entry of multi-line forms.

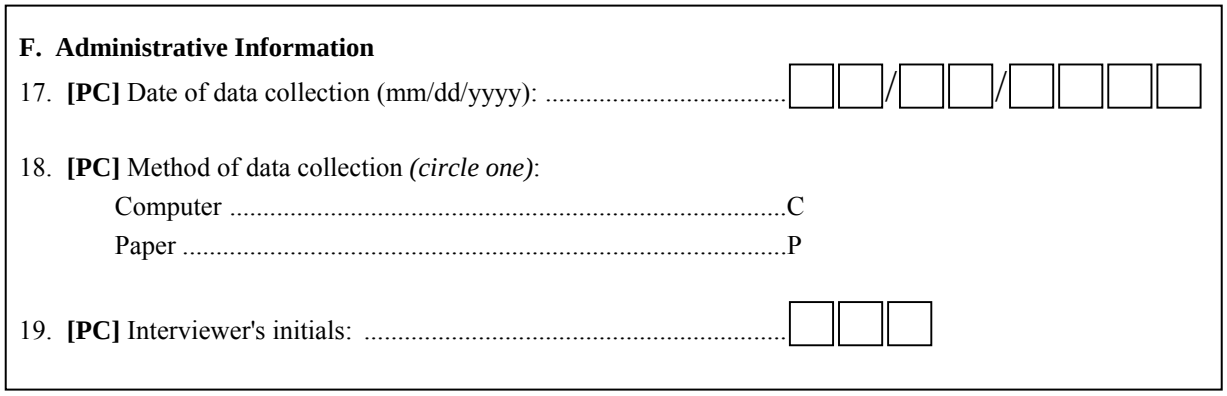
13.6.2.4 Participant Name

This item appears on the paper forms only, and serves as another way for clinic staff to link data collection forms to participant records. Record the participant's full name in the blank provided. The participants name is not entered into the study DMS. A participant's name should never be included on any materials that are sent to the DCC, or be in the studies database.

13.6.3 End of Form Administrative Data

At the end of each form, there is a section titled "Administrative Information." This section provides information regarding when, how, and who is responsible for the data collected on each form, and must be completed for every form.

EXAMPLE:



13.6.3.1 Date of Data Collection

For this item, record the date that the data was collected. This date may not be the date of data entry if data was collected on paper forms first. The RIVUR DMS system uses the U.S.

date format: MM/DD/YYYY. For more complete instructions on entering dates, please refer to section 13.4.3.1. of this chapter.

13.6.3.2 Method of Data Collection

In this item, the original method of data collection (on paper form and entered from the form, or entered directly into the DMS) must be recorded. This documents the source of data in the database.

13.6.3.3 Interviewer or Examiner's initials

The interviewer's initials will be the first, middle, and last initials of the staff person who originally collected the data. If someone does not have a middle initial, leave this field blank. To distinguish between two staff members who have the same initials, one of them should consistently use either their first or last initial as the middle initial.

13.6.4 General Instructions for Recording and Correcting Responses

Review each form and its instructions prior to use. Verify that you are using the appropriate form by checking its 3 letter form code, version, and date, all located in the lower left corner of the page. Each unique form type will have specific instructions for filling out that form in the Procedures Manual. Be familiar with the instructions in the Procedures Manual before attempting to complete a form.

When completing official study paper forms, use black ballpoint pen. Print all text responses legibly; do not use cursive writing. Do not attempt to correct errors on paper forms by using correction fluid or erasers at any time. Data collection forms need to maintain the history of data recorded in the event of an audit. Carefully proofread each page of data for legibility, accuracy, and completeness prior to transferring the form to the data entry staff.

All items fall into one of three main categories: (1) "fill ins", (2) multiple-choice (circle or check), and (3) qualitative information (comments/short-answer questions). Techniques for completing each of these types of items, as well as making corrections, are described below. A general rule is to record information only in the spaces provided (except for some error corrections).

13.6.4.1 Fill-In Boxes

13.6.4.1.1 Alphabetic Responses

When alphabetic information is required, enter the response beginning in the leftmost box using capital letters. Punctuation may be included.

For example: If the name of the investigator who authorized randomization is Bob O-Reilly, then you would enter:

Eligibility Criteria reviewed and randomization authorized by (name of investigator):

B	O	B		O	'	R	E	I	L	L	Y												

If the response contains more characters than there are boxes, beginning with the first character enter as many characters as there are boxes, then enter the remaining data on the form either next to the boxes or directly under, in such a way that anyone entering the data will know that this is a continuation of the response. When this is entered into the DMS, when you run out of field space in the DMS add a "notelog" with the complete information Refer to Chapter 14: Data Management for instructions on data entry of notelogs.

For example: If the name of the investigator who authorized randomization is Stephanie Jones-Hobgoodnotting, then you would enter:

Eligibility Criteria reviewed and randomization authorized by (name of investigator):

S	T	E	P	H	A	N	I		E		J	O	N	E	S	-	H	O	B	G	O	O	N	O	T

(enter the final T-I-N-G into a notelog)

13.6.4.1.2 Numeric Responses

Whenever numerical responses are required, enter the number so that the last digit appears in the rightmost box. Enter leading zeros where necessary to fill all boxes. (This does not apply to the address section or to any item which combines alphabetic and numeric information. Such items should be treated as alphabetic.)

For example: If the participant's diastolic blood pressure is 96, it should be coded as:

Diastolic BP:

0	9	6

It is possible that numeric fields could have a pre-printed number of decimal places. In this case, the QxQ instructions will specify the number of decimal places to be recorded. Instructions on how to round values to the expected number of decimal places are found in the QxQ instructions. When necessary, enter trailing zeros to fill the requested number of places to the right of the decimal point. Leading zeros may be needed so that all boxes to the left of the decimal are also filled.

For example: If a participant's temperature is 99.0°F, then it should be entered as:

Temperature:

0	9	9	.	0

13.6.4.1.3 Dates

In most cases when dates are recorded, slashes ("/") are to be used as the separator characters for month, day, and year. While these are pre-printed on the paper forms, they are **not** pre-printed in the DMS response fields and must be entered along with the numbers of the date. RIVUR uses the U.S. order for recording dates (month/day/year) in the following format: MM/DD/YYYY. The QxQ instructions may also contain information on how to handle

partial dates. When necessary, use leading zeros within each date unit (month or day or year) so that each box is filled.

For example: Data collected on April 3, 2005 would be recorded as:

Date of data collection: 0 4 / 0 3 / 2 0 0 5

13.6.4.1.4 Time

RIVUR usually records time using a 24-hour clock. When necessary, use leading zeros within each time unit (hour or minute) so that each box is filled. Note that midnight is recorded as 2400, and noon is recorded as 1200.

For example: If a participant was contacted at 1:45 PM, then it would be entered as

Time of contact: 1 3 4 5

13.6.4.1.5 Fill-In Boxes: Correcting Mistakes

To correct mistakes in the DMS, simply log onto the Web DMS in change mode and correct the affected fields. For complete instructions on correcting data in the DMS, please refer to chapter 14 of this manual.

On paper forms, if a number or letter is entered incorrectly, mark through the incorrect entry with an "X". Code the correct entry clearly above the original incorrect entry. The person making the corrections should initial the correction, using his/her first, middle and last initials, and record the date of the correction.

For example: If the participant's systolic blood pressure was actually 130, but was incorrectly entered:

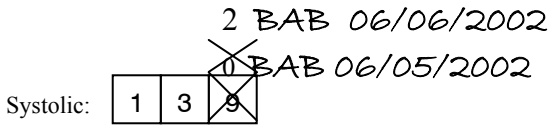
Systolic: 1 3 9

The correction would look like:

0 BAB 06/05/2002

Systolic: 1 3 ~~9~~

If a mistake is made, corrected, and then it is discovered that the correction is incorrect, make a second correction as shown below:



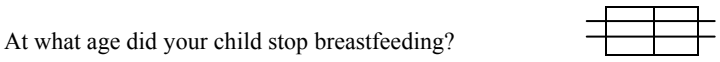
13.6.4.1.6 Fill In Boxes: Unknown or Not Applicable Information

In the DMS, if a data item is not applicable, then the item will automatically be skipped. For example: If you entered 'N' for the question, "Was your child ever breastfed," then you will not be prompted to answer the question "At what age did your child stop breastfeeding." (Please see "Skip Patterns" section later in this chapter.) If you are prompted for a data item in the DMS and the answer is applicable, but unknown, then leave the item blank unless otherwise instructed in the QxQs.

For paper forms, if an item *does not apply* to the participant being interviewed, and there is no clear skip pattern, then simply leave it **blank**. For example, on the Participant Contact Form there are spaces to provide multiple phone numbers for a participant. If the participant does not have an "other" phone number, then simply leave it blank and go on to the next question. Similarly, if the form provides spaces for three measurements, but only two are taken, the third space is left blank.

If the item *does apply*, but the response is unknown, mark through the box(es) with two horizontal lines (like long equal signs).

For example: During the Baseline Medical History interview, the parent guardian indicated that the child was breastfed at one time, but does not recall at what age the child stopped, and is unable to provide an estimate. The item "At what age did your child stop breastfeeding" *does apply* because it has been established that the participant was previously breastfed, but the answer to this question is *not known*. In this case, the response on the paper form would look like:



13.6.4.2 Multiple Choice: Recording Information

In this type of question several alternatives are given for the answer, each having a corresponding letter. When it is decided which alternative is most appropriate, circle the corresponding letter in the space provided. Always circle one letter only.

Example: If the participant indicates that they were told by their physician that their renal graft function has deteriorated, the response would look like:

Have you been told by your physician that your renal graft function has deteriorated? Y Yes

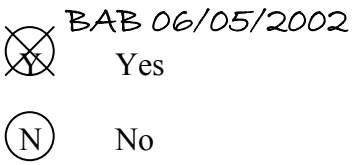
(N) No

13.6.4.2.1 Multiple Choice: Correcting Mistakes

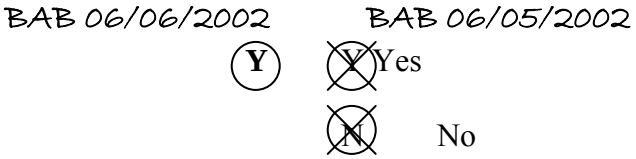
To correct mistakes in the DMS, simply log onto the Web DMS in change mode and correct the affected fields. For complete instructions on correcting data in the DMS, please refer to chapter 14 of this manual.

On paper forms, if a response is coded incorrectly, mark through the incorrectly coded response with an "X" and circle the correct response. The person making the corrections should initial the correction, using his/her first, middle and last initials, and record the date of the correction.

Example 1: The actual response is No, but Y was circled incorrectly. The correction looks like:



Example 2: If a mistake is made, corrected, and then it is discovered that the correction is incorrect, make a second correction as shown below:



13.6.4.3 Qualitative Data

Some forms need to collect a substantial amount of qualitative data, which will not fit in pre-designated boxes. An example of this would be the description of a serious adverse event. These responses should be as short and succinct as possible. Handwriting on paper form should be written carefully and legibly. Many of these items will be entered into the DMS as notelogs, which will allow variable length fields. Some will be items that were triggered to automatically pop up the notelog feature, others may require the user to open the notelog feature.

In addition to qualitative responses requiring entry via notelogs, all handwritten comments on a paper form, should be entered as a notelog associated with the specific item the comment refers.

Refer to the DMS User's Guide regarding notelog data entry.

13.6.4.4 Skip Patterns and "Go to" Boxes

Skip patterns occur in many multiple choice type items. Here, if a certain response is selected, it is necessary to skip over one or more items to the next applicable item. This is indicated by an arrow from the response which necessitates a skip, to a box containing a "go to" statement. If that response is selected, the next item to be entered is the one indicated in the box. If the other response is selected, always proceed to the next item unless otherwise directed in the QxQ.

Example: 18. Is this a Telephone Contact? Y Yes → [Go to Item 20]

N No

In this case, if the response is "Yes", skip to item 20. If the response is "No", proceed to the next question, item 19.

Occasionally, a skip pattern will occur in a fill-in type item. In those instances, specific instructions are provided on the form and QxQ. Again, if the skip criteria are not satisfied, continue with the next item.

A few items may trigger a skip regardless of the response. For these, follow the instructions on the form.

13.6.5 Problem Clarification and Data Queries

The DMS is programmed to automatically query out of range values during the data entry process. In addition, the DMS has a query resolution feature. Programmed edits regarding data values within or across forms will generate queries in the DMS. There may also be additional query from the DCC regarding data values discovered to be questionable during analysis or other more complicated data checks. These queries will be sent electronically to the data manager, forms will be identified by header information, data items will be identified by question numbers, the original response will be indicated, and the reason for query will be described. Corrections to these queries are also made through the DMS.

13.6.6 Permanently Missing Contacts

Follow-up and tracking of participants is critical in a randomized trail. A missed contact is never interpreted as a participant's withdrawal. In this type of study a participant is never considered withdrawn from the study, even when refusing contact. In the event that a participant's parent/guardian refuses consent for continued contact then the Consent Tracking Form (CTF) must be modified to stop any data queries from the DCC regarding expected forms not received. In the event that a protocol scheduled contact is missed, an FUP form for the missed Contact Occasion should be completed and noted in Section A of the form, this too will avoid queries for expected forms.

13.7 Data Management

13.7.1 Web Based Data Management

The RIVUR Data Management System [DMS] is a set of programs, which the DCC uses to manage data collected in the RIVUR Clinical Centers. This DMS has been designed for flexibility using World Wide Web systems. It is designed for data entry from paper forms or interactively as data is collected. The system can be used from any computer with a high speed Internet connection. Data entry computers must have Microsoft Internet Explorer 6. The RIVUR DMS User's Guide, Chapter 14 of the RIVUR MOP, provides specific instructions on its use. Username and Passwords to use the system will be provided to each site's Project Coordinator from the DCC in a secure and confidential manner.

The DMS provides several major functions:

- Data Entry: Allows data collection forms to be keyed, edited and updated, locally through the RIVUR internet DMS.
- Randomization: Provides interactive randomization through the RIVUR Web database.
- Data queries: The DMS has a data query and resolution feature that us run by the user.
- Reports: Provides reporting based on study need.

13.7.2 Clinical Center Data Management

The DMS will have numerous reporting programs designed as a tool to help facilitate data management at the sites. The RIVUR DMS reporting systems will generate participant lists, form inventories, scheduling reports, recruitment reports, missing forms reports, query reports, etc to help the field centers with any data management tasks. Requests for additional reports or lists can be made from a field center to the DCC.

Actual scheduling and other managing of participant flow, data collection, and filing of paper source data is the responsibility of the clinical site.

Chapter 14: the DMS User's Guide will contain documentation of the reporting facilities. Information on updates and changes to these reports will be provided through the Numbered Memo communication (Section 13.8.1). As these reports get updated and changed, additional training will occur during the monthly Project Coordinator conference calls.

13.7.3 Laboratory Data Management

Various specimen Collection and Processing Forms will allow tracking of laboratory specimen collection and processing. Additional specimen Shipping and Inventory Logs will also provide a specimen shipping and tracking system.

Refer to Chapter 5: Specimen Collection and Processing of the RIVUR MOP for further details..

13.7.4 Radiographic Images Data Management

Radiographic image Shipping and Inventory Logs will allow tracking of radiographic image collection and mailing.

Refer to Chapter 3: Radiology for detailed procedures regarding radiographic image collection and processing.

13.7.5 Data Management Reporting

The DMS will have numerous reporting programs designed as a tool to help facilitate data management at the sites. Chapter 14: Data Management User's Guide will contain documentation on the DMS reporting facilities. As these reports get updated and changed, training conference calls may be scheduled.

13.7.6 DMS Training and Certification

DMS training will be held in Chapel Hill during the studies central training before the study start. Project Coordinators of each site are required to be present, any site may send additional staff to these trainings.. Those attending may provide additional training to other staff members at their sites. Follow-up conference call training sessions will also be scheduled as needed. As new clinics are brought into the study, or as new Project Coordinator's are hired additional central training sessions will be scheduled as needed. There will also be site monitoring visits throughout the study and some DMS training can occur during these visits as well ,(depending on available time and resources.)

Refer to Chapter 12: Staffing and Training regarding the studies staffing and training requirements.

13.8 Official Study Documents

Current versions of all study documents, protocol, data collection forms, chapters of the MOP, user's guides, and other important documents are available on the study website at http://www.cscc.unc.edu/rivur/. These require the appropriate username and password for entry into the documents section. Each document exists as a PDF file in order to retain any necessary formatting.

IMPORTANT: Versions of these documents that are designated as usable in the field will have been sent to each study site in an official RIVUR Study Documents Notebook. One notebook will be provided to each Project Coordinator. Section 13.8.3 describes the process of communicating and verifying receipt of communication on modifications and updates of documents.

13.8.1 Numbered Memos:

The DCC will routinely send various emails or memos that are numbered and identified as "Numbered Memos". These memos are considered official documents and are to be stored at the back of the documents notebook. Updated information regarding the protocol, forms, MOP chapters, QxQ's, and other documents being used in the field will be sent to the centers as Numbered Memos. Numbered Memos will be sent to all RIVUR Project Coordinators and Steering Committee members. It is the site's Coordinator's responsibility to make sure this notification goes to all RIVUR staff at each site that is affected. Each Project Coordinator must send email confirmation of receipt of the Numbered Memo to Dana Edelen NEED ADDRESS.

The numbered memo will instruct the recipient to print from the Web the updated version and place this into the Site's Manual of Procedures Notebook (Project Coordinator's notebook), replacing the older version. Numbered memos should be stored at the back of each binder form back to front with the most recent memo on top. Each site should provide archival storage of previous versions of documents according to their Institutional requirements. The DCC will also keep all versions of official documents archived. Only memos that say DCC Memo # should be filed in the Numbered Memos section.

The Project Coordinator's notebook (not the PI's notebook) is considered each site's official documentation. The status of this notebook is monitored during any site monitoring visits.

13.8.2 Adding Revisions to the Manual of Procedures

All forms, MOP pages/chapters, MOP table of contents and QXQ's are saved in PDF format and are located on the RIVUR website at http://www.rivur.net. The DCC will send each Study Coordinator numbered memos via email regarding revisions to the MOP.

13.8.3 Instructions for Adding New/Corrected Materials

Forms:
Any new or corrected form will be available to print from the website. Forms should be replaced and copied for immediate use. Email confirmation to the DCC (Dana Edelen dana.edelen@mail.cscc.unc.edu) when the revised forms are downloaded.

Manual:
The revised pages/chapters of the FAVORIT Manual of Procedures should be printed from the website and filed immediately in the MOP binder. Email confirmation to the DCC (Dana Edelen dana.edelen@mail.cscc.unc.edu) when the revised pages/chapters are downloaded.

QXQ's:
Any new or corrected QXQ will be available to print from the website. They should be printed and filed immediately together with the appropriate form in the MOP binder. Email confirmation to the DCC (Dana Edelen email address dana.edelen@mail.cscc.unc.edu) when the new QXQ's are downloaded.

13.8.4 Instructions for Outdated Materials:

Take all outdated pages of the MOP, forms and QXQ's, attach to a copy of the appropriate numbered memo, and place in a permanent, chronological "Archive Manual" binder or file folder.

13.8.5 General Filing Instructions

All randomized participants should have either a binder or file folder filed in chronological order by participant ID. If the center prefers to file by last name there should be a cross-reference available with the corresponding ID number. It is important for centers to be able to communicate effectively with DCC by the participants' ID number. Data queries sent to the sites from the DCC will only identify participant ID numbers. **Remember, before sending any hospital records or forms to DCC, blind all personal information pertaining to the participant.**

Forms used for participants should be separated with index tab dividers or colored paper by the contact occasion/sequence #. This organization will expedite your response to data queries and facilitate site monitoring. For numerous hospitalizations, file by contact occasion and then by sequence number (example 1st hospitalization CO: 05, seq 01, 2nd hospitalization CO: 05, seq 02). Forms should be filed consistently with each contact occasion.

Each clinical site is responsible for assuring that participant study data is stored in a secure location that meets participant confidentiality requirements and assures the necessary masking of treatment assignment among the staff.

File all non-randomized participant forms together in a file.

13.9 Techniques for Conducting the Questionnaire Interviews

13.9.1 Introduction

This section stresses the importance of interviewer-participant's perceptions and introduces the concept of the interview as a one-sided passing of information. The interviewer's most important technique is analytic listening. Listening affects the interviewer-participant relationship as well as the content of the interview. There are several hallmark barriers to listening that every skilled interviewer recognizes:

- interviewer expectations
- interviewer fatigue and/or boredom
- interviewer anxiety
- interviewer impulsiveness

- note taking
- tendency to evaluate
- distractions and interruptions

Although no one interviewer experiences every one of these during any one interview, four remedies to the above barriers to listening are often suggested:

- Be prepared; lack of organization is in and of itself a distraction.
- Involve yourself in the interaction.
- Concentrate on listening to what is being said and what you are recording.
- Integrate the messages; does a response require further clarification or does it present contradiction to a previous statement?

When completing paper questionnaire forms, the recording practices below must be followed at all times. This will assure that the response recorded accurately reflects the participant's answers, and that the questionnaire data can be easily entered into the DMS.

- You must listen to what the participant says and record the appropriate answer if the response satisfies the objective of the question.
- In recording answers to open-ended questions or "other" categories, print the response verbatim.
- Use a black ballpoint pen.
- Record in the white space below the questions any responses "that don't quite fit" in one of the response categories. Your notes will help the analysts in understanding points of confusion, difficulty, etc. Notes on paper forms can be entered as notelogs in the DMS.
- Print or write legibly.
- If a participant refuses to answer a question, write "refused" in the left margin beside the question and enter equal signs in the response field.
- A single answer choice code must be circled in each question to represent the participant's answer, unless the item states you can circle all that apply.

Some of the questions in the RIVUR study ask about recall of events over time. You may assist the participant without violating probing rules by working with him/her on math or pinpointing dates or events. Another way to help pinpoint more accurate information is to ask the participant to think about time of year or season when an event occurred.

13.9.2 Response Styles

A structured interview, as is proposed here may sound like a conversation, but it is in fact not a conversation. It is rather one-sided passing of information. The interviewer can help to

maintain control of the interview by controlling his/her response style. It should be recognized that a large portion of the impression that the participant has of the interviewer is based on the interviewer's voice and the manner with which the interviewer responds to the participant's comments. Along this line, the interviewer may **never** respond in an **evaluative or judgmental manner**. Such a response would indicate that the interviewer has made a judgment of the relative goodness, appropriateness, effectiveness, or rightness of the participant's statement. Thus if the participant says, "I think I must have had 3 or 4 strokes before my wife made me call the doctor," the interviewer should not say, "Well, maybe you should have called him sooner." That type of response suggests that the participant has made an error which may, in fact, have resulted in causing his current medical problems. It should be borne in mind that the interviewer, by announcing affiliation with a medical study and conducting the interview in the hospital or clinic, has invested in him/herself the potential in the participant's mind for being part of the treatment staff, and this divestment of the role of caregiver while conducting the interview can be particularly difficult when the interviewer is at other times an active member of the institution's health care delivery system. Confronted with such a situation of answering an evaluative statement on the part of the interviewer, the participant may wish to terminate the interview.

A second type of response style is **interpretative** which might also be called teaching or preaching. An interpretative response is one which indicates that the interviewer's intent is to teach. This type of response is also not appropriate, as it would detract from the verbatim type of narrative that is required here. For instance, if the participant says that he/she experienced a sudden episode of right arm paralysis that went away after several hours, the interviewer should not say, "You probably had a TIA." We are interested in the participant's impression of what was happening, and not in the interviewer's impression. We are, further, interested in the facts that lead the participant to make an interpretative judgment, not in the interpretation itself.

A third response style that would be inappropriate would be **interrupting or sentence completion**. However slowly the participant is speaking, putting words in the participant's mouth, or not allowing the participant to finish thoughts will, in general, alter the information which the participant is attempting to give. However, long hesitations may be bridged by asking appropriate questions.

Appropriate response styles are discussed below. First, **supportive remarks** are ones that indicate that the intent of the interviewer is to reassure, to pacify, or to reduce the intensity of the participant's feelings. The general clucking, or understanding murmuring, are both supportive type remarks. Another, in response to the participant experiencing a sudden loss of sight might be, "That must have been difficult for you. Can you tell me what happened next?" Such remarks may help the participant to feel that the interviewer is still listening, is feeling empathy, and yet may not intrude on the flow of the conversation interview. Other supportive remarks, such as "Yes, my grandfather recently had a stroke, and it was a similar situation" probably will detract from the interview. Such remarks will certainly lengthen the interview in that the participant will probably want to go through the interviewer's grandfather's situation as well. While the interview with the participant may eventually be

completed, discussion of the interviewer's personal situation is non-productive and irrelevant.

The second appropriate response style is the **nondirective or understanding response** style. This is more frequently used when an interview includes a third person, acting as informant when the participant is experiencing a communication deficit. Should the participant's informant say, "My husband went into the bathroom, and then I heard a crash," the interviewer might respond by saying "I see." This is the general idea again of understanding murmuring or clucking. The interviewer also might repeat what the participant has just said, "Your husband went into the bathroom and you heard a noise." This may prompt the participant to elaborate.

A third appropriate response style which will be necessary in both types of interview is **probing**, although probing will be more restricted when the interviewer cannot speak directly with the participant who is reporting an event. A probe is a response that indicates that the interviewer's intent is to seek further information, to provoke further discussion along a certain line, to question the participant. Direct probes will be specific questions about details of what the participant has said. The interviewer is cautioned to limit the probes to those provided in this chapter. Another type of probe would be a request for clarification. Thus the interviewer might say, "I didn't understand that fully" or "Would you please elaborate on that?" Additional information on appropriate probing will be discussed in a later section.

13.9.3 Tempo of the Interview

Since the interview is focused on the participant, it must proceed at the pace which the participant, not the interviewer, finds comfortable. A deliberate, careful participant will be irritated and confused by having questions delivered too rapidly. It is well to remember that the participant is doing you a favor. If you go faster than s/he wants to, you give the impression that you are not really interested in what the answer is. If you go too slowly for a quick, decisive person, you will lose his/her interest, and s/he will be bored. Establishing the right tempo takes practice and observation.

13.9.4 Communication Traps

All interviewers, even those with a great deal of previous interviewing experience, should be aware of common communication problems in order to avoid them when conducting interviews. Some of these faults in communication are:

1. Anticipating and answering questions with the interviewer's own thoughts rather than the participant's. Thinking ahead and mentally finishing the participant's sentences will interfere with the interviewer's understanding of what the participant is really saying.
2. The interviewer hearing what he/she expects to hear rather than what is really being told to them. The interviewer must keep listening attentively.

3. Being drawn into the conversation personally by the participant. When dealing with an emotional participant there might be a tendency on the part of some participants to draw the interviewer into a discussion of his/her own similar experiences. The interviewer must guard against being made the "star" of the interview rather than the interview being centered on the participant. If this does occur, the interview will be longer than necessary or will fail to get the information needed.

13.9.5 Probing

Many participants will begin to pour out a good deal of information with little prompting. Others will have to be encouraged to give the information needed. With both types of participants, subsidiary questions may be needed to direct the conversation and elicit more complete answers.

A probe is a neutral, non-leading question designed to start an individual talking or to channel the conversation toward the information that is desired. Probes are used when an answer is unclear, incomplete, appears to be untrue or inconsistent, or when no response is given. There are precautions: do not interrupt the participant; do not give the impression that you are not listening; do not paraphrase the participant's words, and do not suggest an answer.

With the above caveats in mind, there are several types of probes which could be used effectively in the interview. Neutral probes include:

1. Silence: Silence is the most valuable probe. Many people react to silence. The interviewer who waits quietly and patiently will find a few seconds of silence is sufficient and the participant will often clarify a previously inadequate answer.

2. Repeating the question or a previous answer: If the answer given was irrelevant, be sure to repeat the question as stated in the questionnaire. In some cases, it will be necessary to remind the participant of the frame of reference, i.e., to remind him/her of a previous answer which led you to ask the current question.

3. Encouragement: "I see, un huh, hmm!" are effective. Without interrupting, the interviewer lets the participant know that s/he is still there and listening. Avoid comments like "okay" and "all right", which can be misinterpreted as being judgmental.

4. Definition: When asked by the participant for a definition of a term in the question, the interviewer can use the probes suggested in the instructions.

5. Clarification: Explanations to clear up an ambiguity: Could you explain that a little more?," "I'm sorry I didn't understand that." (This puts the onus of being unclear onto the interviewer rather than on the participant.)

6. Channeling is used with talkative individuals to focus on one aspect at a time "Tell me more about _____."

7. Continuation keeps the conversation moving with a non-verbal individual “And then what happened?", "What did you/he/she do then?"

8. Completion makes sure that all information on a participant is given before moving onto another area “Anything else?", "Can you tell me more about that?"

If the participant does not understand the question after one reading:

1. Repeat the question as worded, more carefully and slowly this time. (Often initial confusion is due to the interviewer's having read the questions too fast the first time. This extra time allows the participant to think and may be all that is needed for him/her to understand the question.)

2. Precede the (repeated) questions with a statement like, "Let me repeat the question....", so that the participant will understand that you are attempting to clarify the question for him/her.

If the participant still does not understand the question or asks you about its meaning:

1. Repeat the question exactly as worded.
2. Read the question slowly.
3. Precede the question with a phrase like, "The question I need to ask you..." so that again, the participant will not feel that you are simply impatiently reading the question as a command for his/her prompt answer.

Do not leave a probe dangling. Always record the response to a probe even if it's only "No" or "That's all I can think of."

Always cross-reference. When you probe to clarify a response, always indicate which response you are clarifying. There will be times when a participant will say something ambiguous and continue talking. When you probe to clarify the ambiguous response, indicate the question being clarified.

Examples of Neutral Probes:

- How do you mean that?
- I would like your opinion....
- Can you tell me more about this?
- Can you give me an example? Or, for example?
- Can you explain that in a little more detail?
- How are you using the term....?

- How is that?
- If you had to choose, which would you say?
- What else can you tell me about that?

Chapter 14: RIVUR Data Management System User's Guide

Table of Contents

Chapter 14: RIVUR Data Management System User's Guide

This User's Guide contains instructions pertinent to the operation of version 1.0 of the RIVUR Data Management System [DMS]. When the DMS is updated to a later version, the Coordinating Center will send update memos. Please refer to the update memos and any available addenda to this guide for complete instructions. In the event of significant changes to the DMS, a complete updated User's Guide will accompany the update.

14.1 RIVUR DMS

The RIVUR DMS is accessible over the World Wide Web. It will run on any computer with a high speed Internet connection. The computer must have Microsoft Internet Explorer 6 installed.

To access the system, open IE6**.**

Go to the URL https://dms.cscc.unc.edu/RIVUR.

14.2 Overview of Data Collection

In the course of performing a study, data for a number of participants must be collected at various times for later analysis. These data items are organized into groups of logically related information called forms or form types. Each form is then assigned a brief mnemonic code for easy reference, i.e. "BDF" for Baseline Demographics Form, "FUP" for Follow-up Form, etc.

It is sometimes necessary to change the content of a form during the course of a study. To allow for such changes, we assign a version letter to each form. The initial version is "A", and subsequent versions follow alphabetically. Thus, "BDFA" refers to "Baseline Demographics Form, Version A."

Since each form is be collected one or more times for each study participant, extra information is included to uniquely identify each recorded instance, or record, of a form. These identifiers, or key fields, include Study ID (ID) and Visit #. The ID is a unique code assigned to the participant. The Visit specifies the contact at which the form was collected. If more than one record is collected for a participant at a given Visit, a unique Form Sequence number must be assigned to each record.

We refer to all data items on a form as questions and assign a question number to each item. Typical question numbers may include both letters and numbers, e.g. 1, 2, 3a, 3b, etc.

Data items may be initially collected on paper forms and subsequently entered (or keyed) into an electronic database for statistical analysis. Or data may be recorded directly on the screen without being transcribed from a paper form.

A database consists of tables of data, arranged into fields and records. Each table (form) can store many records (instances of a form), each containing a set of values for every field (question) in the table.

Each table in the database must have a unique name for identification, as must each field in a table. We assign each table's name to be the form and version of the source of its data. We assign each field's name to be the name of its table and the question number of the source of its data. Hence, the table containing data for form BDF, version A, is named BDFA and contains fields named BDFA1, BDFA2, BDFA3, etc.

Each record in a table is uniquely identified by its set of key fields. Thus, no two records in a table may have the same set of key field values (ID, Form, Visit, Form Sequence).

14.3 DMS Functions

The RIVUR Data Management System [DMS] is a set of programs which manage data collected in the RIVUR Clinical Centers.

The DMS provides several major functions:

- Data Entry: Allows data to be keyed, edited and updated.
- Data Transfer: Allows laboratory data to be sent to the RIVUR Coordinating Center for inclusion in a consolidated database
- Randomization: Determines patient eligibility and, if a patient is eligible, assigns a treatment code to the patient.
- Reports: Provides eligibility reports, counts of records entered by form type, missing forms reports, query reports, form prints, etc.
- Query: Runs cross-form and cross field validation checks and generates error reports. Provides a mechanism for query resolution.

14.3.1 User Interface Standards

The DMS uses a combination of menus, mouse clicks and a few control keys to control its actions.

14.3.1.1 Keyboard, Mouse and Menus

The DMS uses the keyboard in a conventional way, i.e. the typewriter keys are used to type numbers, letters and symbols.

Items such as fields, menus and Ids and forms from the hierarchical menu can be selected using the mouse. To select an item, move the pointer to the item and press the left mouse button once.

Menu items can be selected using the mouse. Some menu options have further choices which are displayed in a pull-down list when the option is selected. Use the up and down arrow keys to move the bar to the desired option and click once.

Some submenu options have shortcut keys which are a combination of the ALT key and a letter, or the CTRL key and a letter. To use the shortcut hold down the ALT or CTRL key and simultaneously press the letter. Specific shortcut keys will be described when the menus are discussed.

Under some conditions menu options are unavailable. For example if a user does not have delete privileges, the Delete option is not available. Unavailable options are not highlighted and cannot be selected.

14.3.1.2 Lists

Some fields, for example the form field on the ID screen, can be selected from master lists. When the cursor is on the form field, put the cursor on the drop down arrow and click the left mouse button once. To select an item, place the highlighted bar on the item and click on the desired option. The item selected will be put in the field.

14.3.2 Information and Warning Messages

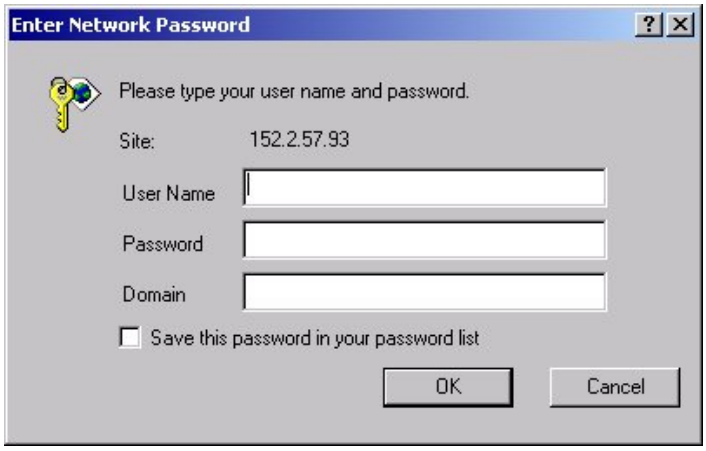
Messages from the DMS display a message box with the OK button:

The message remains on screen until you click OK or press Enter.

14.4 Data Entry

Start Internet Explorer 6. Enter the URL: **https://dms.cscc.unc.edu/RIVUR**

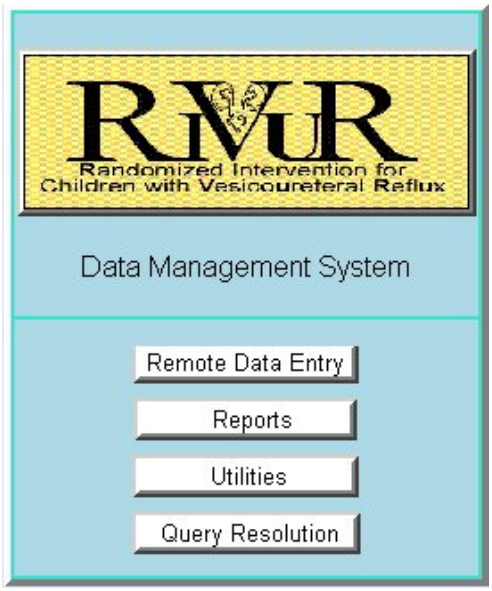
After your browser connects to the site, you will get the following login screen.



This Windows login provides the first level of security for accessing the RIVUR Data Management System. The Coordinating Center will assign you a User name and password.

14.4.1 System Menu

After you successfully log in to Windows, the DMS menu is displayed:



'Remote Data Entry' is available when the computer you are using is connected to the internet. The Remote data entry option writes data directly to the RIVUR study database at the coordinating center.

To remove the IE tools bars and thus have more area on which to display data entry screens, press F11. This toggles the tool bars on and off.

14.4.2 Login and Timeout

The second level of ID and password security require you to enter another ID and password in order use any. The data coordinator at each site will assign these IDs and passwords.

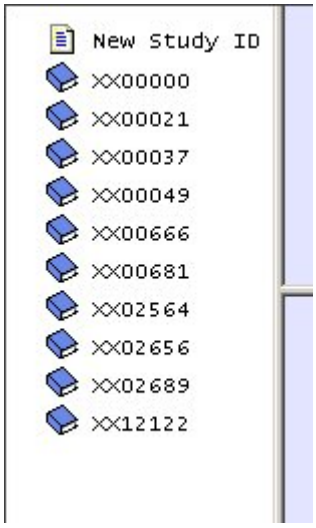
Enter your user name and password. Then click the 'Login' button. If the user name or password is invalid you will see the following screen:

After the DMS is started, leaving it unattended presents a security problem because an unauthorized person could view confidential data. If no contact is made between the browser (running on your computer) and the server (saving a form, requesting an existing form) for 10 minutes, the system will time out. If the system times out, you see the following screen:

If you were working on a form and had made changes, the changes will be saved. You must log in again.

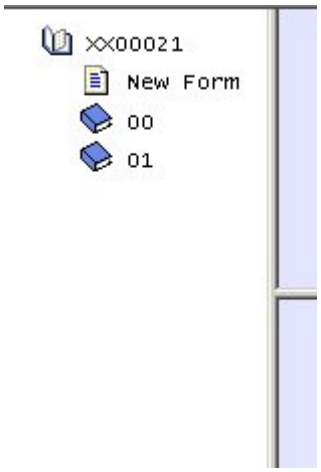
14.4.3 Entering Data

After you enter a valid user name and password, a screen with 3 panels will be displayed. The panel or frame on left displays the hierarchical menu of IDs for your center. This menu can be expanded to display all forms entered for an ID. It is the mechanism by which you can move from one form to another or from one ID to another.



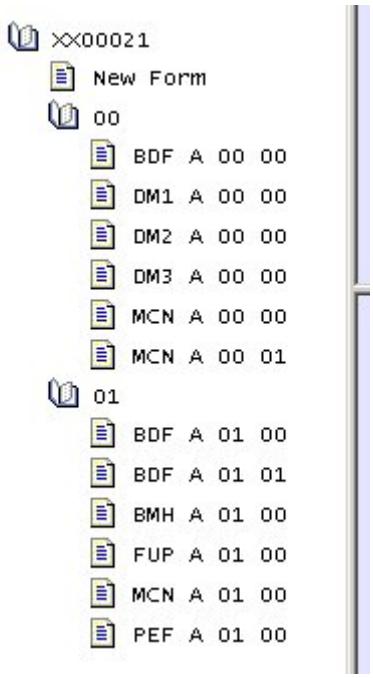
The first selection in the menu is 'New Subject. Click 'New Subject' to add an ID not in the list.

To display all forms for an ID, click on the ID. A list of visits for the ID will be displayed. In the example below, the user clicked on ID XX00021. All visits which have at least one form are listed.



Click on 'New Form' to add a form for a visit which currently has no forms.

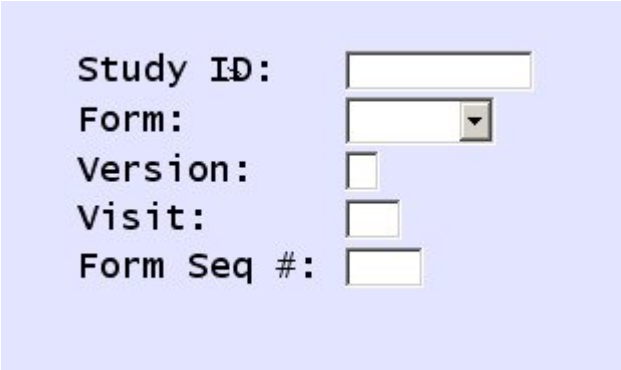
Click on a visit to show all forms entered for that visit. In the example below the user clicked on visit 00. The form mnemonic, version, visit and sequence number are shown in columns. In the example below, Subject XX00021 has 6 forms at visit 00 – BDF, DM1, DM2, DM3 and 2 MCN forms. The form sequence numbers – 00 and 01 – are listed beside visit 00. Subject XX00021 has 6 forms at visit 01.



To return to the complete list of Ids, click on the ID at the top of the menu.

14.4.4 Adding a New Form

When you click New Subject to add the first form for a Subject or when you click on New Form to add the first form for a visit or a new form to an existing visit, the ID screen will be displayed:



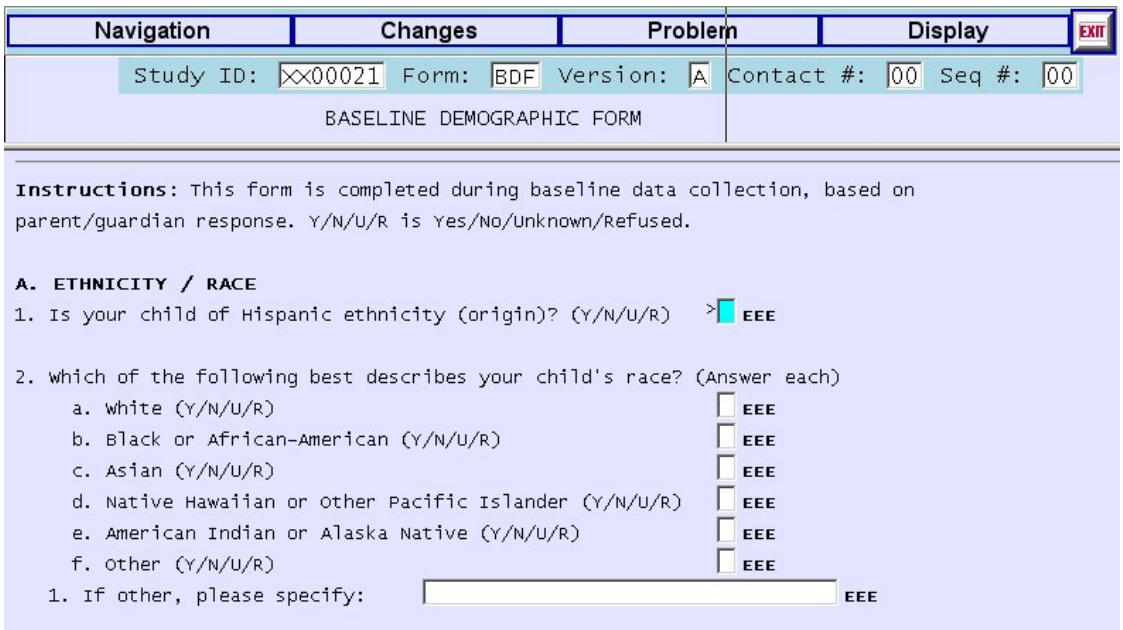
Enter the key fields for the form you are adding. After you enter the last field, a blank form of the type specified will be displayed.

14.4.5 Changing an Existing Form

To change an existing form, click on the row in the hierarchical menu which gives the form, version, visit and sequence number. The form with data will be displayed.

14.4.6 Form Entry

When a form is displayed, the top frame of the screen shows the key fields for the record. The cursor is on the first data field of the record. A menu bar fills the first line of the screen.



There are 3 types of entry fields: text boxes, drop down lists and check boxes.

1. Text Boxes: (all fields in example above.) When entering data in text fields, the cursor will move to the next field automatically if the response fills the field. If the response does not fill the field, you must press enter to advance the cursor.

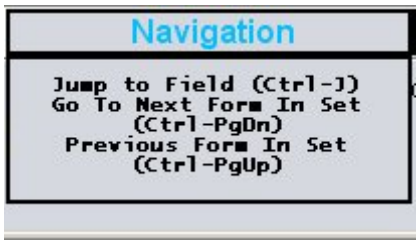
2. Select Lists: (not shown in example above.) To select a response from a drop down list, click on the down arrow on the right end of the response box. A list of valid responses will be displayed. Click once on the appropriate choice. Once you have selected a response, the cursor will advance to the next field.

3. Check Boxes: (not shown in example above.) To choose a check box, click on the box. Clicking once checks the box; a '1' will be stored in the database for a checked box. Clicking again, un-selects the box; a '0' will be stored in the box. If a box is not touched, a missing will be stored in the database.

14.4.7 Menu Options

14.4.7.1 Navigation Option

The options under 'Navigation' allow you to 'Jump to Field' or move to the previous or next form in a form set.



Jump to Field allows you to move to a specific question on the form. Selecting this option brings up a menu in which you enter the number of the question to which you want to go:

If you enter an invalid question number you will be alerted.

Jump to Field allows you to go to skipped fields. Jump to field will not let you bypass a must enter (mandatory) field. If you enter a question number which falls after a must enter field which is blank, the cursor instead stops at the must enter field.

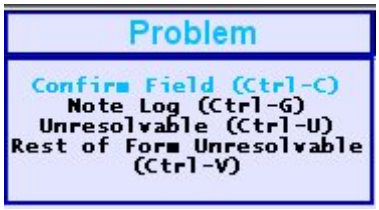
Form sets

Some forms are grouped into 'form sets'. The group is given a form mnemonic and that is the form name entered on the ID screen. Forms in a form set come up in a pre-determined order. When you are entering a form set once you save the first form, you can choose 'Go to Next form in Set' from the Navigation menu or press CTRL+PGDN to move to the next form in the set.

14.4.7.2 Problem Option

As you enter data values into a record, they are edited. Each data field that you enter has an associated status byte vector which stores editing information about the field, such as whether the field is empty, missing, or contains an out-of-range value. The status byte value for an empty field is 'E'. When a valid value is entered, the status byte becomes 'A'. Other status byte values are determined by the user when selecting choices from the Problem option.

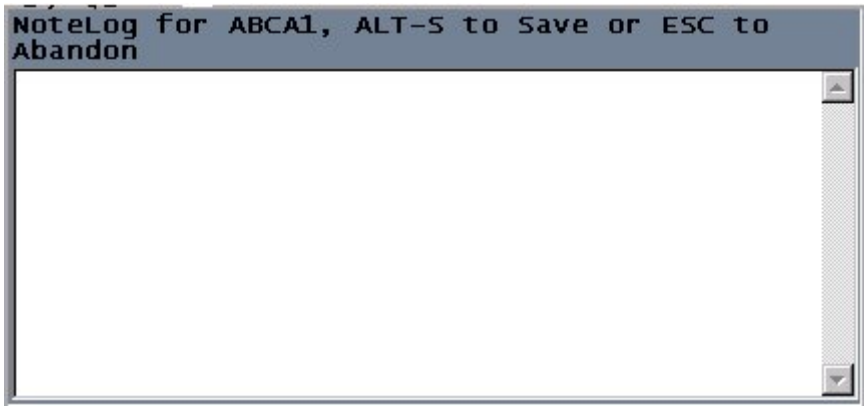
The problem option allows the following choices:



If a value fails an edit, for example if it is out of range or inconsistent with other values, an error window alerts you and gives the valid range or list of valid values:

Press OK to clear the message. Check that what you entered is what was collected on the form. If not, retype the value. If the value is correct but out of range, confirm it. using the first choice of Problem Option. This sets the status byte for the field to 'C'.

Some fields may require additional comments. A note log can hold a value for an 'other' option or a comment on the value of a field. The responses to some fields cause a note log to be displayed automatically. You can also create a note log manually by selecting 'Note Log' from the Problem Menu. The following screen is displayed:



Enter the text for the note. Press ALT+S to save the note log or press ESC to cancel the note log.

If a field has an associated note log the 3rd status byte changes from 'E' to 'N'.

To delete a note log, open the note log and delete all text. Then press ALT+S to save.

If a value cannot be collected or when the value you did collect is suspicious and should not be used in analysis, you can set the field to Unresolvable. You can also set all remaining fields on a form to Unresolvable.

Unresolvable sets the first status byte to 'U' and, if the field is blank, fills the field with equal signs (==) or for a select list field, sets the value to '= unresolvable'. Note that you can set a field to Unresolvable by keying the equal signs into the field rather than using the Problem menu.

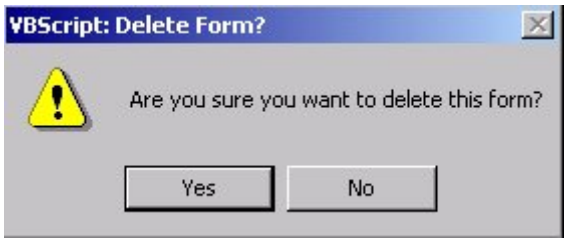
Set rest of form to Unresolvable fills all remaining fields on a form with equal signs and sets their first status bytes to 'U'.

14.4.7.3 Changes Option

The Changes Menu provides options that allow you to save a new form, save changes to an existing form, cancel changes or delete a form or set a form to Permanently Missing.

Select **Save** to save the current state of the record to the database.

Select **Cancel** to cancel all changes to an existing record or to cancel the addition of a new record.
Select **Delete** to delete an existing form from the database. You will be prompted:



If a form is expected at a visit but cannot, for some reason be collected, set the form to **'Permanently Missing'** using the 'Perm. Missing' option on the Changes menu. This alerts the coordinating center that you are not able to collect these data. The coordinating center will know not to query you about the record. A record can be set to permanently missing only in Add mode.

When a record is set to permanently missing, the first status bytes for all fields are set to 'P'. When displaying a permanently missing record, the header frame indicates the record is permanently missing.

You cannot save changes to any field.

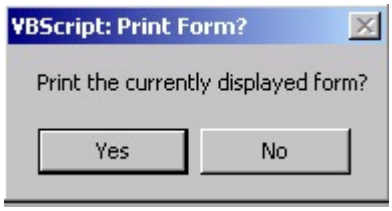
Key fields, fields that uniquely identify a record, can be change by selecting **'Key Field Change'** from the Changes menu. After you select 'Key Field Change' the cursor will be focused on the ID field in the header frame of the screen. You can change the ID, Visit or Form Sequence Number using this option. You cannot change the key fields of a record if a record with the new key fields already exists in the database.

14.4.7.4 Display Option

The display option allows the user to turn off display of the status vectors. The display is turned off only while the current form is displayed. When you display a new form, the status vectors reappear.

14.4.7.5 Print Form

To print a paper copy of a DMS form, display the form on the screen. With the cursor in the body of the form, right click. The following message will be shown:



Choose "Yes" to print.

Print form should be used only when a printer is attached to the DMS computer or laptop

14.4.8 Skips

Some fields are answered conditionally. That is, a certain response to one field can cause subsequent fields to be unnecessary or irrelevant. In the DMS these fields are skipped. After a response is entered into the trigger field, the cursor skips ahead to the next relevant field. Since the cursor is sometimes hard to find after a long skip, the currently active field is identified by a ">" symbol.

You cannot move to a skipped field.
The status bytes of skipped fields are changed to indicate the fields were skipped. The status byte values remain the same but are changed from upper to lower case.

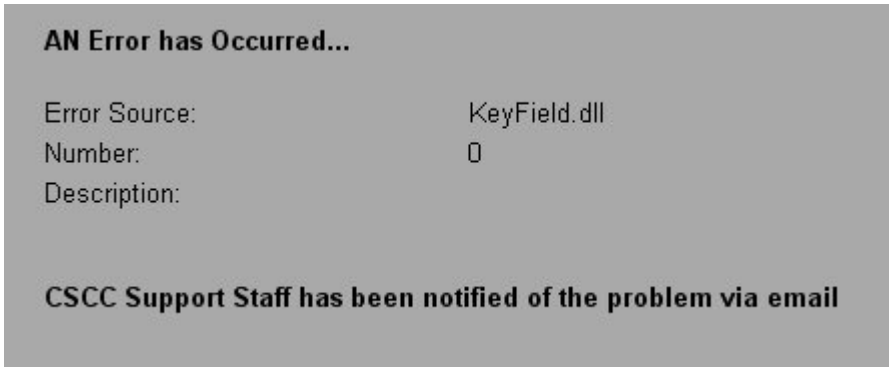
14.4.9 Saving a Form

There are several ways to save a new form or to save changes made to an existing form.

1. Select 'Save Form' from the Changes Menu.
2. Press ALT+S when the cursor is in the data frame section of the screen.
3. Click another item in the Hierarchical Menu.
4. Close the browser by clicking on the "X" in the right corner.
5. Click the 'Exit' button on the menu bar.

14.4.10 Fatal Errors

Occasionally the system might experience a fatal error. When this happens you will see the following screen:

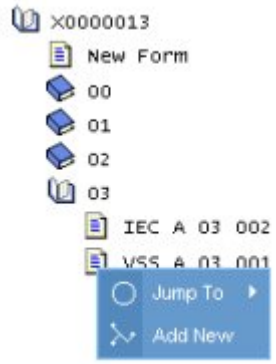


When a fatal error occurs, an email is automatically sent to the DMS staff at the coordinating center. They will work on a solution as soon as possible. You can also call to verify that they received an email. It will not damage the system to go back in and try another task.

14.4.11 Multi-Line Forms

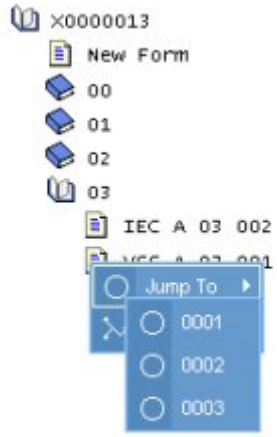
Some forms are arranged with many lines of values for a small set of data items. These **Multi-Line** forms are keyed in much the same way as other forms. To add a new form, enter the key fields on the ID screen. Once the record is displayed, you will notice that only the values of a single line appear on the screen. The line number of the current line is displayed in the **Header Window.** Once you have keyed all values for the line, the line is saved.

To add another line for the same form, **right** click on the **icon of the page** beside the form name in the hierarchical menu. (If you click anywhere else in the hierarchical menu, you will be asked if you want to print the ID list.)



Click on "Add New" from this pop-up. A new set of blank fields will appear for entry and the cursor will move to the first field of the screen. Continue adding new lines until you have added all lines which appear on the form.

You may move from a line to another in a multi-line form by selecting “Jump To” from the pop-up in the hierarchical menu.

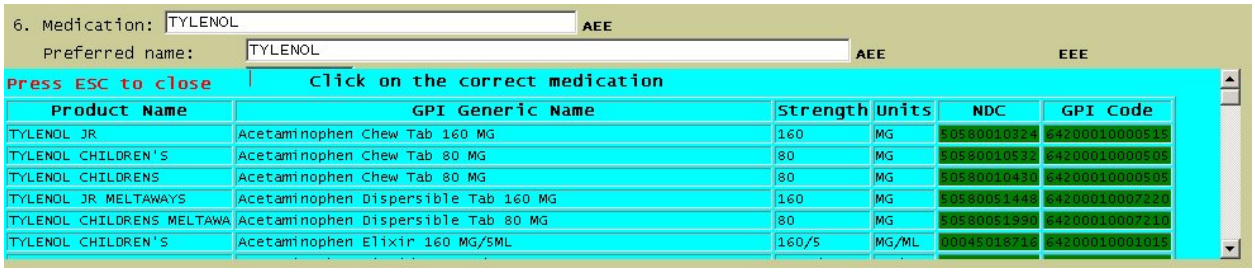


Left click on the line number you want to display.

If you wish to delete a line from the record, use the **Delete form** option on the “Change” menu.

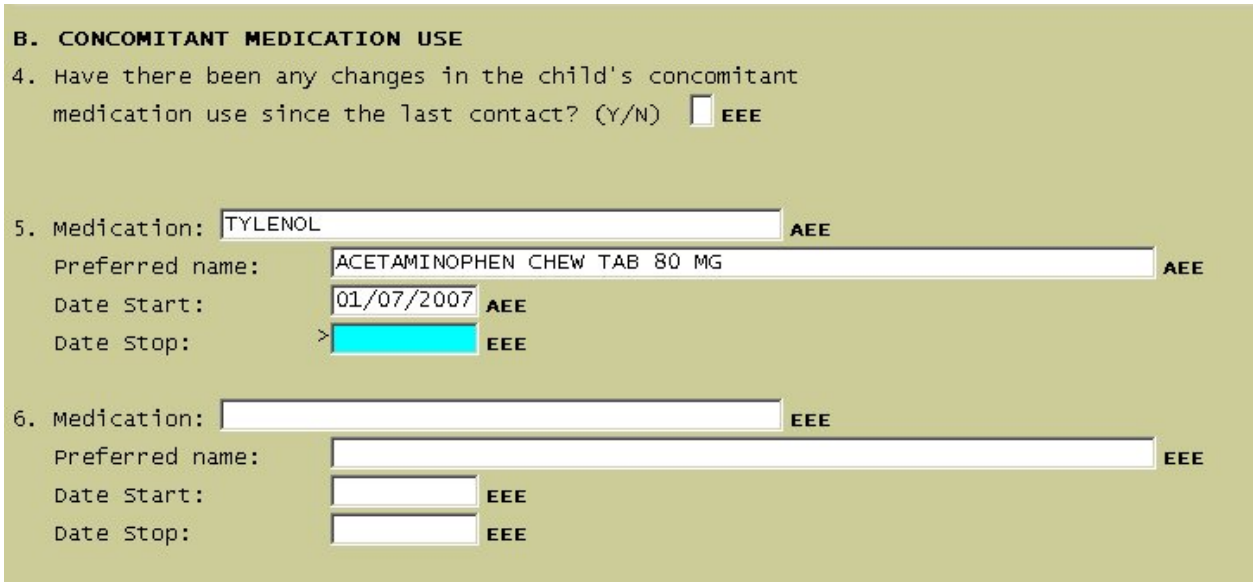
14.4.12 Look-up Fields

Some fields are entered and then coded using a standard coding scheme. Medications and adverse events are both coded by the DMS. On the CMF form, there are sets of fields for recording medication names and the start and stop date for each. To perform the coding, enter the medication name in the field labeled ‘Medication’. Enter the same name in the field labeled ‘Preferred Name’. When you press Enter after the ‘Preferred Name’ field, a look-up table will be displayed with potential matches for the medication. For example, if ‘Tylenol’ is entered, the following list is displayed:



Product Name	GPI Generic Name	Strength	Units	NDC	GPI Code
TYLENOL JR	Acetaminophen Chew Tab 160 MG	160	MG	50580010324	64200010000515
TYLENOL CHILDREN'S	Acetaminophen Chew Tab 80 MG	80	MG	50580010532	64200010000505
TYLENOL CHILDRENS	Acetaminophen Chew Tab 80 MG	80	MG	50580010430	64200010000505
TYLENOL JR MELTAWAYS	Acetaminophen Dispersible Tab 160 MG	160	MG	50580051448	64200010007220
TYLENOL CHILDRENS MELTAWA	Acetaminophen Dispersible Tab 80 MG	80	MG	50580051990	64200010007210
TYLENOL CHILDREN'S	Acetaminophen Elixir 160 MG/5ML	160/5	MG/ML	00045018716	64200010001015

The list is long so there is a scroll bar on the right. Find the correct medication and then click on the product name or generic name you want. That name will replace what you have typed into the ‘Preferred Name’ field. The code associated with your selection is stored in the database.



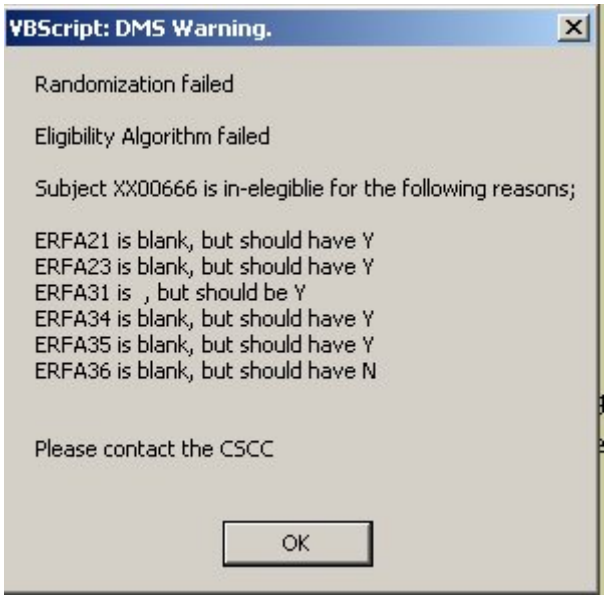
The AEF form has a similar look-up feature for coding Adverse Events.

14.5 Randomization

To randomize a patient, select 'Data Entry' and enter an ERF form for the patient. The ERF form must be entered at Visit 01, Form Seq # 01.

The ERP includes questions to determine whether the patient is eligible. After entering eligibility information, you are asked if you want to randomize. If you respond 'Y', the the randomization program checks the eligibility criteria.

If the patient is ineligible the program warns you:



If the patient is eligible on all criteria, the system assigns a treatment group and displays a message that the randomization was successful.

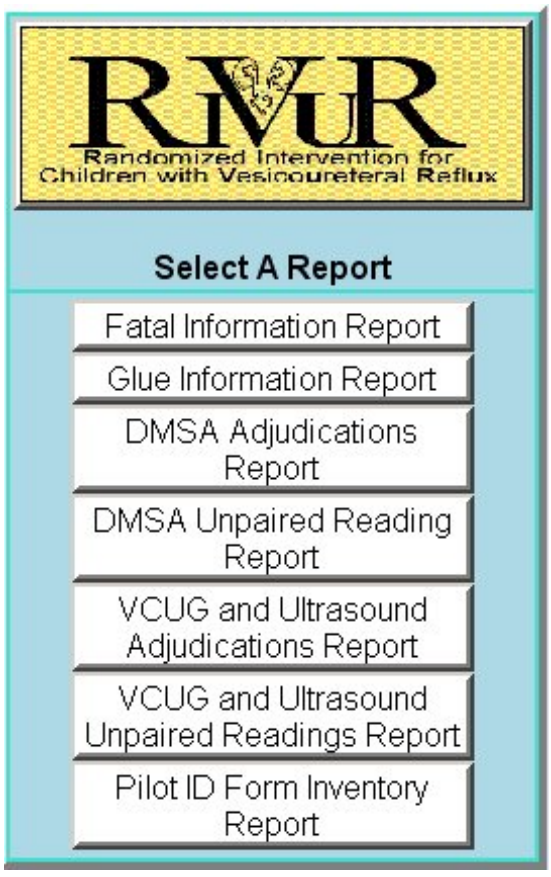
Once a patient is randomized, you can neither delete the ERF form nor change its values. If you access the form, you are automatically forced into Browse only mode.

To determine which bottles to prescribe to a patient, you fill out the MDD form. The MDD form determines the dosage and the bottle numbers to give to the patient based on the patient's weight and the randomization assignment.

14.6 Reports

The RIVUR DMS has several reports including the recruitment and randomization report and form inventory report.

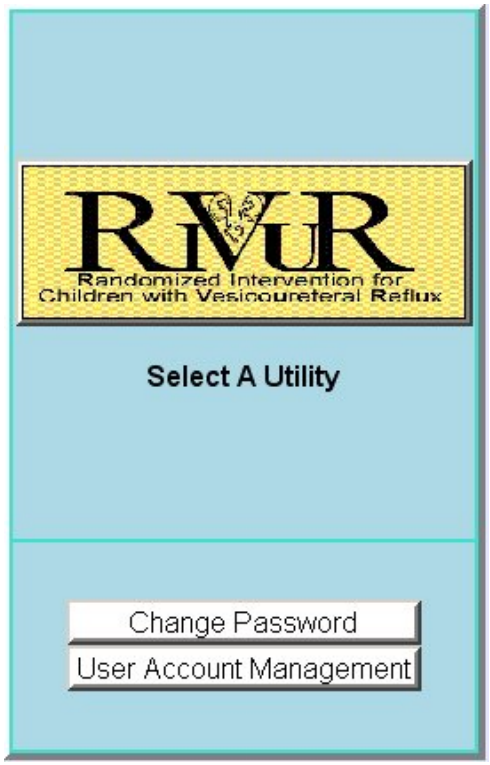
To run reports, choose Reports from the main menu. After you log in with your RIVUR user name and password you get the Report Menu:



Details of the individual reports are in a separate appendix.

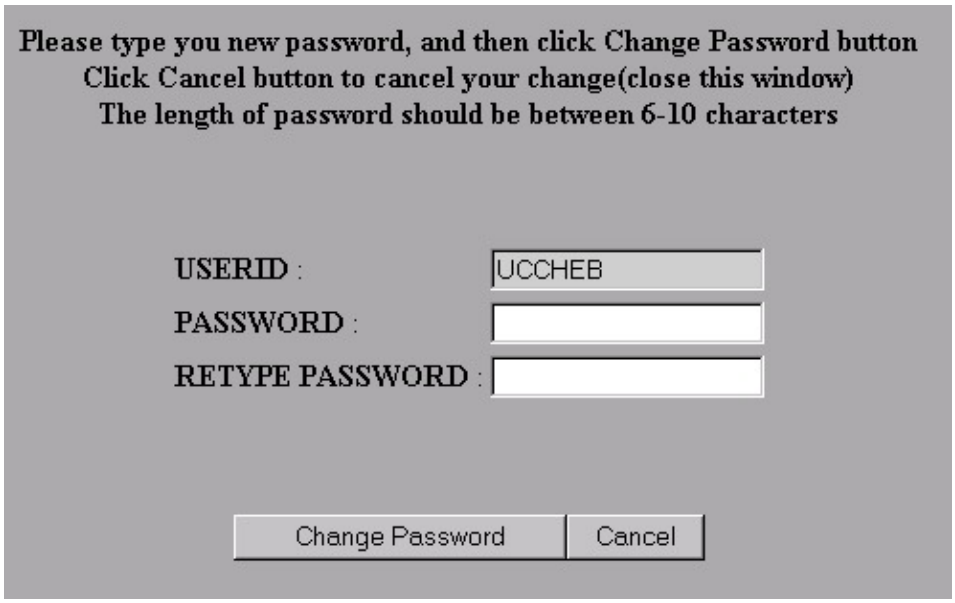
14.7 Utilities

The Utilities are a set of programs with perform functions outside normal data entry and reporting. To run the Utilities, choose Utilities from the RIVUR main menu. The Utilities menu is displayed:



14.7.1 Change Password

Each user can change his own password by running the 'Change Password' utility. You are prompted to enter your new password and then re-enter it for confirmation:



If you enter a valid password and confirm it, you get the message:

14.7.2 User Account Management

The User Account Management utility is used to create new users, assign them privileges and change the privileges of existing users.

Privileges are granted or revoked for groups of tasks such as entering forms, running reports and running utilities. Each group of tasks has an associated set of permissions. The default groups are Form_alluser, Form_randomization, Report_alluser, Utility_Coordinator and Utility_alluser. The default permission set for each group is as follows:

Task	Default Permission
Form_Alluser	Add, browse, change, delete
Form_Randomization	Ability to randomize a patient

Report_Alluser	View all available reports
Report_Radiology	Report for radiologists
Utility_coordinator	Account management, change password, other study utilities such as data upload
Utility_alluser	Change Password

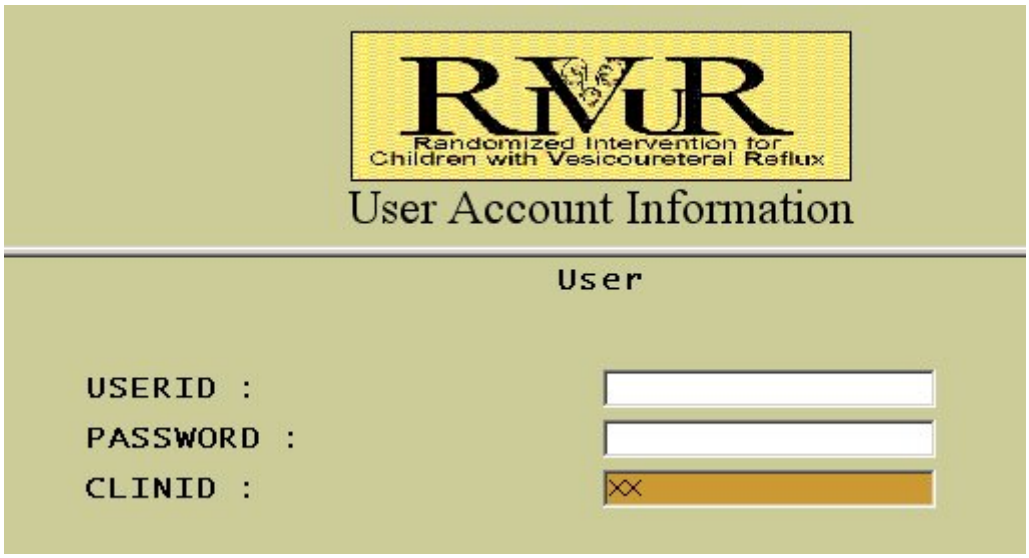
A user who has permission for Utility_coordinator can grant or revoke the default permissions for any task for any user using 'User Account Management'. For most users, Utility_alluser is the appropriate utility group. This allows them to change their own passwords but nothing else.

These are the groups and permissions set up by default. If, at your site, you need more finely tuned permissions, please make a request to the coordinating center detailing the tasks to include. For example, you may wish to grant some users only browse permission to all forms or you may wish to allow some users full access to a subset of forms

When you select User Account Management from the Utility menu the following screen is shown:

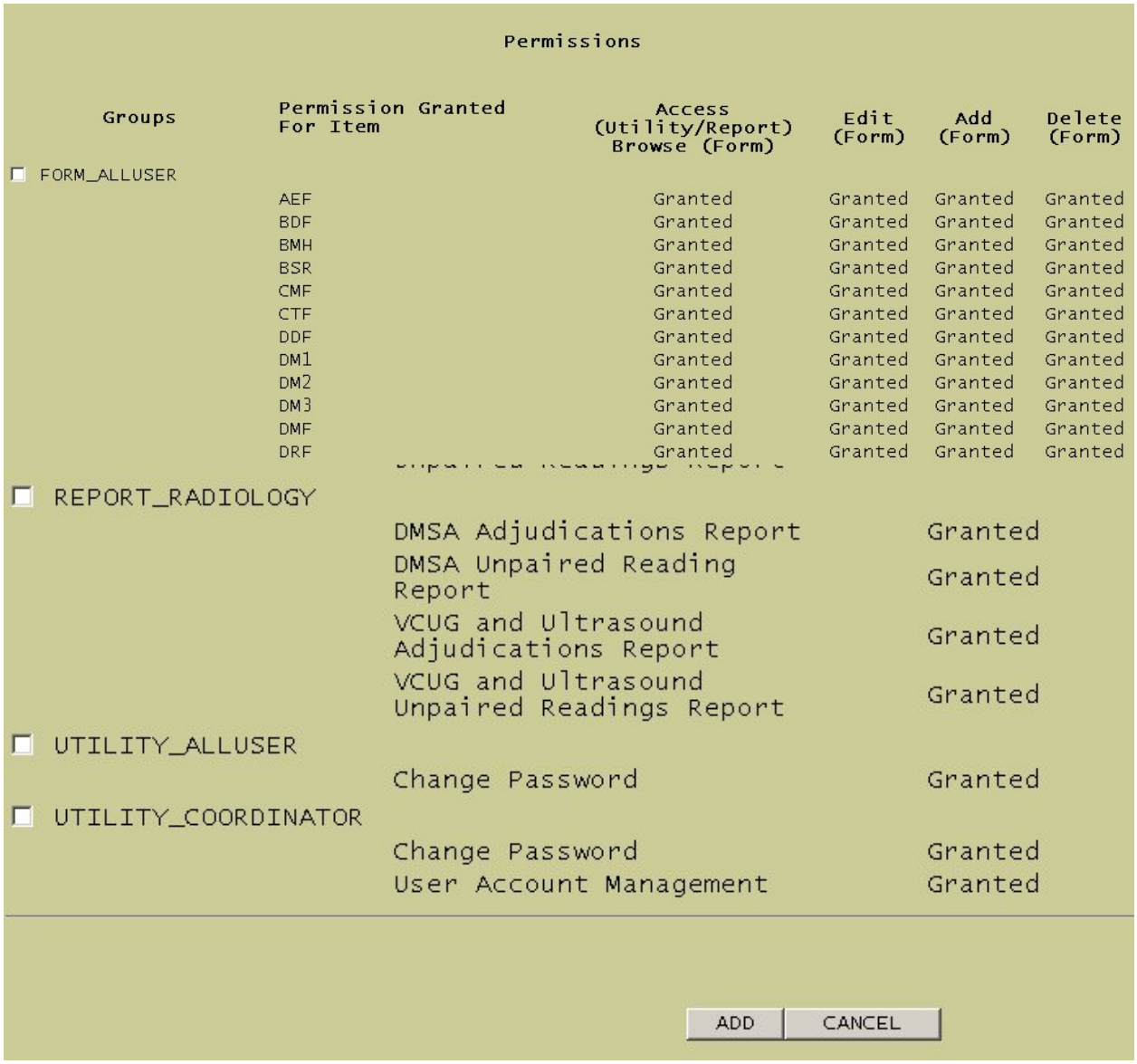
All user names from the current user's site are listed on the left side of the screen.

To add a new user, click the 'New User' item. A screen is displayed:



Enter the user name and password in the top panel.

Select the privileges to grant to the user in the second panel. Click the 'Add' button to add the user.



Click 'Add' to add the new user.

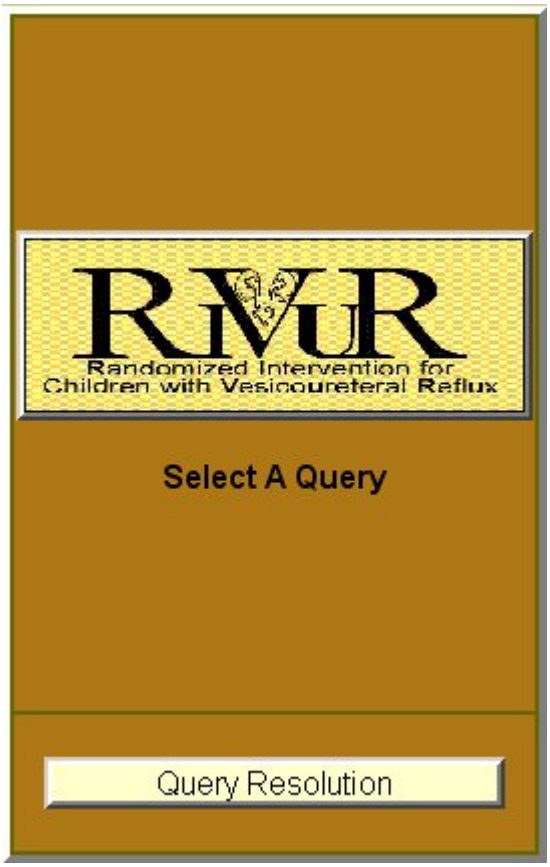
To change the password or privileges of a user, select the user from the list and make the desired changes. Click the 'Update' button to commit the changes.

14.8 Queries

Data queries are generated automatically by the system. Some examples of queries which will be included in the system are:

1. Missing forms, based on expected forms per visit.
2. Missing fields identified as critical.

Query reports are run overnight and are available for viewing, printing and resolving the following day. To access query report, select the "Queries" item on the main menu. Enter your DMS user ID and password. The following menu will be displayed:



Select 'Query Resolution' to go into a data entry system which allows you to resolve queries. The menus and features are almost identical to normal data entry. The main difference is that when you display a form which contains outstanding queries, only the fields involved in a query are accessible. The other fields are only for display.

14.9 DMS Updates

During the course of the study, the coordinating center will update the Data Management System software. These updates may include new or updated forms for data collection, new features or reports, and corrections for errors which are detected in the system. Each update will include a memorandum detailing the changes to the DMS which are included in the update. Please insert this memorandum at the end of the User's Guide so that it includes the most up-to-date information about the DMS.

Appendix 14.1 – RIVUR DMS Quick Start Instructions

These instructions are intended to serve as a quick reference for using the RIVUR Data Management System (DMS), and are not a substitute for mastering the contents of the User's Guide.

Whom do I contact if I have a problem / question / concern?

Contact Dana Edelen or Dawn Stewart at the RIVUR Coordinating Center.

Starting the System

Connect to the RIVUR Web site at https://dms.cscc.unc.edu/RIVUR using Windows Internet Explorer 6.
Log in to Windows with your Windows ID and password.
Choose an option from the RIVUR DMS menu.
Log in to the DMS by keying your initials and your password. If you key the wrong initials, go ahead and key your password. You'll see the message "Login Failed." Key both in again.

Exiting the System

To exit the system, close IE6.

Appendix 14.2 – RIVUR Data Management System Security

Several measures are in place on the RIVUR Web server to ensure the security of study data. The site runs SSL (secure sockets layer) to encrypt data as it is transmitted from the user to the server. The SSL encryption is provided by 128 bit session keys provided by digital certificates. A user must provide a Windows 2000 user name and password to access the RIVUR main menu. To use the DMS, the user must also supply a DMS user name and password. Users have differing permissions. Users with full permission can add, change and delete records, randomized participants and run reports. Other users may only have permission to browse records and view reports.

The servers hosting the RIVUR DMS Web site have implemented many security measures recommended by security experts such as disabling unused ports and services, applying all operating system and Internet Server patches as they are released and running automated reports on certain access logs.

RIVUR Publication and Presentation Policy
September 14, 2012

A. Introduction and Overview

The aim of the following publication policy is to ensure scientific quality and facilitate the production of novel research contributions based on data collected by RIVUR. A secondary aim of this publication policy is to ensure a fair collaborative effort among RIVUR investigators. The publication policy follows the JAMA guidelines for all issues not explicitly discussed herein.

1. Objectives of Publication Committee

a. To encourage timely development and submission of high quality publications and presentations from the RIVUR trial.

b. To provide all collaborating investigators with equitable opportunity to participate in and author publications and presentations

c. To prevent premature dissemination of results that might jeopardize the scientific integrity of the study or compromise publication in peer-reviewed journals.

2. Guiding Principles

a. The data collected by RIVUR study are the joint property of the Principal Investigators and NIDDK.

b. No data collected as part of the RIVUR study will be presented, published, or otherwise disseminated, except as provided for under these guidelines.

c. Ultimately, RIVUR data, with appropriate provisions for protection of participant privacy and confidentiality, will be made publicly available, as specified in the NIH policy on data sharing. Use of that version of the database is not controlled by this policy.

All material to be presented orally or submitted for publication or dissemination by individuals associated with the RIVUR and dealing with any aspect of the RIVUR must receive prior review and approval by the Publications Committee (PC) with the following exception:

The PC need not review material prepared for publicity purposes, either nationally, or within the recruitment region of a RIVUR site, or presentations designed to inform professional audiences about the RIVUR study design and objectives. Such material must not include RIVUR data that have not been approved by the PC and presented or published previously.

B. Organization

1. Publications Committee

a. The Publications Committee will be responsible for reviewing proposals for manuscripts and presentations, for managing the development of manuscripts, and for reviewing and approving manuscripts, abstracts and presentations prior to submission. The Committee will be responsible for adjudicating any conflicts that may arise between writing groups.

b. The Publications Committee will be chaired by the Chair of the Steering Committee and will include one member each from the Data Coordinating Center, the NIDDK Project Office, and each of the five core clinical sites.

c. The Steering Committee will monitor the progress of data collection and database closure and will announce the points at which proposals for baseline and outcome manuscripts will be acted on by the PC.

d. The Chair of the PC will review each manuscript proposal for overlap with existing proposals. In such cases, the overlap will be communicated to the proposer and to the lead of the relevant Writing Group. The proposer will then be responsible for contacting the lead of the existing writing group to adjudicate the overlap.

e. The PC will prepare a list of potential publications and presentations and delegate the responsibility for a particular project to the appropriate individual(s).

2. Writing Groups (WG)

Topics suggested for presentation or publication will be discussed by the PC, which will decide on the lead author and the composition of the writing group. This initial WG will suggest and justify names for authors to be reviewed by the PC. If a topic is suggested by a participating investigator in the RIVUR trial, the writing group will be formed as just described except that the person making the suggestion may be considered as the lead author.

The PI of an ancillary study would be the lead author of material derived from that study. Disputes regarding authorship will be settled by the PC Chair after consultation with the members of the PC. All writing groups that require analysis of RIVUR data will be assigned a member from the DCC.

a. In general writing groups should include no more than eight or nine individuals. Where practical, members should be included from a variety of RIVUR sites (i.e., clinical centers, DCC, central laboratory, clinical endpoints committee, reference radiologists, and the NIDDK)

b. Each writing group for a manuscript or presentation that will include RIVUR data must include a statistician from the DCC.

c. The Chair of the writing group is responsible for communicating with the members to develop the manuscript. This ordinarily will involve a series of conference calls, e-mail communications, and perhaps, in-person meetings. The analysis plan provided in the manuscript proposal may be elaborated through a Statistical Analysis Plan developed by the DCC statistician, and will be used to create one or more statistical computing requests. These computing requests will be prepared by the DCC representative on the writing group. The DCC representative will provide the group with statistical reports, including tables, figures, and text with results of those analyses.

d. Membership on a writing group is not sufficient to warrant authorship credit. Each individual listed as a co-author is expected to make significant scientific contributions to the manuscript (see, as an example, the JAMA instructions for authors for definitions of "significant scientific contributions").

2A. Typical Features of Writing Group

Generally, a writing group consists of four to eight or nine investigators and its composition may vary to include core site investigators, satellite site investigators and ancillary study investigators as well as statisticians from the DCC and NIDDK representatives. The investigator who submits the manuscript proposal may either be the lead or senior author. During its review of the manuscript proposal, voting members of the PC may name study representative co-authors. If none are specified within two weeks of proposal approval, it may result in no co-author from the voting member's site. Periodically, the Steering Committee may be polled for interest in joining recently approved writing groups. The writing committee for unapproved or withdrawn manuscript proposals is disbanded.

Ancillary or secondary studies do not need to have a co-author from each of the six sites of the study, but should represent the cores that contributed data to the study being reported. In accordance with the responsibility of co-authorship in scientific publications, individuals should only be co-authors if they have substantially contributed to the manuscript. Each voting member of the PC reserves the right of not naming a member of the team as a co-author. Such right is appropriate, for example, not to include authors in specialized methodological papers when there are no individuals with expertise at a particular center (e.g., a new genetics method or radiologic techniques).

The writing group lead is responsible for the completion of the manuscript, as well as the determination of authorship order. The writing group lead is also responsible for communicating significant problems or delays to the PC in a timely manner. Complete draft manuscripts should be submitted to all co-authors for substantive, methodological, and/or statistical review. All members of the writing group must participate in the writing and/or review process, returning edited drafts within a two week period. In the event that a writing group member disagrees with a revised manuscript, an attempt should be made within the writing group to resolve the issue. If such an effort fails, the issue should be brought by the writing group lead to the PC. If a member of the writing group does not actively participate in the preparation of the manuscript including responding to analysis and manuscript drafts, then he/she may be removed from the writing group.

After writing group approval, the draft should be emailed to the Publication Committee for approval prior to journal submission. The DCC representative can facilitate this distribution once the writing group lead indicates the manuscript is ready. A member of the PC will be assigned as the primary reviewer and will have a target date of two weeks to review the draft and bring comments before the PC by meeting, conference call or email for approval. **Manuscripts must be approved by the PC prior to submission.** Primary investigators are responsible for informing PC and DCC about the disposition of submitted manuscripts. If a manuscript is accepted for publication, the primary investigator must send a portable document format (.pdf) version of the published article to the DCC for distribution to the PC.

Prior to or concurrent with the PC review of the final manuscript draft, the DCC will complete a data verification process. During this process, results reported in the manuscript are verified relative to the statistical output generated during data analysis. **All manuscripts must complete the data verification process prior to submission to a journal.**

2B. Study Acknowledgment

All manuscripts derived from data collected by RIVUR must include the following acknowledgment:

> The authors thank the RIVUR participants, their families and the participating physicians, investigators and staffs for making this research possible. The Randomized Intervention for Children with Vesicoureteral Reflux trial was

supported by cooperative agreements U01 DK074059 (Carpenter), U01 DK074053 (Hoberman), U01 DK074082 (Mathews), U01 DK074064 (Keren), U01 DK074062 (Mattoo), U01 DK074063 (Greenfield) from the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services. The trial was also supported by the Children's Hospital of Philadelphia Clinical and Translational Science Award (UL1TR000003) from the National Center for Research Resources, now at the National Center for Advancing Translational Sciences, National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Diabetes and Digestive and Kidney Diseases or the National Institutes of Health. The RIVUR website is located at http://www.cscc.unc.edu/rivur/.

2C. Categories and Timing of Manuscripts and Presentations

1. Background papers: Manuscripts that describe the justification for the RIVUR study.

2. Methodological papers: Manuscripts describing the design and/or scientific methods used in the RIVUR trial.

3. Baseline papers: Manuscripts that report only data collected at the time of or prior to randomization.

4. Outcome papers: Manuscripts including data collected following randomization of participants.

Development of baseline papers is encouraged as soon as randomization is complete and the baseline database is closed (i.e., while follow-up is on-going). The first baseline paper submitted will be a description of the general characteristics of the overall RIVUR population. Other baseline papers may not be submitted until this first paper has been accepted. Development of outcome manuscripts can begin once collection of follow-up data is complete and the corresponding database is closed. The first outcome paper submitted will be the primary results manuscript. Other outcome manuscripts cannot be submitted until the primary results paper has been accepted. Methodological papers which do not require RIVUR data may be developed at any time. Those methodological papers that include substantial data, particularly outcome data (e.g., results of a quality control program) will follow the timeline required for the data included.

In general, RIVUR manuscripts are expected to include data from all of the relevant participants. Papers that include only a subset of the participants (e.g., first 200 patients randomized, participants from a subset of sites) are strongly discouraged.

2D. Proposal Development for Manuscripts and Presentations: Mechanism of Proposals

1. Any RIVUR Investigator can propose a manuscript or presentation by completing the manuscript proposal form online in the secure area of the RIVUR.net website (Figure 1).

2. Proposals are submitted to the Data Coordinating Center which logs them and forwards them to the Publications Committee for review.

3. After review, the PC may approve the proposal, request revisions, defer, or recommend that the topic not be pursued. In the case of a rejection, the Publications Committee will provide an explanation for the reason that the topic was judged impractical, duplicative, etc. The PC convenes every two months and will attempt to complete this review during the next scheduled call following receipt of a proposal by the DCC.

4. As part of the review process, the PC may suggest additions to the writing group.

5. The PC will indicate if a member of the writing group other than the investigator who submitted the proposal is to serve as the writing group lead. The WG lead will have primary responsibility for communicating with the DCC, making writing assignments, and other tasks necessary to produce a complete draft manuscript. The WG lead will report regularly on the status of the manuscript to the DCC, who will produce a status report for distribution to the PC.

6. The PC will establish general guidelines for the timely completion of manuscripts. The Committee will periodically monitor the progress of manuscripts and take corrective action as needed to insure their timely completion. In extreme cases, this could include replacing the lead of a writing group for a manuscript that is not progressing.

7. When there are more manuscript proposals approved than the DCC has resources to actively work on, the PC will set priorities for the order in which analyses will be conducted.

8. In general, Investigators are discouraged from submitting more than a few manuscript proposals at any one time. In the case of an Investigator with multiple approved proposals, the PC may identify which proposal(s) will receive active attention from the DCC at a particular point in time.

2E. PROCESS FOR RIVUR PROPOSALS

2E.1 Development of Proposals for Analyses of Core RIVUR Study Questions

The PC is responsible for overseeing specific written and oral communications concerning *core* hypotheses/research questions. To facilitate this process, initial discussion and prioritization of publications or presentations based on the primary research questions will be generated by the PC.

Submissions dealing with the *core* hypotheses will have priority over ancillary submissions, both in terms of timing and in use of study resources for data analysis. Analyses of hypotheses related to RIVUR shall not be published or presented using individual site data prior to the submission for publication of these hypotheses using pooled (study-wide) data unless approved by the PC.

2E.2 Submission of Manuscript Proposals

Requests to use data collected by RIVUR must be completed using the RIVUR study proposal form available online at http://www.cscc.unc.edu/rivur/. Following completion of the online manuscript proposal, the submitter should contact the DCC PC liaison. The proposal should be brief (2-3 pages), use the latest version of the submission form:

a. proposed title, and names of possible investigators
b. background information, rationale for the analyses
c. specific aims, hypotheses to be tested
d. study design (i.e., type of study) and methods
e. specific inclusion and exclusion criteria
f. laboratory methods
g quality assurance/quality control procedures
h. statistical approaches to be used and rationale for analyses: this should include power calculations relevant to the proposed study question
i. identification of variables and description of their role: dependent, independent, effect modifier, etc.
j. specific timetable for completion of project, including deadlines for submission of abstract, data analyses, and first draft of paper

External investigators submitting a RIVUR manuscript proposal must submit their proposal by email to the DCC PC liaison, who will enter it into the secure online form. External investigators should include a biosketch in NIH format, and are encouraged to team with a RIVUR investigator as a collaborator to facilitate the timely conduct of the proposed initiative and to appropriately place initiatives in the context of the overall study data.

2E.3 Review and Approval of Proposals

Manuscript proposals not submitted appropriately will be held and the DCC will provide a request for a revised submission.

If overlapping proposals are submitted to the PC, it is the PC's responsibility to suggest how they may be combined and re-submitted as one proposal potentially involving investigators from more than one research area or how they may be revised and re-submitted as two separate, non-overlapping proposals, or to choose the proposal with the greatest overall merit.

Once submitted, the manuscript proposal will be posted to the "Proposals in Progress" page on the RIVUR private web site. One week prior to the next scheduled PC meeting or call, the DCC will provide all new or revised manuscript proposals to the PC for review. The PC will review all study proposals on the bi-monthly conference call. This process will occur in a timely manner, attempting to provide feedback to the primary investigator within 2 weeks following PC review. The PC will assess the manuscript proposal using various criteria: whether the work is duplicative, whether the manuscript proposal reflects high quality science, whether the manuscript proposal presents a significant use of resources, whether data are available, and whether the concept represents “hot” science and might be eligible for fast-tracked journal submission. The PC can also suggest corrections and revisions. Comments on a particular proposal may be posted as a reply on the secure publication website. The PC will include all comments in their decision. The PC will inform the primary investigator of the status as: approved, rejected or deferred (revisions requested).

The primary investigator will be emailed the final decision and project number (see below), referencing any recent changes to the manuscript proposal, and request their response to any comments.

2F. Authorship Guidelines and Policy

1. Authorship Policy and Guidelines

a. Selection of persons to be named as authors and the order of authorship will conform to generally accepted standards. In particular, the standards published by the International Committee of Medical Journal Editors (Oct, 2004 which is published in JAMA) will be used to guide decisions on authorship credit.

b. Authorship for pivotal manuscripts (e.g., primary baseline and outcomes manuscripts) will name authors from the writing group and credit the entire RIVUR Study group, e.g.: “Jones, Smith, and Brown, for the RIVUR Trial Investigators”.

c. Authors for other manuscripts based on RIVUR data will be individually named from among the members of the writing group, based on the ICMJE guidelines referenced above.

d. Authorship for manuscripts in which RIVUR data is essential but not the primary focus (e.g., publications from RIVUR ancillary

studies) should include at least one RIVUR investigator or DCC statistician.

Specific tasks of the lead author include:

a) Determining authorship order.
b) Obtaining consensus on the authorship order from the writing committee.
c) Notifying DCC within one month of appointment of:
    i. the list and proposed order of the writing group membership;
    ii. proposed analysis target dates for abstract and first draft of paper;
    iii. proposed target date for paper submission. (The timeline should follow the standards set in Section 2E.3)
d) Coordinating with DCC and PC to ensure that data analyses are distributed to writing committee members in a timely fashion.
e) Notifying the PC (or designated committee) of significant problems or delays in completion of analyses or writing of drafts, or the need for changes in authorship.
f) Notifying the writing group of manuscript submission to the PC.
g) Notifying DCC and the PC chair's assistant of outcomes of journal submission.

2G. Timelines and Milestones for Manuscript Development

At the time of writing group assembly, a biostatistician will be assigned to the project. That individual will contact the investigator as soon as that proposal reaches the top of the queue, or within a week of assignment if there is no queue, to discuss the statistical analysis plan (SAP). Following the SAP, technical specifications for creating the analysis dataset and programming the necessary analyses (statistical computing request) will be prepared and submitted to the DCC programming staff. Programming will be completed in priority order relative to other work in the queue and each manuscript's priority assigned by the PC. Subsequent milestones and sample time-line would be: Assembly of analytical data set should follow 0.5 to 1 month after receipt of request. Preliminary statistics, data visualization, decryptions, exploration should be complete within 1 to 2 months. A focused statistical analysis aimed at addressing research questions including draft of figures and tables to be included in the paper would follow within a month. The DCC statistician on the writing group will prepare an initial draft of the methods and results sections of the manuscript. Statistical results dissemination and manuscript development activities will take place on the RIVUR Sharepoint site. Each writing group will have a secure space in which to develop the manuscript, and record communications and approvals/comments.

Co-authors should be explicitly informed when a complete draft manuscript is available for substantive, methodological, and/or statistical review. All members of the writing group must participate in the writing and/or review process, making edits to the Sharepoint draft within a two week period. If a writing group member does not actively participate in the writing and/or review process, then he/she may be removed from the

writing committee. Also, in the event that a writing group member disagrees with a revised manuscript, an attempt should be made within the writing group to resolve the issue. If such an effort fails, the issue should be brought by the primary investigator to the PC. **Each co-author should indicate in the Announcement section of the writing group page that he/she approves submission of the manuscript.**

2I. Review of Manuscripts by Steering Committee

Once the manuscript has been approved by the co-authors, it must be submitted electronically to DCC for distribution and review by the PC prior to submission to any journal. The review version of the manuscript will be posted to the secure PC Sharepoint site. The posting will include the writing group number. The PC Chair will determine if the manuscript should be reviewed by all PC members, or if one member of the PC will be assigned as the primary reviewer. Two weeks is the goal to review the draft and bring comments before the PC by meeting, conference call, or email discussion for approval. If appropriate, at the same time a scientific subject-area expert will be assigned to review the manuscript. Data verification by the DCC is also to be completed during this two week review period.

2H. Preparation of Abstracts and Presentations

All presentations should be developed in coordination with the DCC. Scientific abstracts and presentations typically flow from approved manuscript proposals for which analyses are underway. In rare cases, the PC may approve the preparation of an abstract or presentation in the absence of an active manuscript writing group. In this case, analyses will be expedited by the DCC based on deadline dates, provided the work meets with PC approval and NIH guidelines.

Prepared abstracts and presentations should be submitted online through the secure area of the RIVUR.net web site using the 'Abstract and Presentation Submission' Form under the 'Publications' section of the site (http://www.cscc.unc.edu/rivur/pubprop/add_proposal_pub_abst.php). An email to the DCC (suitable for forwarding to the PC) should include information on the intended meeting, due date for the abstract, and type of study (core, site-specific, etc.), and associated writing group number. Depending upon the deadline, the abstract will either be distributed immediately to the PC by email or will be held until the packet for the next scheduled call is prepared. The PC should have 1-2 weeks to comment on the abstract and recommend acceptance, rejection or acceptance with revisions. The investigator will receive all comments and have the opportunity to make changes. The core site PI will have the responsibility to review the final abstract to be sure it incorporates critical comments. Investigators will be encouraged to follow the above procedure. Last minute abstracts should be few, and the review/comment/disposition process will occur via email or special PC call.

2I. Review of Abstracts and Presentations

Final abstracts and presentations must be received by the DCC a minimum of 14 days prior to the deadline for submission in order to be reviewed by the PC. All abstracts and presentations must be reviewed and approved by a majority of PC voting members before any presentation at a formal scientific meeting or prior to submission for publication.

2J. Outside Analysis

If data analysis was not carried out at the DCC, the lead author is responsible for preserving and archiving all computer programs and associated data sets associated with the manuscript. The programs and data should be labeled table1.dat, table1.sas (if SAS was used for table1) whereby running table1.sas on table1.dat will produce the statistics presented in table 1 of the paper. RIVUR data will only be provided by the DCC to investigators in conjunction with an approved Data Use Agreement. Use of the received data is confined to the specific aims of the analysis proposed and approved. No further use or distribution of the RIVUR data is permitted.

2K. PROCESS FOR SECONDARY AND ANCILLARY PUBLICATIONS

Secondary publications refer to investigations using data collected as part of the core RIVUR protocol but which are not directly related to the hypotheses of the RIVUR research. (See Section 1 of the Manual of Procedures for the RIVUR core research questions and the list RIVUR Core Manuscripts.) While the primary RIVUR hypotheses shall have priority in terms of data analysis, proposals to study other PC scientific questions using RIVUR data are encouraged. (RIVUR members may propose such studies on their own behalf or on behalf of other qualified investigators from their own or other institutions.) These studies will generally fall into three categories: a) secondary studies among investigators from each of the sites utilizing pooled RIVUR data, b) ancillary studies that use study data in conjunction with data from individuals who are not participants in RIVUR, and c) site-specific data which does not substantively involve the pooled RIVUR data (although some RIVUR-gathered demographic or clinical information relevant to local data might be used). These will be considered separately.

1. Secondary studies require PC approval. The proposing investigator will follow the guidelines outlined in Section 2E3. The PC review of such plans should assure that the study will not interfere with the conduct of the core studies, and that publications arising from the study will not compete with or conflict with similar reports from RIVUR primary investigations (as previously defined). A timetable for analyses of the data by DCC will be approved by the PC, taking into account other analyses and data management priorities.

2. Ancillary investigations that use study data in conjunction with data from individuals who are not participants in the RIVUR must seek approval from the RIVUR PC. The proposing investigator will follow the RIVUR publication guidelines. The PC review of such proposals should assure that publications arising from the ancillary study will not compete or conflict with the reporting of the core or secondary findings of the RIVUR data. A timetable for analysis of the

data by DCC will be approved by the PC, taking into account other analyses and data management priorities.

2N. Complying with NIH Public Access Policy

Award recipients are required to comply with the NIH Public Access Policy. This includes submission to PubMed Central (PMC), upon acceptance for publication, an electronic version of a final peer-reviewed, manuscript resulting from research supported in whole or in part, with direct costs from National Institutes of Health. The author's final peer-reviewed manuscript is defined as the final version accepted for journal publication, and includes all modifications from the publishing peer review process. For additional information, please visit http://publicaccess.nih.gov/.

Agreement to Abide by RIVUR Publication and Presentation Policy created on September 14, 2012

I have read the RIVUR Publication Policy above and agree to abide by it. Realizing this policy may be updated during the course of the trial, I also agree to review and adhere to future versions of this Publications Policy that are in place at the time manuscript of presentation activity is on-going.

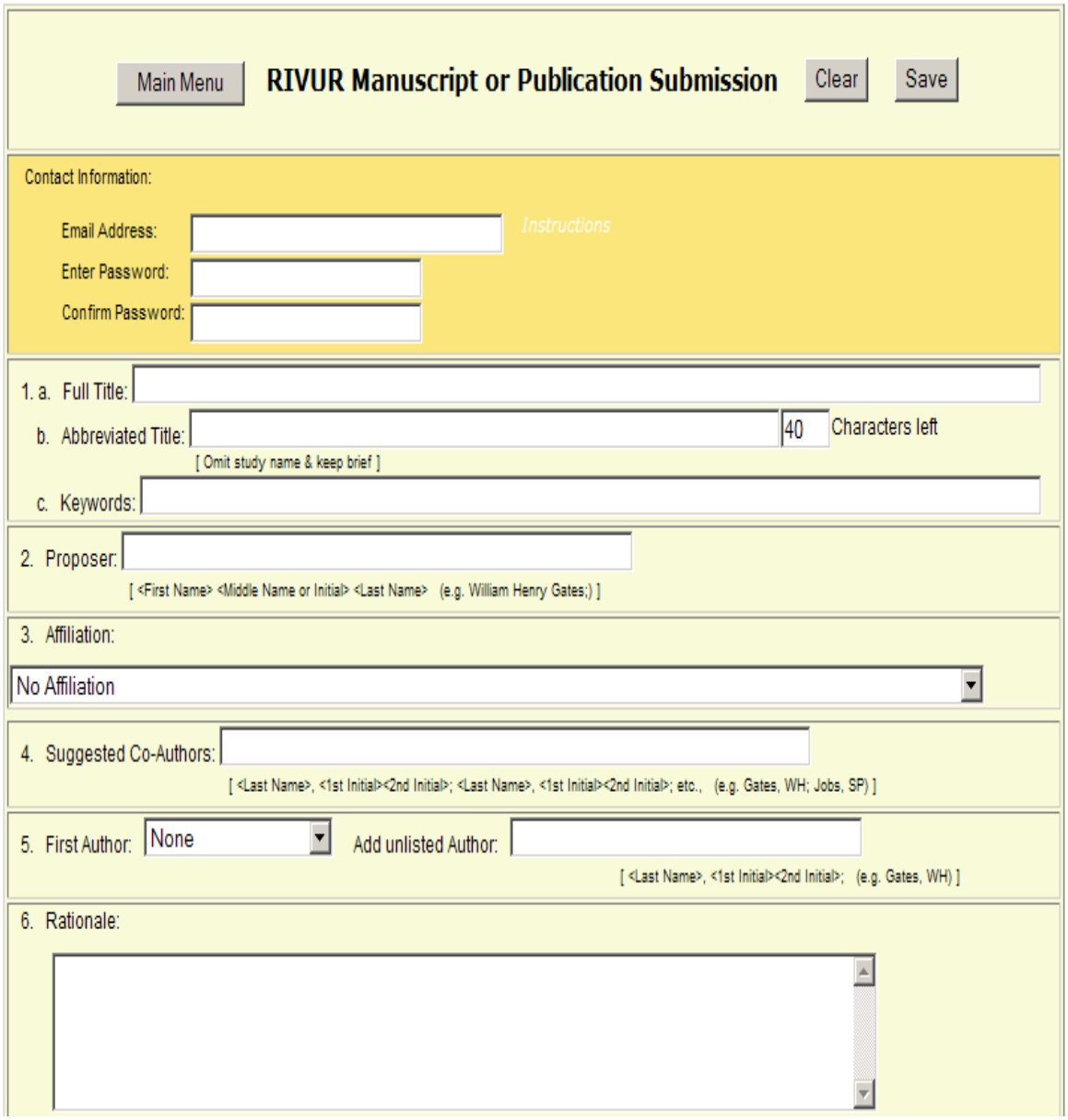
Name (printed/typed):

Title:

Date:

Signed: _____

Figure 1.
RIVUR Manuscript Proposal Form Screenshot



7. Hypothesis / Objective:

8. Research Methods (study design, inclusion/exclusion criteria):

9. a. Will any non-RIVUR data be analyzed (e.g. ancillary study)? Yes: ○ No: ○
   b. If so, please document approval or explain data access:

10. a. Will any outcome (post-randomization) data be utilized? Yes: ○ No: ○
    b. If so, please review the "Categories and Timing of Manuscripts and Presentations" section of the RIVUR Publication and Presentation Policy:

11. Data (varibles to be used in the analysis):

12. Statistical Analysis Plan: ‡

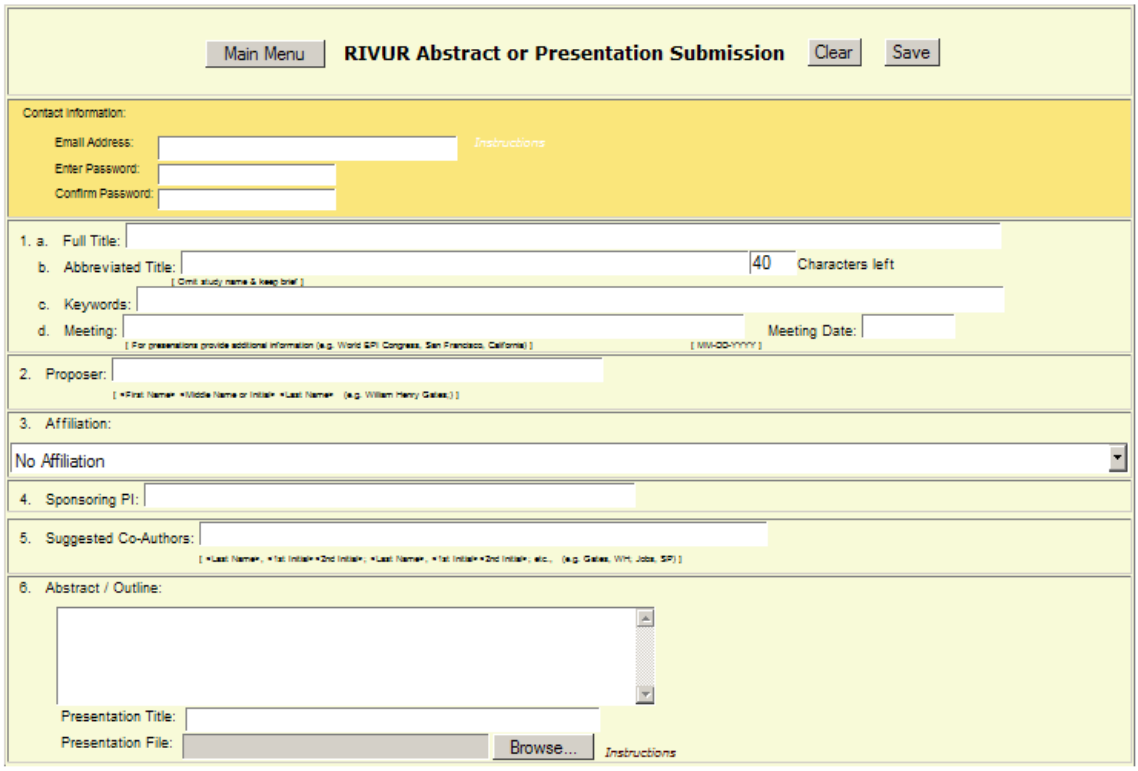
‡ Be sure to provide the following details for inclusion/exclusion, outcome and variable definition, other variables of interest [potential confounders], statistical analysis, power considerations, any anticipated challenges if present.

Table Shell Title:

Table Shell File: Browse... *Instructions*

If you desire to provide / attach additional shell tables, provide an illustrative file name. (e.g. Example table for CVD Risk Comparisons), then click to "Browse..." and upload a single file from your computer to include in the submission for review (you may need to combine multiple figures, tables etc. into one file to append).

Figure 2.
RIVUR Abstract or Presentation Submission Form Screenshot



I. General Policy

To enhance the value of the RIVUR Clinical Trial (RIVUR-CT), the Steering Committee welcomes proposals from individual investigators to carry out ancillary studies. However, to protect the integrity of the RIVUR-CT, ancillary studies must be reviewed and approved by the Ancillary Studies Committee (ASC) and the voting members of the Steering Committee (SC) before the inception or submission of an ancillary study proposal for external funding consideration.

II. Definitions

Ancillary studies of concern to the parent study will include those that involve:

1) Secondary analysis of data collected as part of the parent study.
2) The collection and analysis of supplementary data that was not originally collected as part of the parent study.
3) Studies conducted with participants who are recruited to but not enrolled in the parent study.
4) Studies involving repository samples

The **RIVUR Ancillary Studies Committee (ASC)** is comprised of:

- One PI or Co-I from each of the five RIVUR Clinical Trial Centers (CTCs)
- One representative from the RIVUR Data Coordinating Center (DCC)
- One representative from the NIDDK.

III. Who can submit and participate in ancillary studies?

Investigators both within the parent study as well as those not involved in the parent study are eligible to submit ancillary study proposals. After review of ancillary study proposals, the RIVUR ASC, in consultation with the ancillary study PI, may choose to invite PIs from the parent study CTCs to participate as collaborators in an ancillary study.

IV. Funding

External funding is required for all ancillary studies. Before applying for external grant funding, investigators must receive an approval letter for their ancillary study proposal from the RIVUR SC. The level of funding requested must be sufficient to support the additional data collection, management, and analysis required by the ancillary study. Investigators planning an ancillary study are encouraged to consult with the ASC during development of the proposal to ensure consensus on the resources required for the project. Funding of a grant proposal for an ancillary study at a reduced level from that proposed will likely require corresponding modifications to the workscope of the ancillary study. The ASC will review the proposed modifications before submitting it to the Steering Committee for final approval, as outlined in the instructions below.

V. Instructions for Preparation of Ancillary Study Proposals

All proposed ancillary studies must be reviewed by the RIVUR ASC and approved by the Steering Committee before submission to a funding agency. Studies should be submitted to the ASC chairman for review a minimum of 10 weeks before a grant deadline.

Ancillary study proposals should not be longer than 7 pages and should include the following elements.

1) Cover page with Project Title, Investigator Names and brief Abstract (<500 words). (1 page)

2) Research Plans including Specific Aims/Hypotheses, Background and Significance, Research Design and Methods, and Statistical Analysis. (3 pages)
3) Description of specimen or data request (1 page)
    a) Specific type(s) of samples
    b) Volume of each sample
    c) Time of sample collection (baseline vs. post-baseline)
    d) Use of thawed vs. unthawed specimens - for blood and urine, proposals must indicate whether previously thawed specimens can be used.
    e) Number of participants
    f) Type of storage – for urine, -20 or -70^{0}F
    g) Proposed laboratory that will perform the assays
    h) DNA specimens – special needs should be delineated.
    i) Other study data (e.g. baseline and/or follow-up data)
4) Time table with key dates (grant submission, target date for receipt of specimens, and completion of study)
5) Agreement to return any unused biological specimens and data sets
6) Budgetary issues
    a) Source(s) of funding
    b) Draft budget – should describe costs related to:
        1. Space, personnel, equipment, and IRB approval
        2. Statistical analysis and data management
        3. Visits or examinations outside of the primary study protocol.

    PI should consult with DCC in preparing budget if their data management and analysis services are requested.

(2 pages total for items 4, 5, and 6)

7) NIH-style Biosketches for all Key Personnel. (No page limits).

Authorization of an ancillary study requires review by the ASC and formal approval by the Steering Committee (SC) The PI should send the ancillary study proposal to the Chair of the ASC (Dr. Ron Keren, CHOP, 3535 Market Street, Room 1524, Philadelphia, PA 19104). Upon receipt of the fully-developed proposal, it will be distributed to the ASC for review. To ensure thorough scientific review, the Chair of the ASC may elect to seek outside expert opinion. The ASC will recommend approval or rejection to the SC, or will request modification. The ASC members will have fourteen days from receipt of the proposal to provide an opinion to the SC. No response will be considered an affirmative vote. A proposal, which receives an affirmative majority from the ASC, will be forwarded to the SC for authorization. The SC will have 14 days to authorize proposals approved by the ASC. A failure of the SC to provide an opinion to the ASC will be considered an affirmative vote. Approval or disapproval in both the ASC and SC is based on majority opinion.

If a proposal is not approved by the ASC and SC, the Chair of the ASC may discuss potential revisions with the ancillary studies investigator. If resubmitted, the ASC will reconsider the proposal on one additional occasion only. If an affirmative majority is obtained in the ASC after re-review, the proposal will be sent to the SC for authorization. The investigator may only proceed with the ancillary study after he/she has received a formal approval letter from the RIVUR SC.

Any changes that occur in the structure or concept of an ancillary study that has been approved must be submitted to and reviewed by the ASC and SC according to the policies outlined for initial submissions.

Principal investigators of all ancillary studies will provide a written annual report to the ASC and SC on study progress.

VI. Considerations for approval:
The strength of ancillary study proposals will be evaluated based on the following criteria:

- High scientific merit
- Appropriate research design, methods, and data analysis
- Qualifications of the investigator and research environment
- Opportunity for acquisition of new scientific knowledge
- Does not interfere with the parent study objectives
- Does not hamper continued participation in the parent study
- Produces minimum burden (time, discomfort, risk, cost) on parent study participants (enrolled patients and participating site providers)
- Adequacy of resources to effectively complete the project, including both financial support and personnel.
- Has objectives directly related to the main study
- Requires the unique characteristics of the study participants
- Does not create a serious diversion of study resources (personnel, equipment or study samples) or investigator/staff time at the CTCs or DCC.
- Does not require outcome information until the trial is completed
- Agreement to return the complete ancillary data set back to the DCC, if requested.

VII. Requests for Ancillary Studies as Part of Training or Career Awards
The RIVUR-CT investigators and the NIH anticipate that the RIVUR-CT may be an important resource for career development and training among members of the academic community. As these funding mechanisms typically provide funding only for investigator effort, not additional data collection, special consideration will need to be given to requests for ancillary studies to be funded through training grants or career development awards through the NIH or other funding sources. The ASC will consider the scientific gain to the RIVUR-CT from the addition of the proposed ancillary analyses as well as the training and career development opportunities afforded to the applicant by the proposed ancillary study. Proposals for ancillary studies as part of training or career awards will be submitted and reviewed according the guidelines outlined for all other ancillary studies.

VIII. Human subjects/data confidentiality
Confidentiality of RIVUR-CT enrolled patients must be guaranteed. Individually identifiable data may not be released. If the data requested for an ancillary study is not covered in the original informed consent process for the main RIVUR-CT, then a signed consent must be obtained from every participant in the ancillary study. Any investigator or personnel having access to RIVUR-CT data must receive an orientation on the Trial's confidentiality policy. Key personnel of the ancillary study must be certified in the NIH OHSR or equivalent training course.

A copy of the IRB letter for the ancillary study should be sent to the DCC. If a separate consent form is required for the ancillary study, a copy of the signed ancillary study

consent form for each study participant must be included in the RIVUR-CT record. A data file tracking all signed ancillary consent forms must be maintained by the ancillary study and an electronic copy of that file must be delivered to the RIVUR DCC.

The principal investigator of an ancillary study will be responsible for monitoring the study to assure continuing compatibility with confidentiality and consent policies of the RIVUR-CT and providing written progress reports on the ancillary study.

IX. Analysis and Publication of Results of Ancillary Studies

Unless specifically arranged for and specifically provided for in the Ancillary Study application, all data analyses will take place at the DCC. Ancillary studies funded as career or training awards as well as studies taking place in a subset of clinical sites will be situations in which data analysis may occur outside the DCC. These situations will require approval by the ASC and SC and the investigator of the ancillary study to provide interim reports on analyses to the DCC to ensure (1) consistency with data in the RIVUR-CT database and (2) the quality of the analytic approach.

Proposals for manuscripts resulting from all ancillary studies will be submitted for review to the Publications Committee and will require approval by the SC prior to submission for publication or presentation. Publications reporting baseline data from an ancillary study will only be approved following the publication of the main study baseline manuscript. Publications based on outcome data will follow the primary study outcome manuscript. The phrase "RIVUR Clinical Trial" should be included in the title in all scientific presentations and manuscripts and listed as a key word whenever possible. Manuscripts should also contain an appendix listing RIVUR-CT investigators when appropriate.

X. Feedback of Results of Ancillary Studies to Participants

Results of ancillary studies will be reported to enrolled patients and/or their physicians if medically useful. Such reporting should follow standard RIVUR-CT protocol for notification of participants.

XI. Handling of RIVUR Clinical Trial Data and Specimens

At the time of distribution of RIVUR-CT specimens and/or information, the RIVUR ASC, in coordination with the DCC, will make explicit arrangements with the ancillary study PI for the security of these study materials, and for their final disposition at the conclusion of the ancillary study. The safety and confidentiality of the RIVUR-CT data at the collaborating institution is the responsibility of the ancillary study PI, as is the appropriate disposition of biological materials after the ancillary study has been completed. An archival copy of the newly collected data and/or laboratory results not already held at the DCC will be sent to the RIVUR-CT DCC at the conclusion of the data analysis and publication of ancillary studies. Once transferred back to the RIVUR-CT DCC, these ancillary data will become part of the aggregate RIVUR-CT data. Subsequent access to these data will be governed by the RIVUR-CT Study Policy on Use of Archived Study Data.

XII. Ancillary Studies Committee Membership

Ron Keren, MD, MPH, Children's Hospital of Philadelphia (Chair)
Nader Shaikh, MD, MPH, Children's Hospital of Pittsburgh
Barbara Fivush, MD, The Johns Hopkins School of Medicine
Saul P. Greenfield, MD, Women and Children's Hospital of Buffalo
Timothy P. Bukowski, MD, University of North Carolina at Chapel Hill
Marva M. Moxey-Mims, MD, NIH/National Institute of Diabetes and Digestive Kidney Disease

Consent Form Template v 11

TITLE OF STUDY: ***R***andomized ***I***ntervention for Children with ***V***esico***U***reteral ***R***eflux

(RIVUR)

PRINCIPAL INVESTIGATOR:

PHONE NUMBER:

Evening/Week-end Coverage: 24 Hour Phone Number

ADDRESS:

CO-INVESTIGATORS:

SPONSOR: National Institutes of Health (NIH)

NAME OF SUBJECT: _____ MEDICAL RECORD NUMBER: _____

You are being asked to volunteer your child for a research study because your child has had a urinary tract infection (UTI) and also has a condition called VUR (vesicoureteral reflux), a condition where urine from the bladder flows back toward the kidney. This form will help you understand your child's condition, and what can be done to treat it. Please read this form carefully. As the research study staff discusses this informed consent form with you, please ask him/her to explain any words or information that you may not clearly understand.

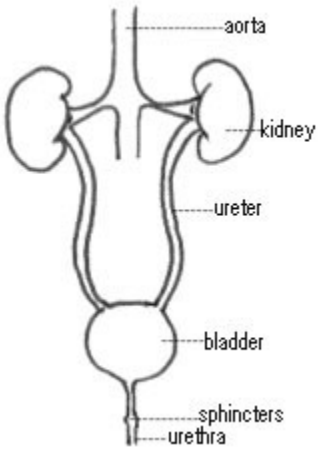
This research study will allow your medical team the chance to improve the care that they give to children with VUR. Taking part in this research study is entirely your choice. Your child will receive medical care for his/her VUR whether you participate in this study or not.

The researcher will explain how the study will be carried out and what you will be expected to do. This form describes the importance of the study as well as the benefits and risks of taking part in the study. The researcher will answer your questions about the study. If you decide to volunteer your child to be in the study, please sign and date this form.

What is my child's health condition?

Your child had a urinary tract infection (UTI) and has also been diagnosed with vesicoureteral reflux (VUR). VUR is the backflow of urine from the bladder up into the kidney. We are studying whether or not children with VUR need to take an antibiotic everyday in order to prevent more urinary tract infections from occurring.

What is the urinary tract and how does it work?



The Urinary System is made up of two kidneys, the bladder and two ureters. The kidneys remove waste from the body by making urine. The urine flows from the kidneys down through the ureters (tubes) to the bladder (balloon-shaped pouch). The ureters have a one-way valve that should only allow urine to flow downward into the bladder.

What is VUR and when do we worry about VUR?

VUR happens when the valve where the ureter meets the bladder is not working properly. This allows urine to flow backwards up to the kidney after it has already been in the bladder. This backflow of urine is a problem if germs enter the bladder and infect the urine. VUR can then allow germs in the infected urine to flow backward up to the kidney and cause a kidney infection. Children can have kidney scarring (damage) after the infection. Kidney damage may lead to high blood pressure or kidney failure.

How is VUR usually treated?

Children with VUR take a low dose of antibiotic once a day to prevent UTIs. A low daily dose of antibiotic to prevent infections is called prophylactic antibiotic treatment. The prophylactic use of an antibiotic does not stop the backflow of urine. Prophylactic antibiotic treatment prevents your child from getting a urinary tract infection by killing germs in the infected urine that backflows toward the kidney. Preventing UTIs may prevent kidney damage. Children with VUR are usually treated with a prophylactic antibiotic until the VUR disappears. VUR often disappears as children get older, but it may take from one to more than five years. Sometimes it never disappears. Some children have surgery to repair the VUR when it does not go away as the children grow.

What is the purpose of this study?

The purpose of this study is to learn whether or not all children with VUR should be treated with antibiotics. The study will tell us if prophylactic antibiotic treatment will effectively prevent urinary tract infections in children with VUR and will give more information on prophylactic antibiotic use and kidney scarring. New research suggests that if a child with VUR has close follow-up with his/her doctor for every illness with fever, a UTI can be treated early with antibiotics and kidney scarring can be prevented without the use of prophylactic antibiotics. By conducting this study, we hope to determine which of the two strategies, (1) careful follow-up of every illness with fever OR (2) treatment with daily low-dose antibiotic is more appropriate for children with VUR.

This study will include children from across the United States and Canada. About 600 children, ages of 2 – 72 months, will take part in this study. Our goal at (SITE) is to recruit (NUMBER

AT SITE). The staff is being reimbursed from the National Institutes of Health for the time and materials involved in carrying out this study.

What are my child and I being asked to do?

You are being asked to volunteer your child for a research study. Taking part in this research study is your choice. Your child does not need to participate. Your child may leave this research study at any time. There will be no penalty or loss of health care benefits if your child does not participant or withdraws from this study. This form will help you understand what we think is hurting your child's health, and what we think can be done to treat your child's condition. This form tells you what will happen in the research study. This form also tells you about the risks, discomforts, and other information about the research study. Medical language may be hard to understand. If there is anything which you do not understand, please ask questions.

This is a double-blind, randomized study. This means that neither you nor your doctor will know which treatment your child will be given. Randomization means that a computer will choose the treatment to be given in a manner similar to that of flipping a coin. There is an equal chance of receiving either treatment. Information about which treatment your child is receiving will be available to your doctor in case of emergency. Your child will have a 50% chance of receiving one of the following treatments during the study: 1) Prophylactic antibiotic; or 2) placebo (no active medication.) A prophylactic medication is one that may *prevent* a medical condition. The placebo will look and taste exactly like the prophylactic antibiotic.

Trimethoprim-sulfamethoxazole will be used as the prophylactic antibiotic unless your child has an allergy to trimethoprim-sulfamethoxazole (TMP/SMZ). If your child is allergic to TMP/SMZ (or any medication that contains sulfa), then your child is not eligible for this study. If your child develops an allergy to TMP/SMZ or the placebo for TMP/SMZ during the study, then your child will remain in the study but will discontinue study medication and be treated according to standard care practices for UTI and VUR.

The study may last for up to 2 years. Participation includes the following study clinic visits and telephone contacts described below:

Screening Visit: This visit will help to determine whether your child is eligible for this study. After you have been explained the details of this study you will be asked to sign this consent form. To help determine your child's eligibility in the study, we will be asking you questions about your child's medical history and current illness. Your child will have a physical exam and will be scheduled for some radiological tests (if they have not already been done in the course of your child's medical care for his/her UTI). These radiological images include a voiding cystourethrogram (VCUG), nuclear renal scan (DMSA scan), and ultrasound, are standard tests for your child's condition, and will be used to help us finalize the eligibility determinations.

Baseline Visit: This visit will occur within 3-6 weeks of your child's screening visit after the VCUG and ultrasound imaging. Your child will have a physical exam. We will ask questions about your child's health and any medical problems that have happened since the screening visit, and ask you to complete a short self-administered questionnaire. We will also collect from your child a small stool sample from a rectal swab, a teaspoon size sample of blood, and a urine sample. At the end of the visit, you will be given study medication (it may be antibiotic or placebo) that your child will take daily for the duration of the study.

Follow-up Visits (6, 12, and 18 Month Visits): Your child will have a physical exam and we will ask you about any medical problems that have happened since the last visit. A small blood

sample (about one-tenth of a teaspoon) will be collected. You will be given additional study medicine and your empty or used bottles of study medicine will be collected. You may also be asked to fill out a short questionnaire about your child's health and wellbeing. At the 12-month visit, your child will be scheduled for another DMSA scan to monitor any changes in your child's renal scarring since the baseline DMSA.

End of Study Visit (24 Month Visit): Your child will have a physical exam. We will ask you questions about your child's health and any medical problems that have happened since the earlier study visits. At this visit, we will also collect from your child a small stool sample from a rectal swab, a teaspoon sample of blood, and a urine sample. Radiographic VCUG and DMSA imaging performed at the beginning of the study will be repeated or scheduled at this visit.

Phone calls: We will call you every 2 months during the study to find out how your child is doing. We will ask questions about the study medicine and about any medical problems that have happened since we last talked with you.

Special procedures for children with moderate scarring on the first DMSA scan: If your child's baseline DMSA scan shows moderate renal scarring, then your child will have a DMSA scan after each UTI that causes a fever. If any DMSA scan shows worsening of the renal scarring, then your child will be taken off the study medication and be treated with a prophylactic antibiotic prescribed by your doctor. Your doctor may discuss the option of surgical repair of the VUR. Your child's continued participation in the study will still be important to us even though his/her treatment has changed. We will still continue the study clinic visits and phone calls.

Special procedures for children with new or worsening scarring on the 12-month DMSA scan: If the 12-month DMSA scan shows a new renal scar or worsening of a previous scar, then your child will be taken off the study medication and be treated through routine clinical care, for example, a prophylactic antibiotic may be prescribed by your doctor. Your doctor may discuss the option of surgical repair of the VUR. Your child's continued participation in the study will be important to us even though his/her treatment has changed. We will still continue the study clinic visits and phone calls.

Special procedures for children with recurrent UTIs: If your child has 2 UTIs with fever during any 12 month period or 4 UTIs with or without fever during the entire study, then your child will be taken off the study medication and be treated with a prophylactic antibiotic prescribed by your doctor. Your doctor may discuss the option of surgical repair of the VUR. Your child's continued participation in the study will still be important to us even though his/her treatment will have changed. We will continue the study clinic visits and phone calls, and will schedule your child for a DMSA scan 4 months after he/she stops receiving the study medication.

Release of additional medical information: We will ask you to sign a Release of Medical Information form so that we can find out details of any medical problems, particularly as they may relate to any urinary tract infections, for which your child has received care from doctors other than those at (SITE). We will also ask you to allow us to contact a family member or other individual you've identified if (SITE) staff is unable to make contact with you during the study. We will ask for permission to release medical information to your child's physician regarding your child's care in the study.

Will my child's primary care doctor be notified about his/her participation in this study?

Your primary care doctor will be told that your child is participating in this study. We will send your primary care doctor reminders that your child is participating in this study. We are doing this so your primary care doctor knows how to treat your child if he/she gets a UTI.

What are the risks of participating in this research study?

Potential risks to your child while participating in the study are described below. You should discuss these with the researcher and/or your regular doctor.

Risks of Study Medication – Antibiotic group: The study medication (TMP/SMX) is commonly used in the treatment and prevention of UTI, and has an established record of safety in children. However, patients may have adverse reactions to these medications. The study medications may cause allergic reactions that range from mild (skin rash, nausea, vomiting) to severe (difficulty breathing, severe allergic reaction), although severe reactions are extremely rare. Other potential side effects include sun sensitivity, vaginal irritation, low white blood cell count, and dizziness. Other drugs may be given to make side effects less serious and uncomfortable. Many side effects go away soon after the drugs are stopped. In some cases, side effects can be serious, long lasting or permanent. There also may be other side effects that we cannot predict.

There is a chance that daily treatment with antibiotics, such as the study drug, may lead to the development of UTIs with resistant bacteria. This may require treatment with intravenous (IV) antibiotics.

Risks of Study Medication – Placebo group: If daily antibiotic prophylaxis protects children against recurrence of UTI and renal scarring, then your child will be exposed to a higher risk of recurrent UTI and renal scarring.

Risks of Blood Drawing: Risks associated with drawing blood from your child's arm include minimal discomfort and/or bruising. Infection, excess bleeding, or clotting (blockage of the vein) are also possible, although very rare.

Risks of a voiding cystourethrogram (VCUG): A voiding cystourethrogram (VCUG) is an x-ray examination of the bladder and lower urinary tract. A VCUG involves inserting a catheter through the urethra and filling the bladder with contrast material, both of which can be uncomfortable to children. A series of X-rays are taken as the contrast material is voided from the bladder. The radiation exposure from a VCUG is similar to the natural background radiation during one year.

Risks of DMSA scans: A DMSA renal scan is a diagnostic imaging procedure that is used to show areas of kidney infection or kidney damage. A DMSA scan requires inserting an intravenous (IV), injecting a radioisotope (radioactive substance) into the blood stream, and taking pictures of the kidney with a special camera. Your child may experience some discomfort associated with the placement of the IV. IVs can be dislodged and some fluid can go into the arm outside of the vein. The radiation exposure from a DMSA scan is less than half of the natural background radiation usually received during one year.

Risk of loss of confidentiality: In order to minimize the risk of loss of confidentiality, all records related to study data will be kept in locked cabinets, and access to this information will be restricted. A password system (like an electronic lock) will be used to control access to all information stored on a computer. All reports or articles based on this study will be prepared such that no individual patient can be identified.

What if problems occur during this study?

Your child's health is more important than following the research plan. If any changes are needed to protect your child's health, we will talk with you about them before they are made. We will also tell you if a better treatment is discovered somewhere else. If you want this treatment, your child's physician can provide this in place of or in addition to the treatment you are receiving at the time.

The researchers have taken steps to minimize the known or expected risks. However, your child may still experience problems or side effects. It is important that you tell the researchers about any injuries, side effects, or other problems that your child experiences during this study.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study to provide further safety and ethical assurances.

We will inform you of new information from this or other studies that may affect your child's health, welfare, or your willingness to stay in this study.

You can withdraw your child from this study at any time, without penalty. The researchers also have the right to stop your child's participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

If you withdraw your child from the study early, you may be asked to come in for one more clinic visit. This visit will allow your study doctor to collect outcome data about your child. Your child will have a physical exam. We will ask you questions about your child's health and any medical problems that have happened since the earlier study visits. At this visit, we will also collect from your child a small stool sample from a rectal swab, a teaspoon sample of blood, and a urine sample. Radiographic VCUG and DMSA imaging performed at the beginning of the study may be repeated or scheduled at this visit.

What are the possible benefits of your child being in this study?

There is no guarantee that you will receive any direct benefit from participating in this study. The information which is obtained will be useful scientifically and possibly helpful to others. We hope that this study may benefit society by showing which of these two approaches is better for children with VUR, but this is not guaranteed.

The standard testing in this study will provide information about your child's disease that may be beneficial to your child's wellbeing. For example, the DMSA scan could allow early discovery of kidney scars. This would alert the doctors to closely monitor your child so that the risk of new scars might be decreased. The blood and urine tests may also provide early information about kidney damage.

Benefits of Study Medication – Placebo group: Children in the placebo group may be less likely to become infected with resistant organisms that would require treatment with intravenous (IV) antibiotics. Children in this group will not develop the potential allergies or adverse events caused by antibiotic prophylaxis.

Benefits of Study Medication – antibiotic group: If daily antibiotic prophylaxis is protective against recurrence of UTI and renal scarring, then children in the antibiotic group may have fewer UTIs and less risk of renal scarring.

What are the financial costs of this study?

You will not be charged for the study medication or any of the study examinations while your child is a participant in this study. You will not be charged for testing of the stool specimen, or for the special blood test measuring kidney function. All other laboratory tests and radiographic imaging are considered routine care (the normal course of treatment for your child's illness) and will be billed to you or your insurance company. All costs not paid by your insurance will be your financial responsibility. Please ask about any expected added costs or insurance problems. Financial Counselors are available to discuss insurance, costs and other issues.

How will my child and I be compensated for taking part in this research study?

To help cover any expenses such as transportation or time off from work during the clinic visits, you will be given $25 for each visit. If you complete every follow-up during the study, you will also receive a $25 bonus at the last visit.

What alternatives are available to my child if I don't give my OK for him/her to participate in this study?

Children with VUR are usually treated with antibiotics to prevent infections. If you choose not to enroll in the study, your child's doctor may prescribe antibiotics to decrease the risk of your child having a UTI. For certain children, surgery may be an alternative treatment. Participation in this study is entirely up to you. Choosing not to participate in this study will not affect you or your child's present or future relationship with the (SPECIFIC SITE) or any affiliated health care provider.

Consent for Storing Blood, Tissue, or Body Fluid for research purposes

Optional Biological Samples: During the already planned blood and urine specimen collection at baseline and the 24 month visit, we would like to collect an additional small amount of blood and urine to send to the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) Central Repository. This is also referred to as specimen banking. The purpose of specimen banking is to provide available samples for future research. Sending samples to the Repository may give scientists valuable research material that can help them to develop new diagnostic tests, new treatments, and new ways to prevent disease. The amount of extra blood will be about 1-2 teaspoons at each visit that the specimens are drawn for the Repository, depending upon your child's age.

The Repository will take measures to protect your privacy, although no guarantee of confidentiality can be absolute. Before your child's sample is sent to the Repository, the sample will be labeled with the RIVUR study identification number. Personal identifying information such as name, address, and date of birth will be removed. The Repository will have some data about your child such as age, sex, race, and diagnosis. You will not be given any information, nor will any appear in your child's medical record, as to how these samples are used.

You will not receive any direct benefit or payment for participating, but your child's sample may benefit other people with VUR. It is possible that data resulting from use of your child's sample may eventually be used in a research publication. If that happens, your child's name and other personal information will not be included.

There is no cost to you or your insurance company for the storage and use of the specimens. Your child's donation does not entitle you or your child to compensation from any commercial

use of the products that may be derived from the specimen. You and your child will not be informed about future use or results. Your child's donation is voluntary, and if you choose not to have your child participate in this portion of the study, your child can still participate in the rest of the study.

If you agree to have your child's sample stored in the NIDDK Central Repository, you can change your mind up until the end of the RIVUR study. All that is needed is an instruction from you to the study researchers and they will destroy your child's sample and all information that identifies your child. Once the study has concluded, the sample will stay in the Repository indefinitely.

You understand and agree that any tissue, blood, cell, or other biologic samples that your child provides as a participant in this research study are donations of these samples to the NIH. You and your child will not have any property rights to the samples, nor will you or your child have any property rights to or be entitled to compensation of any type for any products, data, or other items or information that is developed from the samples.

If at any time during the study you would like your child's blood or urine sample to be destroyed, you can contact SITE PERSONNEL NAME at SITE PHONE NUMBER.

If you consent to the use of your child's biological (urine and blood) samples for future scientific studies, please initial one or both of the statements below. If you do not consent to the use of your child's biological samples, then leave the statements blank

Statement of Consent for blood specimen Banking:

_____ _____ I **do** give permission for my child participate in the blood sample
Initials Date banking part of the study.

Statement of Consent for urine specimen Banking:

_____ _____ I **do** give permission for my child to participate in the urine sample
Initials Date banking part of the study.

Optional Genetic Sample: Also during the baseline visit, we would like to collect another small amount of blood that will be sent to the NIDDK Genetic Repository. The amount of extra blood will be about 1-2 teaspoons depending on your child's age. The same standards and guidelines outlined above regarding protection of privacy for the Biological Samples apply to the Genetic Samples. Cells collected from your child's blood that can be used to make DNA (heredity material) will be stored indefinitely for future research purposes. Scientists will use this DNA of the blood to help them develop new diagnostic tests, new treatments, and new ways to understand diseases.

There is no cost to you or your insurance company for the storage and use of the specimens. Your child's donation does not entitle you or your child to compensation from any commercial use of the products that may be derived from the specimen. You and your child will not be

informed about future use or results. Your child's donation is voluntary, and if you choose not to have your child participate in this portion of the study, your child can still participate in the rest of the study.

If you agree to have your child's DNA stored in the NIDDK Genetic Repository, you can change your mind up until the end of the RIVUR study. All that is needed is an instruction from you to the study researchers and they will destroy your child's sample and all information that identifies your child. Once the study has concluded, the sample will stay in the Repository indefinitely.

You understand and agree that any DNA that your child provides as a participant in this research study is a donation of these samples to the NIH. You and your child will not have any property rights to the samples, nor will you or your child have any property rights to or be entitled to compensation of any type for any products, data, or other items or information that is developed from the samples.

If at any time during the study you would like your child's DNA sample to be destroyed, you can contact SITE PERSONNEL NAME at SITE PHONE NUMBER.

If you consent to the use of your child's genetic samples for future scientific studies, please initial the statement below. If you do not consent to the use of your child's genetic samples, then leave the statement blank

Statement of Consent for genetic sample Banking:

_____ _____ I **do** give permission for my child participate in the genetic sample

Initials Date banking part of the study.

What if you have more questions?

For questions about the study or a research-related injury, contact the study coordinator at SITE PHONE NUMBER. A member of the study team will be available to speak to you 24 hours per day, 7 days per week at SITE PHONE NUMBER. If additional questions arise, you can also speak with your doctor.

This research study has been reviewed and approved by the Human Research Review Board, whose purpose is to see that the rights and welfare of research participants are adequately protected, and that risks are balanced by potential benefits. A member of this committee is available to speak to you or your child about any questions or complaints. The SITE INSTITUTION Human Research Review Board can be reached at SITE IRB PHONE NUMBER.

If you choose to participate, you will receive a copy of this consent form. You may also request a copy of the protocol (full study plan).

Will information be kept confidential?

Your child's personal information may be disclosed if required by law. Research information will be sent to the RIVUR Data Coordinating Center at the University of North Carolina. Also, scientific data from this study may be presented at meetings and published so that it may be useful to others, as long as your child is not identifiable. Organizations that may inspect and/or copy your child's research records for quality assurance and data analysis include:

- The research team, which includes personnel listed on this form and other persons involved in this study at SITE INSTITUTION.
- The SITE INSTITUTION Human Research Review Board,]
- The National Institutes of Health and/or other regulatory agencies, including the Data Coordinating Center team at the University of North Carolina.
- Doctors and other researchers coordinating this study at other participating institutions.

Because this study could affect your medical care, a copy of this consent form will be placed in your permanent medical record. This will allow the doctors caring for you to obtain information about what drugs or procedures you are receiving in the study and treat you appropriately, if you have other health problems or needs during the study.

Permission to proceed and Statement of Consent

The signing of this consent does not absolve the study doctors from the responsibility for proper medical care at all times.

When you sign this form, you agree that you have read the above description of this research. You also agree that your questions have been answered, and that you want to take part in this research.

Statmenent of consent

I understand the above information. The study has been explained to me and my questions have been answered. I, the undersigned, give permission for _____ to participate in this study.

_____ _____

Signature of subject or authorized representative Da te

_____

Relationship to the child

The proposed research study and consent has been explained to you by:

_____ _____

Name of Principal or Co-Investigator Signature of Principal or Co-Investigator

COSTART Coding

ABDOMEN ENLARGED	ABDO ENLARGE
ABDOMEN MIMICKING ACUTE	ABDO SYND ACUTE
ABDOMINAL CRAMP	PAIN ABDO
ABDOMINAL DISCOMFORT	PAIN ABDO
ABDOMINAL DISTENSION	ABDO ENLARGE
ABDOMINAL DISTRESS	DYSPEPSIA
ABDOMINAL PAIN	PAIN ABDO
ABDOMINAL PAIN LOWER	PAIN ABDO
ABDOMINAL PAIN PEPTIC ULCER TYPE	PEPTIC ULCER SYND
ABDOMINAL PAIN UPPER	PAIN ABDO
ABDOMINAL SYNDROME ACUTE	ABDO SYND ACUTE
ABORTION	ABORTION
ABORTION COMPLETE INCOMPLETE MISSED ETC.	ABORTION
ABORTION MISSED	ABORTION
ABORTION THREATENED	ABORTION
ABRUPTIO PLACENTAE	PLACENTA DIS
ABSCENCES	CONVULS
ABSCESS	ABSCESS
ABSCESS BACTERIAL	INFECT BACT
ABSCESS BREAST	ABSCESS BREAST
ABSCESS EYE	OPHTHALMITIS
ABSCESS GUM	ABSCESS PERIODONT
ABSCESS INJECTION SITE	ABSCESS INJECT SITE
ABSCESS KIDNEY	ABSCESS KIDNEY
ABSCESS PARADONTAL	ABSCESS PERIODONT
ABSCESS PERIODONTAL	ABSCESS PERIODONT
ABSCESS STERILE	ABSCESS
ABSENCE CONGENITAL	ANOMALY CONGEN
ABSENCE OF CRANIAL VAULT CONGENITAL	ANOMALY CONGEN CNS
ABSENCE OF LIMBS	ECTROMELIA
ABSENCE SEIZURE	CONVULS
ABUSE	DRUG DEPEND
ABUSE WITH ADDICTION	DRUG DEPEND ADDICT
ACANTHOSIS	HYPERTROPHY SKIN
ACANTHOSIS NIGRICANS	SKIN DISCOLOR
ACATHESIA	AKATHISIA
ACCIDENT	INJURY ACCID
ACCIDENT AUTOMOBILE	INJURY ACCID
ACCIDENT CEREBROVASCULAR	CEREBROVASC ACCID
ACCOMMODATION ABNORMAL	ACCOMMODATION ABNORM
ACCOMMODATION DARK DISORDER	BLIND NIGHT
ACCOMMODATION DISORDER	ACCOMMODATION ABNORM
ACCOMMODATION DISTURBANCE	ACCOMMODATION ABNORM
ACCOMMODATION PARALYSIS	ACCOMMODATION ABNORM
ACCOMMODATION SPASM	ACCOMMODATION ABNORM
ACETONE BREATH	KETOSIS
ACETONEMIA	KETOSIS
ACETONURIA	KETOSIS
ACHALASIA	CARDIOSPASM
ACHALASIA CARDIAE	CARDIOSPASM
ACHALASIA ESOPHAGEAL	CARDIOSPASM
ACHE	PAIN
ACHE BREAST	PAIN BREAST

ACHE STOMACH	PAIN ABDO
ACHLORHYDRIA	ACHLORHYDRIA
ACHONDROPLASIA	CHONDRODYST
ACHYLIA GASTRICA	ACHLORHYDRIA
ACID INDIGESTION	DYSPEPSIA
ACIDOSIS	ACIDOSIS
ACIDOSIS COMPENSATORY	ACIDOSIS
ACIDOSIS DIABETIC	ACIDOSIS DIABET
ACIDOSIS HYPERCHLOREMIC	ACIDOSIS HYPERCHLOREM
ACIDOSIS LACTIC	ACIDOSIS LACTIC
ACIDOSIS METABOLIC	ACIDOSIS
ACIDOSIS RENAL TUBULAR	KIDNEY TUBUL DIS
ACIDOSIS RESPIRATORY	ACIDOSIS RESP
ACNE	ACNE
ACNE BROMATA	BROMISM
ACNE FOLLICULAR PAPULAR PUSTULAR ETC.	ACNE
ACNEIFORM DERMATITIS	ACNE
ACROCYANOSIS	CYANOSIS
ACRODYNIA	ACRODYNIA
ACTIVITY MOTOR EXAGGERATED	HYPERKINESIA
ACTIVITY MOTOR RETARDED	HYPOKINESIA
ADAMS STOKES SYNDROME	ADAMS STOKES SYND
ADAMS-STOKES SYNDROME	ADAMS STOKES SYND
ADAPTABILITY DIMINISHED	PERSON DIS
ADDICTION	DRUG DEPEND ADDICT
ADDISON'S DISEASE	ADREN INSUFFIC
ADDISONIAN CRISIS	ADDISON CRISIS
ADENOCARCINOMA	CARCINOMA
ADENOCARCINOMA ENDOMETRIAL	CARCINOMA ENDOMETR
ADENOCARCINOMA GASTRIC	CARCINOMA GI
ADENOCARCINOMA LUNG	CARCINOMA LUNG
ADENOCARCINOMA NOS	CARCINOMA
ADENOCARCINOMA THYROID	CARCINOMA THYR
ADENOMA	ADENOMA
ADENOMA ADRENAL	ADENOMA
ADENOMA LIVER	NEOPL LIVER
ADENOMA THYROID	ADENOMA THYR
ADENOPATHY	LYMPHADENO
ADENOSIS SCLEROSING	LYMPHADENO
ADH INAPPROPRIATE SECRETION	ADH INAPPROP
ADHESIVENESS PLATELET ABNORMAL (NOS)	PLAT ABNORM
ADIADOKOKINESIS	COORDINAT ABNORM
ADIPOSIS DOLOROSA	LIPODYSTROPHY
ADNEXITIS	SALPINGITIS
ADRENAL CORTEX ACTIVITY INCREASED	CUSHINGS SYND
ADRENAL CORTEX DYSFUNCTION	ADREN DIS
ADRENAL CORTEX DYSPLASIA	ADREN DIS
ADRENAL CORTEX HYPERFUNCTION	CUSHINGS SYND
ADRENAL CORTEX HYPOFUNCTION	ADREN INSUFFIC
ADRENAL CORTICAL INSUFFICIENCY	ADREN INSUFFIC
ADRENAL CRISIS	ADDISON CRISIS
ADRENAL DISORDER	ADREN DIS
ADRENAL HAEMORRHAGE	HEM ADREN
ADRENAL HYPERCORTICISM	CUSHINGS SYND
ADRENAL HYPOFUNCTION	ADREN INSUFFIC
ADRENAL INSUFFICIENCY	ADREN INSUFFIC
ADRENAL STORM	ADDISON CRISIS

ADRENAL SUPPRESSION	ADREN INSUFFIC
ADRENOGENITAL SYNDROME CONGENITAL	ANOMALY CONGEN
ADULT RESPIRATORY DISTRESS SYNDROME	RESPIRAT DISTRES SYND
ADYNAMIA	AKINESIA
AFFECT ALTERED	EMOTION LABIL
AFFECT LACK	APATHY
AFFECT LOSS	APATHY
AFIBRINOGENEMIA	FIBRINOGEN DEC
AFTER IMAGES	VISION ABNORM
AFTER TASTE	TASTE PERVERS
AG RATIO ABNORMAL	AG RATIO ABNORM
AGE BONE RETARDED	EPIPHYS CLOS DELAY
AGEUSIA	TASTE LOSS
AGGLUTINATION LEUCOCYTES	WBC ABNORM
AGGRAVATION OF EXISTING DISORDER	REACT AGGRAV
AGGRAVATION REACTION	REACT AGGRAV
AGGREGATION PLATELET ABNORMAL	PLAT ABNORM
AGGRESSIVE REACTION	HOSTILITY
AGITATION	AGITATION
AGITATION MENTAL	AGITATION
AGITATION NEONATAL	NERVOUSNESS
AGORAPHOBIA	NEUROSIS
AGRANULOCYTIC ANGINA	AGRANULOCYTOSIS
AGRANULOCYTOSIS	AGRANULOCYTOSIS
AGRAPHIA	APHASIA
AIDS	HIV SYND
AIDS RELATED COMPLEX	HIV SYND
AIR HUNGER	HYPERVENTIL
AKATHISIA	AKATHISIA
AKINESIA	AKINESIA
ALANINE AMINOTRANSFERASE INCREASE	SGPT INC
ALARM	ANXIETY
ALBUMIN SERUM PLASMA DECREASED	HYPOPROTEINEM
ALBUMIN-GLOBULIN RATIO ABNORMAL	AG RATIO ABNORM
ALBUMINURIA	ALBUMINURIA
ALCOHOL INTOLERANCE	ALCOHOL INTOLER
ALCOHOL INTOXICATION	ALCOHOL INTOLER
ALDOSTERONE INCREASED	ALDOSTERONE INC
ALEUKIA HEMORRHAGICA	PANCYTOPENIA
ALEXIA	APHASIA
ALKALEMIA	ALKALOSIS
ALKALINE PHOSPHASTASE SERUM INCREASE	PHOSPHATASE ALK INC
ALKALOSIS	ALKALOSIS
ALKALOSIS COMPENSATORY	ALKALOSIS
ALKALOSIS HYPOCHLOREMIC	ALKALOSIS HYPOCHLOREM
ALKALOSIS HYPOKALEMIC	ALKALOSIS HYPOKALEM
ALKALOSIS METABOLIC	ALKALOSIS
ALKALOSIS RESPIRATORY	ALKALOSIS RESP
ALKAPTONURIA	URIN ABNORM
ALLERGIC REACTION	ALLERG REACT
ALLERGIC REACTION (NOS)	ALLERG REACT
ALLERGY	ALLERG REACT
ALLERGY AGGRAVATED	ALLERG REACT
ALOPECIA	ALOPECIA
ALOPECIA AREATA	ALOPECIA
ALPHA-FETOPROTEIN INCREASED	LAB TEST ABNORM
ALT INCREASED	SGPT INC

ALTERED HORMONE LEVEL (NOS)	ALTERED HORMONE LEVEL
ALTERED IMMUNOGLOBULINS (NOS)	IMMUNOGLOBUL INC
ALTERED MOOD	EMOTION LABIL
ALTERED NEUROTRANSMITTER LEVEL (NOS)	ALTERED NEUROTR LEVEL
ALVEOLAR AERATION DECREASED	HYPOVENTIL
ALVEOLAR AERATION EXCESSIVE	HYPERVENTIL
ALVEOLITIS	PNEUMONIA
ALVEOLITIS ALLERGIC	FIBRO LUNG
ALVEOLITIS FIBROSING	FIBRO LUNG
AMAUROSIS	BLIND
AMBITION LOSS OF	APATHY
AMBLYOPIA	AMBLYOPIA
AMELIA	ECTROMELIA
AMENORRHEA	AMENORRHEA
AMENORRHOEA	AMENORRHEA
AMENTIA	MENTAL RETARD
AMINOACIDURIA	KIDNEY TUBUL DIS
AMMONIA INCREASED	NPN INC
AMNESIA	AMNESIA
AMYLASE INCREASED	AMYLASE INC
AMYLASE SERUM INCREASED	AMYLASE INC
AMYLOIDOSIS	AMYLOIDOSIS
ANA	ANA
ANA PRESENT	ANA
ANABOLISM PROTEIN INCREASED	WEIGHT INC
ANAEMIA	ANEMIA
ANAEMIA APLASTIC	ANEMIA APLAST
ANAEMIA B TWELVE DEFICIENCY	ANEMIA B12 DEFIC
ANAEMIA FOLIC ACID DEFICIENCY	ANEMIA FOLIC DEFIC
ANAEMIA HAEMOLYTIC	ANEMIA HEMOL
ANAEMIA HAEMOLYTIC DCN	ANEMIA HEMOL DCN
ANAEMIA HAEMOLYTIC DCP	ANEMIA HEMOL DCP
ANAEMIA HAEMOLYTIC G6PD	ANEMIA HEMOL G6PD
ANAEMIA HAEMOLYTIC ICP	ANEMIA HEMOL ICP
ANAEMIA HYPERCHROMIC	ANEMIA MACROCYT
ANAEMIA HYPOCHROMIC	ANEMIA HYPOCHROM
ANAEMIA HYPOPLASTIC	ANEMIA HYPOPLAST
ANAEMIA MACROCYTIC	ANEMIA MACROCYT
ANAEMIA MEGALOBLASTIC	ANEMIA MEGALOBLAST
ANAEMIA NEONATAL	ANEMIA
ANAEMIA NORMOCHROMIC	ANEMIA
ANAEMIA NORMOCYTIC	ANEMIA NORMOCYT
ANAEMIA SIDEROBLASTIC	ANEMIA REFRACT
ANAEMIA SPHEROCYTIC	ANEMIA HEMOL
ANAESTHESIA LOCAL	HYPALGESIA
ANALGESIA	HYPALGESIA
ANAPHYLACTIC REACTION	ANAPHYL
ANAPHYLACTIC SHOCK	ANAPHYL
ANAPHYLACTOID REACTION	ANAPHYL
ANAPHYLAXIS	ANAPHYL
ANASARCA	EDEMA GENERAL
ANDROGEN DEFICIENCY	ENDO DIS
ANDROGEN EXCESS EFFECT	VIRILISM
ANDROGENS INCREASED	VIRILISM
ANEMIA	ANEMIA
ANEMIA ACHRESTIC	ANEMIA REFRACT
ANEMIA APLASTIC	ANEMIA APLAST

ANEMIA APLASTIC AREGENERATIVE	ANEMIA APLAST
ANEMIA B12 DEFICIENCY	ANEMIA B12 DEFIC
ANEMIA B6 DEFICIENCY	ANEMIA PYRIDOX DEFIC
ANEMIA COBALAMIN DEFICIENCY	ANEMIA B12 DEFIC
ANEMIA FOLATE DEFICIENCY	ANEMIA FOLIC DEFIC
ANEMIA FOLIC ACID DEFICIENCY	ANEMIA FOLIC DEFIC
ANEMIA HEINZ BODY	HEINZ BODIES
ANEMIA HEMOLYTIC (NOS)	ANEMIA HEMOL
ANEMIA HEMOLYTIC AUTOIMMUNE (NOS)	ANEMIA HEMOL
ANEMIA HEMOLYTIC DIRECT COOMBS NEGATIVE	ANEMIA HEMOL DCN
ANEMIA HEMOLYTIC DIRECT COOMBS POSITIVE	ANEMIA HEMOL DCP
ANEMIA HEMOLYTIC G6PD DEFICIENCY	ANEMIA HEMOL G6PD
ANEMIA HEMOLYTIC INDIRECT COOMBS NEGATIVE	ANEMIA HEMOL ICN
ANEMIA HEMOLYTIC INDIRECT COOMBS POSITIVE	ANEMIA HEMOL ICP
ANEMIA HEMOLYTIC OCCULT	ANEMIA HEMOL
ANEMIA HYPERCHROMIC	ANEMIA MACROCYT
ANEMIA HYPOCHROMIC	ANEMIA HYPOCHROM
ANEMIA HYPOPLASTIC	ANEMIA HYPOPLAST
ANEMIA IRON DEFICIENCY	ANEMIA IRON DEFIC
ANEMIA LEUKOERYTHROBLASTIC	MARROW HYPERPLASIA
ANEMIA MACROCYTIC	ANEMIA MACROCYT
ANEMIA MEGALOBLASTIC	ANEMIA MEGALOBLAST
ANEMIA MICROCYTIC	ANEMIA MICROCYT
ANEMIA NEONATAL	ANEMIA
ANEMIA NORMOCHROMIC	ANEMIA
ANEMIA NORMOCYTIC	ANEMIA NORMOCYT
ANEMIA PERNICIOUS TYPE	ANEMIA MEGALOBLAST
ANEMIA PRIMAQUINE SENSITIVITY TYPE	ANEMIA HEMOL G6PD
ANEMIA PYRIDOXINE DEFICIENCY	ANEMIA PYRIDOX DEFIC
ANEMIA REFRACTORY	ANEMIA REFRACT
ANEMIA SIDEROBLASTIC	ANEMIA REFRACT
ANENCEPHALIA	ANOMALY CONGEN CNS
ANENCEPHALY	ANOMALY CONGEN CNS
ANESTHESIA APPLICATION SITE	HYPALGESIA
ANESTHESIA GENERAL	COMA
ANESTHESIA INJECTION SITE	HYPALGESIA
ANESTHESIA LOCAL	HYPALGESIA
ANEURYSM	ANOMALY VASCUL
ANEURYSM ARTERIOVENOUS	ANOMALY ART
ANEURYSM CEREBRAL	ANEURYSM INTRACRAN
ANEURYSM DISSECTING CORONARY ARTERY	OCCLUS CORONARY
ANEURYSM INTRACRANIAL	ANEURYSM INTRACRAN
ANGER	HOSTILITY
ANGIITIS	VASCULITIS
ANGIITIS NECROTIZING	VASCULITIS
ANGINA AGRANULOCYTIC	AGRANULOCYTOSIS
ANGINA AT REST PRINZMETAL'S	ANGINA PECTORIS
ANGINA ATTACK	ANGINA PECTORIS
ANGINA OF EFFORT	ANGINA PECTORIS
ANGINA PECTORIS	ANGINA PECTORIS
ANGINA PECTORIS AGGRAVATED	ANGINA PECTORIS
ANGINAL PAIN	ANGINA PECTORIS
ANGINAL SYNDROME	ANGINA PECTORIS
ANGIO-EDEMA	ANGIOEDEMA
ANGIOEDEMA	ANGIOEDEMA
ANGIOMA	ANOMALY VASCUL
ANGIOMA SPIDER	ANGIOMA SPIDER

ANGIONEUROTIC EDEMA	ANGIOEDEMA
ANGITIS KIDNEY	VASCULITIS KIDNEY
ANGOR MORTIS	ANXIETY
ANHEDONIA	DEPRESSION
ANHIDROSIS	SWEAT DEC
ANISOCORIA	ANISOCORIA
ANISOCYTOSIS	RBC ABNORM
ANKLE EDEMA	EDEMA PERIPH
ANKLES SWELLING	EDEMA PERIPH
ANOMALIES CONGENITAL MULTIPLE	ANOMALY CONGEN MULT
ANOMALY ANOMALY CONGEN	ANOMALY CONGEN
ANOMALY ARTERIAL	ANOMALY ART
ANOMALY CARDIAC	ANOMALY HEART
ANOMALY CONGENITAL	ANOMALY CONGEN
ANOMALY CONGENITAL CENTRAL NERVOUS SYSTEM (NOS)	ANOMALY CONGEN CNS
ANOMALY CONGENITAL GASTROINTESTINAL (NOS)	ANOMALY GI
ANOMALY CONGENITAL MULTIPLE (NOS)	ANOMALY CONGEN MULT
ANOMALY CONGENITAL MUSCULOSKELETAL (NOS)	ANOMALY CONGEN MS
ANOMALY CONGENITAL RESPIRATORY (NOS)	ANOMALY CONGEN RESP
ANOMALY CONGENITAL SPECIAL SENSES	ANOMALY CONGEN SS
ANOMALY CONGENITAL UROGENITAL	ANOMALY CONGEN UG
ANOMALY HEART	ANOMALY HEART
ANOMALY TEETH	ANOMALY TOOTH
ANOMALY VASCULAR	ANOMALY VASCUL
ANOMIA	APHASIA
ANORECTAL DISORDER	RECTAL DIS
ANOREXIA	ANOREXIA
ANOREXIA NEONATAL	ANOREXIA
ANOREXIA NERVOSA	ANOREXIA
ANORGASMIA	ANORGASMIA
ANOSMIA	PAROSMIA
ANOVULATION	OVULAT FAIL
ANOXIA	HYPOXIA
ANOXIA CEREBRAL	ISCHEMIA CEREBR
ANTIBODY ANTINUCLEAR PRESENT	ANA
ANTIBODY AUTO RESPONSE	ANA
ANTICHOLINERGIC SYNDROME	ANTICHOLINERG SYND
ANTICOAGULANT EFFECT DECREASED	ANTICOAG DEC
ANTICOAGULANT EFFECT INCREASED	ANTICOAG INC
ANTIDIURESIS	OLIGURIA
ANTIDIURETIC HORMONE DISORDER	ADH INAPPROP
ANTIFIBRINOLYSIN INCREASED	FIBRINOLYSIS DEC
ANTIFIBRINOLYSIS	FIBRINOLYSIS DEC
ANTIGONADOTROPINS PRESENT	GONADOTR DEC
ANTINUCLEAR ANTIBODY PRESENT	ANA
ANTINUCLEAR FACTOR TEST POSITIVE	ANA
ANTISOCIAL REACTION	ANTISOCIAL REACT
ANURIA	ANURIA
ANUS DISORDER	RECTAL DIS
ANUS IMPERFORATE	ANUS IMPERFOR
ANXIETY	ANXIETY
ANXIETY ATTACK	ANXIETY
ANXIETY COMPLEX	ANXIETY
ANXIETY NEUROSIS	ANXIETY
ANXIETY REACTION	ANXIETY
ANXIETY STATE	ANXIETY
ANXIETY-RIDDEN	ANXIETY

AORTA-PULMONARY ART TRANSPOSITION	TRANSPOS GREAT VESS
AORTIC COARCTATION	STENO AORTIC
AORTIC STENOSIS	STENO AORTIC
AORTIC VALVE STENOSIS	STENO AORTIC
APATHY	APATHY
APHASIA	APHASIA
APHASIA MOTOR	APHASIA
APHASIA NOMINAL	APHASIA
APHASIA SENSORY	APHASIA
APHONIA	VOICE ALTERAT
APHRODISIAC	LIBIDO INC
APLASIA BONE MARROW	ANEMIA APLAST
APLASIA PURE RED CELL	ANEMIA APLAST
APLASIA, PURE RED CELL	ANEMIA APLAST
APNEA	APNEA
APNEA NEONATAL	APNEA
APNOEA	APNEA
APNOEA NEONATAL	APNEA
APOPLEXY	HEM CEREBR
APPEARANCE PERSONAL NEGLECT OF	PERSON DIS
APPETITE ABSENT	ANOREXIA
APPETITE DECREASED	ANOREXIA
APPETITE EXAGGERATED	APPETITE INC
APPETITE EXCESSIVE	APPETITE INC
APPETITE IMPAIRED	ANOREXIA
APPETITE INCREASED	APPETITE INC
APPETITE LOST	ANOREXIA
APPETITE STIMULATED	APPETITE INC
APPLICATION SITE ANESTHESIA	HYPALGESIA
APPLICATION SITE EDEMA	APPLICAT SITE REACT
APPLICATION SITE OEDEMA	APPLICAT SITE REACT
APPLICATION SITE REACTION	APPLICAT SITE REACT
APPREHENSION	ANXIETY
APRAXIA	APHASIA
APTYALISM	DRY MOUTH
ARACHNOIDITIS	ARACHNOIDITIS
ARACHNOIDITIS ADHESIVE CHRONIC	ARACHNOIDITIS
ARDS	RESPIRAT DISTRES SYND
ARGYRIA	SKIN DISCOLOR
ARMS SWOLLEN RED HOT	EDEMA PERIPH
AROUSAL DIFFICULT	STUPOR
ARREST ATRIAL	HEART ARREST
ARREST CARDIAC	HEART ARREST
ARREST ERYTHROID MATURATION	ERYTHRO MATUR ARREST
ARREST MYELOID MATURATION	MYELOID MATUR ARREST
ARREST PULMONARY	APNEA
ARREST RESPIRATORY	APNEA
ARREST SINUS	HEART ARREST
ARRHYTHMIA	ARRHYTHMIA
ARRHYTHMIA ATRIAL	ARRHYTHMIA ATR
ARRHYTHMIA ATRIAL (NOS)	ARRHYTHMIA ATR
ARRHYTHMIA CARDIAC (NOS)	ARRHYTHMIA
ARRHYTHMIA NEONATAL	ARRHYTHMIA
ARRHYTHMIA NODAL	ARRHYTHMIA NOD
ARRHYTHMIA NODAL (NOS)	ARRHYTHMIA NOD
ARRHYTHMIA VENTRICULAR	ARRHYTHMIA VENT
ARRHYTHMIA VENTRICULAR (NOS)	ARRHYTHMIA VENT

ARRYTHMIA SINUS	ARRHYTHMIA
ARTERIAL BLOOD PRESSURE DECREASED	HYPOTENS
ARTERIAL INSUFFICIENCY CORONARY	CORONARY ART DIS
ARTERIAL INSUFFICIENCY PERIPHERAL	VASC DIS PERIPH
ARTERIAL PRESSURE HIGH	HYPERTENS
ARTERIAL SPASM	ARTERIOSPASM
ARTERIOSCLEROSIS	ARTERIOSCLEROSIS
ARTERIOSCLEROSIS CORONARY ARTERY	ARTERIOSCLEROSIS
ARTERIOSCLEROSIS MOENCKEBERG-TYPE	ARTERIOSCLEROSIS
ARTERIOSCLEROSIS RENAL	ARTERIOSCLEROSIS
ARTERIOSCLEROSIS RETINAL	RETINAL VASC DIS
ARTERIOSPASM	ARTERIOSPASM
ARTERIOSPASM ARTERIAL ARTERIOLAR	ARTERIOSPASM
ARTERIOSPASM CORONARY	ANGINA PECTORIS
ARTERITIS	ARTERITIS
ARTERITIS CORONARY	ARTERITIS
ARTERITIS THROMBOTIC	ARTERITIS THROM
ARTERY MALFORMATION	ANOMALY ART
ARTHRALGIA	ARTHRALGIA
ARTHRITIS	ARTHRITIS
ARTHRITIS AGGRAVATED	ARTHRITIS
ARTHRITIS CHARCOT-TYPE	ARTHROSIS
ARTHRITIS GOUTY	GOUT
ARTHRITIS LUPUS ERYTHEMATOSIS	LE SYND
ARTHRITIS MULTIPLE JOINT	ARTHRITIS
ARTHRITIS PYOGENIC	ARTHRITIS PYOGEN
ARTHRITIS RHEUMATOID	ARTHRITIS RHEUMAT
ARTHRITIS RHEUMATOID AGGRAVATED	ARTHRITIS RHEUMAT
ARTHRITIS SEPTIC	ARTHRITIS PYOGEN
ARTHRITIS SINGLE JOINT	ARTHRITIS
ARTHROPATHY	ARTHROSIS
ARTHROPATHY (NOS)	ARTHROSIS
ARTHROPATHY NEUROGENIC	ARTHROSIS
ARTHROSIS	ARTHROSIS
ARTHUS PHENOMENON	SERUM SICK
ASCITES	ASCITES
ASEPTIC NECROSIS BONE	NECRO BONE
ASOCIAL REACTION	ANTISOCIAL REACT
ASPARTATE AMINOTRANSFERASE INCREASED	SGOT INC
ASPERMIA	SPERM ARREST
ASPHYXIA	ASPHYXIA
ASPHYXIA LIVIDA OF NEWBORN	ASPHYXIA
ASPHYXIA NEONATAL	ASPHYXIA
ASPHYXIA PALLIDA OF NEWBORN	ASPHYXIA
ASPIRATION	RESPIRAT DIS
ASPIRATION PNEUMONIA	PNEUMONIA ASPIR
ASSAULT	INJURY INTENT
ASSAULT UNPROVOKED	INJURY INTENT
AST INCREASED	SGOT INC
ASTASIA	COORDINAT ABNORM
ASTERIXIS	MOVEMENT DIS
ASTHENIA	ASTHENIA
ASTHMA	ASTHMA
ASTHMA BRONCHIAL	ASTHMA
ASTHMA CARDIAC	HEART FAIL LEFT
ASTIGMATISM	CORNEAL LESION
ASYNERGIA	COORDINAT ABNORM

ASYSTOLE	HEART ARREST
ATAXIA	ATAXIA
ATAXIA CEREBELLAR	ATAXIA CEREBELL
ATELECTASIS	ATELECTASIS
ATHEROMA CORONARY ARTERY	ARTERIOSCLEROSIS
ATHEROSCLEROSIS	ARTERIOSCLEROSIS
ATHEROSCLEROSIS GENERALIZED	ARTERIOSCLEROSIS
ATHETOID	CHOREOATHETOSIS
ATHETOSIS	CHOREOATHETOSIS
ATONIA	PARALYSIS FLACCID
ATONY SKELETAL MUSCLE	PARALYSIS FLACCID
ATONY STOMACH	STOMACH ATONY
ATONY URINARY BLADDER	URIN RETENT
ATONY UTERINE	UTER ATONY
ATRESIA BILIARY	BIL ATRESIA
ATRESIA ESOPHAGUS	STENO ESOPH
ATRIAL FIBRILLATION PAROXYSMAL	FIBRILLAT ATR
ATRIAL SEPTAL DEFECT	ATR SEPT DEF
ATRIAL TACHYCARDIA	TACHYCARDIA SUPVENT
ATRICHIA	ALOPECIA
ATRICHOSIS	ALOPECIA
ATRIOVENTRICULAR BLOCK	AV BLOCK
ATRIOVENTRICULAR BLOCK (NOS)	AV BLOCK
ATROPHY ACUTE YELLOW LIVER	NECRO LIVER
ATROPHY ADRENAL	ATROPHY ADREN
ATROPHY ADRENAL CORTEX	ATROPHY ADREN
ATROPHY APPLICATION SITE	ATROPHY SKIN
ATROPHY BREAST	ATROPHY BREAST
ATROPHY INJECTION SITE	ATROPHY INJECT SITE
ATROPHY KIDNEY	URIN TRACT DIS
ATROPHY LIVER	NECRO LIVER
ATROPHY MUSCLE	ATROPHY MUSCLE
ATROPHY OPTIC NERVE	ATROPHY OPTIC
ATROPHY OVARY	OVAR DIS
ATROPHY PANCREAS	PANCREAS DIS
ATROPHY SKELETAL MUSCLE	ATROPHY MUSCLE
ATROPHY SKIN	ATROPHY SKIN
ATROPHY TESTICULAR	ATROPHY TESTIS
ATROPHY THYROID	ATROPHY THYR
ATROPINE-LIKE SYNDROME	ANTICHOLINERG SYND
ATTACK CORONARY	CORONARY ART DIS
ATTACK HEART (NOS)	INFARCT MYOCARD
ATTITUDE CHANGED	PERSON DIS
AUDIOMETRIC ABNORMALITIES	LAB TEST ABNORM
AUDITORY DISORDER	DEAF
AUDITORY DISORDER (NOS)	DEAF
AUDITORY HYPERACUITY	HYPERACUSIS
AUDITORY HYPOACUITY	DEAF
AURA	HALLUCIN
AURICULAR FIBRILLATION	FIBRILLAT ATR
AUTISM	SCHIZOPHRENIC REACT
AUTO-ANTIBODY RESPONSE	ANA
AUTOANTIBODY RESPONSE	ANA
AUTOIMMUNE DEFICIENCY SYNDROME	HIV SYND
AUTOMATISM EPILEPTIC	CONVULS
AUTOMOBILE ACCIDENT	INJURY ACCID
AV BLOCK	AV BLOCK

AV BLOCK (NOS)	AV BLOCK
AV BLOCK COMPLETE	AV BLOCK COMP
AV BLOCK COMPLETE WITH SYNCOPE	ADAMS STOKES SYND
AV BLOCK FIRST DEGREE	AV BLOCK FD
AV BLOCK SECOND DEGREE	AV BLOCK SD
AV BLOCK THIRD DEGREE	AV BLOCK COMP
AVITAMINOSIS	AVITAMINOSIS
AVITAMINOSIS A B B1 B2 ETC.	AVITAMINOSIS
AWAKENING EARLY	INSOMNIA
AXILLARY ARTERY THROMBOSIS	THROM ART
AZOSPERMIA	FERTIL DEC MALE
AZOTEMIA	NPN INC
AZOTEMIA PRERENAL	NPN INC
AZOTEMIA RENAL	UREMIA
BABINSKI SIGN POSITIVE	BABINSKI SIGN POS
BABY PREMATURE	BIRTH PREMAT
BACK ACHE	PAIN BACK
BACK ARCHED BACKWARD	OPISTHOTONOS
BACK DISCOMFORT	PAIN BACK
BACK DISTRESS	PAIN BACK
BACK PAIN	PAIN BACK
BACTERIAL RESISTANCE	BACT RESIST
BAD BREATH	HALITOSIS
BAD TASTE	TASTE PERVERS
BALANCE DIFFICULTY	ATAXIA
BALANITIS	BALANITIS
BALANOPOSTHITIS	BALANITIS
BALDNESS	ALOPECIA
BARBITURATE INTOXICATION (NOS)	BARBITUR INTOX
BASAL CELL CARCINOMA	CARCINOMA SKIN
BASOPHILIA	BASOPHILIA
BASOPHILIA STIPPLING	BASOPHILIA
BATTERY	INJURY INTENT
BEARING DOWN FEELING PAINFUL	TENESMUS
BEHAVIOR ABNORMAL	PERSON DIS
BEHAVIOR DISORDER	PERSON DIS
BEHAVIOR HYPERACTIVE	HYPERKINESIA
BEI DECREASED	BEI DEC
BEI INCREASED	BEI INC
BELCHING	ERUCTAT
BELL'S PALSY	PARALYSIS FACIAL
BELLIGERENCY	HOSTILITY
BELLY ACHE	PAIN ABDO
BENCE JONES PROTEINS PRESENT BLOOD URINE	GLOBULIN INC BJ
BENEFIT UNEXPECTED	UNEXPECTED BENEFIT
BEWILDERMENT	CONFUS
BEZOAR	BEZOAR
BICARBONATE DECREASED SERUM	ACIDOSIS
BIGEMINY	EXTRASYSTOLES BIGEM
BILE DUCT CARCINOMA	CARCINOMA GI
BILE DUCT STRICTURE	GI DIS
BILE DUCTS ABSENCE OF (CONGENITAL)	BIL ATRESIA
BILIARY ATRESIA	BIL ATRESIA
BILIARY COLIC	PAIN BIL
BILIARY PAIN	PAIN BIL
BILIARY STASIS	BILIRUBINEM
BILIARY STONES	CHOLELITH

BILIRUBIN INCREASED	BILIRUBINEM
BILIRUBINAEMIA	BILIRUBINEM
BILIRUBINAEMIA AGGRAVATED	BILIRUBINEM
BILIRUBINEMIA	BILIRUBINEM
BILIRUBINEMIA AGGRAVATED	BILIRUBINEM
BILIRUBINEMIA NEWBORN	JAUNDICE NEONAT
BILIRUBINURIA	BILIRUBINURIA
BILIVERDIN INCREASED	BILIRUBINEM
BIRTH DISORDER (NOS)	PERINATAL DIS
BIRTH POSTMATURE	BIRTH POSTMAT
BIRTH PREMATURE	BIRTH PREMAT
BIRTH TRAUMA	PERINATAL DIS
BIRTH TRAUMA INTRACRANIAL	PERINATAL DIS
BIRTHWEIGHT EXCESSIVE	BIRTH POSTMAT
BIRTHWEIGHT SUBNORMAL	BIRTH WEIGHT SUBNORM
BLACK-OUT (NOT AMNESIA)	SYNCOPE
BLACKHEADS	ACNE
BLACKOUT SPELL	SYNCOPE
BLADDER ATONY	URIN RETENT
BLADDER CALCULUS	BLADDER CALCULUS
BLADDER CARCINOMA	CARCINOMA BLADDER
BLADDER INABILITY TO EMPTY	URIN RETENT
BLADDER INCONTINENCE	INCONTIN URIN
BLADDER INFECTION	CYSTITIS
BLADDER IRRITATION	CYSTITIS
BLADDER NEUROGENIC	INCONTIN URIN
BLADDER PAIN	PAIN
BLADDER PAPILLOMA	NEOPL BLADDER
BLADDER PARALYSIS	URIN RETENT
BLADDER RETENTION	URIN RETENT
BLEEDING ANOVULATORY	WITHDRAW BLEED
BLEEDING BREAKTHROUGH	METRORRHAGIA
BLEEDING BREAST	HEM
BLEEDING GASTROINTESTINAL	HEM GI
BLEEDING GINGIVAL	HEM GUM
BLEEDING INTERMENSTRUAL	METRORRHAGIA
BLEEDING INTRACRANIAL	HEM INTRACRAN
BLEEDING MENSTRUAL HEAVY	MENORRHAGIA
BLEEDING NOSE	EPISTAXIS
BLEEDING POSTPARTUM	HEM POSTPARTUM
BLEEDING RECTAL	HEM RECTAL
BLEEDING TENDENCY	HEM
BLEEDING TIME DECREASED	BLEED TIME DEC
BLEEDING TIME INCREASED	BLEED TIME INC
BLEEDING URINARY TRACT	HEMATURIA
BLEEDING VAGINAL	HEM VAGINAL
BLEEDING WITHDRAWAL (CONTRACEPTIVE)	WITHDRAW BLEED
BLEPHARITIS	BLEPHARITIS
BLEPHAROSPASM	TWITCH
BLINDNESS	BLIND
BLINDNESS COLOR	BLIND COLOR
BLINDNESS COLOUR	BLIND COLOR
BLINDNESS CONGENITAL	BLIND
BLINDNESS DAY	BLIND
BLINDNESS NIGHT	BLIND NIGHT
BLINDNESS TEMPORARY	VISION ABNORM
BLINDNESS TRANSIENT	VISION ABNORM

BLISTERS	RASH VESIC BULL
BLOATING	FLATUL
BLOCK BUNDLE BRANCH	BUNDLE BRANCH BLOCK
BLOCK HEART	HEART BLOCK
BLOCK NEUROMUSCULAR	PARALYSIS FLACCID
BLOCKADE RETICULOENDOTHELIAL	RE BLOCK
BLOOD GASES ABNORM	HYPOXIA
BLOOD LOSS OF (NOS)	HEM
BLOOD PRESSURE DROP ARTERIAL	HYPOTENS
BLOOD PRESSURE HIGH	HYPERTENS
BLOOD PRESSURE INCREASED	HYPERTENS
BLOOD SEDIMENTATION INCREASED	ESR INC
BLOOD STOOL	MELENA
BLOOD SUGAR DECREASED	HYPOGLYCEM
BLOOD SUGAR INCREASED	HYPERGLYCEM
BLOOD UREA INCREASED	BUN INC
BLOOD UREA NITROGEN INCREASED	BUN INC
BLOOD URINE	HEMATURIA
BLUE LINE GUM	GUM BLUE LINE
BLURRED VISION	AMBLYOPIA
BODY IMAGE DISORDER	DEPERSONAL
BODY NUMBNESS	HYPESTHESIA
BODY ODOR	BODY ODOR
BOIL	FURUNCULOSIS
BONE DEVELOPMENT ABNORMAL	BONE DIS
BONE DEVELOPMENT DISORDER	BONE DIS
BONE DISORDER	BONE DIS
BONE DISORDER (NOS)	BONE DIS
BONE FRACTURE SPONTANEOUS	BONE FRACT SPONTAN
BONE IMPLANT LYSIS OF	BONE IMPLANT LYSIS
BONE NEOPLASM	NEOPL BONE
BONE SARCOMA	SARCOMA BONE
BORBORYGMUS	FLATUL
BOWEL INCONTINENA	INCONTIN FECAL
BOWEL ISCHEMIA	GI DIS
BOWEL OBSTRUCTION	OBSTRUCT INTEST
BOWEL PERFORATION	INTEST PER
BRACHIAL ARTERY THROMBOSIS	THROM ART
BRADYCARDIA	BRADYCARDIA
BRADYCARDIA SINUS	BRADYCARDIA SINUS
BRADYPNEA	HYPOVENTIL
BRADYPNOEA	HYPOVENTIL
BRADYPSYCHIC RESPONSES	THINKING ABNORM
BRAIN DAMAGE CONGENITAL	BRAIN SYND CHRON
BRAIN DISORDER (NOS)	BRAIN SYND ACUTE
BRAIN NEOPLASM BENIGN	NEOPL CNS
BRAIN NEOPLASM MALIGNANT	CARCINOMA
BRAIN STEM DISORDER	BRAIN STEM DIS
BRAIN SYNDROME (NOS)	BRAIN SYND ACUTE
BRAIN SYNDROME ACUTE	BRAIN SYND ACUTE
BRAIN SYNDROME CHRONIC	BRAIN SYND CHRON
BRAIN TUMOR	NEOPL CNS
BREAK-THROUGH BLEEDING	METRORRHAGIA
BREAKDOWN NERVOUS	NEUROSIS
BREAST ATROPHY	ATROPHY BREAST
BREAST BLEEDING	HEM
BREAST DISCHARGE FEMALE	LACTATION FEM

BREAST DISCHARGE MALE	LACTATION MALE
BREAST DISORDER FEMALE	LACTATION FEM
BREAST DISORDER MALE	LACTATION MALE
BREAST ENGORGEMENT	BREAST ENGORGE
BREAST ENLARGEMENT	BREAST ENLARGE
BREAST ENLARGEMENT FEMALE	BREAST ENLARGE
BREAST ENLARGEMENT MALE	GYNECOMASTIA
BREAST ENLARGEMENT MALE BILATERAL	GYNECOMASTIA
BREAST FIBROADENOSIS	BREAST FIBROCYST
BREAST FIBROCYSTIC	BREAST FIBROCYST
BREAST FIBROCYSTIC CHANGE	BREAST FIBROCYST
BREAST FIBROCYSTIC DISORDER	BREAST FIBROCYST
BREAST INFECTION	MASTITIS
BREAST INFLAMMATION	MASTITIS
BREAST MALFORMATION	ANOMALY CONGEN
BREAST MASS	NEOPL BREAST
BREAST MASS FIBROCYSTIC	BREAST FIBROCYST
BREAST NEOPLASM BENIGN FEMALE	NEOPL BREAST
BREAST NEOPLASM FEMALE	NEOPL BREAST
BREAST NEOPLASM MALE	NEOPL BREAST
BREAST NEOPLASM MALIGNANT FEMALE	CARCINOMA BREAST
BREAST NEOPLASM MALIGNANT MALE	CARCINOMA BREAST
BREAST NODULE	NEOPL BREAST
BREAST PAIN FEMALE	PAIN BREAST
BREAST PAIN MALE	PAIN BREAST
BREAST SECRETION FEMALE	LACTATION FEM
BREAST SECRETION MALE	LACTATION MALE
BREAST SIZE DECREASE	ATROPHY BREAST
BREAST SIZE INCREASED	BREAST ENLARGE
BREATH HOLDING	RESPIRAT DIS
BREATH ODOR	HALITOSIS
BREATH SHORTNESS	DYSPNEA
BREATHING ABNORMALLY DEEP	HYPERVENTIL
BREATHING ARRESTED	APNEA
BREATHING DIFFICULT	DYSPNEA
BREATHING KUSSMAUL TYPE	HYPERVENTIL
BREATHING SHALLOW	HYPOVENTIL
BREATHING SLOWED	HYPOVENTIL
BRIEF NIGHTMARE	DREAM ABNORM
BROMIDE INTOXICATION	BROMISM
BROMISM	BROMISM
BROMODERMA	BROMISM
BROMODERMA VEGETANS	BROMISM
BROMSULPHTHALEIN RETENTION	BSP ABNORM
BRONCHIAL OBSTRUCTION	LUNG DIS
BRONCHIAL SECRETION EXCESSIVE	SPUTUM INC
BRONCHIECTASIS	BRONCHIECTASIS
BRONCHIOLITIS	BRONCHIOLITIS
BRONCHITIS	BRONCHITIS
BRONCHITIS ACUTE	BRONCHITIS
BRONCHITIS ASTHMATIC	BRONCHITIS
BRONCHITIS CHRONIC	BRONCHITIS
BRONCHORRHEA	SPUTUM INC
BRONCHOSPASM	ASTHMA
BRONCHOSPASM AGGRAVATED	ASTHMA
BRONCHOSTENOSIS	BRONCHOSTENO
BRUISE	ECCHYMOSIS

BSP ABNORMAL	BSP ABNORM
BSP TEST ABNORMAL	BSP ABNORM
BUCCAL INFLAMMATION	STOMATITIS
BUCCAL MUCOSA APHTHOUS ULCERATION	STOMATITIS APHTH
BUCCAL MUCOSA ULCERATION	STOMATITIS ULCER
BUCCOGLOSSAL SYNDROME	BUCCOGLOSSAL SYND
BUDD CHIARI SYNDROME	THROM
BULBAR POLIO	MYELITIS
BULIMIA	APPETITE INC
BULLOUS ERUPTION	RASH VESIC BULL
BUN INCREASED	BUN INC
BUNDLE BRANCH BLOCK	BUNDLE BRANCH BLOCK
BURN LOCAL	APPLICAT SITE REACT
BURNING IN ABDOMEN	PAIN ABDO
BURNING MUCOSAL	STOMATITIS
BURNING RECTAL	PAIN
BURNING SKIN	PAIN
BURPING	ERUCTAT
BURSITIS	BURSITIS
CACHEXIA	CACHEXIA
CALCIFICATION METASTATIC	CALCIUM DIS
CALCINOSIS	CALCIUM DIS
CALCINOSIS RENAL	NEPHROCALCINOSIS
CALCITONIN SERUM LEVEL INCREASED	ENDO DIS
CALCIUM BLOOD DECREASED	HYPOCALCEM
CALCIUM BLOOD INCREASED	HYPERCALCEM
CALCIUM DEPOSITS	CALCIUM DIS
CALCIUM DISORDER (NOS)	CALCIUM DIS
CALCIUM INTOXICATION	HYPERCALCEM
CALCULUS BILIARY	CHOLELITH
CALCULUS COMMON BILE DUCT	CHOLELITH
CALCULUS GALLBLADDER	CHOLELITH
CALCULUS KIDNEY	KIDNEY CALCULUS
CALCULUS URETERAL	KIDNEY CALCULUS
CALCULUS URETHRAL	BLADDER CALCULUS
CALCULUS URINARY (NOS)	UROLITH
CALCULUS URINARY BLADDER	BLADDER CALCULUS
CANCER	CARCINOMA
CANCER (NOS)	CARCINOMA
CANKER SORES ORAL	STOMATITIS ULCER
CAPILLARY DISORDER	CAPILL FRAGIL INC
CAPILLARY FRAGILITY INCREASED	CAPILL FRAGIL INC
CAPILLARY LEAK SYNDROME	CAPILL FRAGIL INC
CAPILLARY PERMEABILITY INCREASED	CAPILL FRAGIL INC
CAPILLARY RESISTANCE DECREASED	CAPILL FRAGIL INC
CARBOHYDRATE TOLERANCE DECREASED	GLUCOSE TOLER DEC
CARBON DIOXIDE BLOOD DECREASED	ALKALOSIS RESP
CARBON DIOXIDE BLOOD INCREASED	ACIDOSIS RESP
CARBUNCLE	FURUNCULOSIS
CARCINOMA	CARCINOMA
CARCINOMA ADRENAL	CARCINOMA
CARCINOMA BASOSQUAMOUS	CARCINOMA SKIN
CARCINOMA BLADDER	CARCINOMA BLADDER
CARCINOMA BODY OF UTERUS	CARCINOMA ENDOMETR
CARCINOMA BONE	NEOPL BONE
CARCINOMA BRAIN	NEOPL CNS
CARCINOMA BREAST	CARCINOMA BREAST

CARCINOMA BRONCHIOGENIC	CARCINOMA LUNG
CARCINOMA CERVIX	CARCINOMA CERVIX
CARCINOMA CERVIX IN SITU	CARCINOMA CERVIX SITU
CARCINOMA COLON	CARCINOMA GI
CARCINOMA CORPUS UTERI	CARCINOMA ENDOMETR
CARCINOMA DUODENUM	CARCINOMA GI
CARCINOMA ENDOMETRIAL	CARCINOMA ENDOMETR
CARCINOMA EPIDERMOID	CARCINOMA SKIN
CARCINOMA GASTRIC	CARCINOMA GI
CARCINOMA GASTROINTESTINAL	CARCINOMA GI
CARCINOMA GLOTTIS	CARCINOMA LARYNX
CARCINOMA INTESTINAL	CARCINOMA GI
CARCINOMA KIDNEY	CARCINOMA
CARCINOMA LARYNX	CARCINOMA LARYNX
CARCINOMA LIVER	CARCINOMA LIVER
CARCINOMA LUNG	CARCINOMA LUNG
CARCINOMA MOUTH	CARCINOMA MOUTH
CARCINOMA PAPILLARY THYROID	CARCINOMA THYR
CARCINOMA PROSTATIC	CARCINOMA PROSTATE
CARCINOMA RECTUM	CARCINOMA GI
CARCINOMA SKIN	CARCINOMA SKIN
CARCINOMA STOMACH	CARCINOMA GI
CARCINOMA TESTES	CARCINOMA
CARCINOMA THYROID	CARCINOMA THYR
CARCINOMA TRANSITIONAL CELL	CARCINOMA
CARCINOMA URINARY BLADDER	CARCINOMA BLADDER
CARCINOMA UTERINE CERIX	CARCINOMA CERVIX
CARCINOMA UTERINE CERVIX IN SITU	CARCINOMA CERVIX SITU
CARCINOMA VOCAL CORD	CARCINOMA LARYNX
CARDIAC ARREST	HEART ARREST
CARDIAC ARREST NEONATAL	HEART ARREST
CARDIAC ARRHYTHMIA (NOS)	ARRHYTHMIA
CARDIAC ASTHMA	HEART FAIL LEFT
CARDIAC FAILURE	HEART FAIL
CARDIAC FAILURE CONGESTIVE	HEART FAIL RIGHT
CARDIAC FAILURE LEFT	HEART FAIL LEFT
CARDIAC FAILURE RIGHT	HEART FAIL RIGHT
CARDIAC INSUFFICIENCY	HEART FAIL
CARDIAC TAMPONADE	EFFUS PERICARD
CARDIOMEGALY	CARDIOMEGALY
CARDIOMYOPATHY	CARDIOMYOPATHY
CARDIOPULMONARY ARREST	HEART ARREST
CARDIOSPASM	CARDIOSPASM
CARDIOVASCULAR COLLAPSE	SHOCK
CARDIOVASCULAR DISORDER (NOS)	CARDIOVASC DIS
CARDITIS PERICARDIUM MYOCARDIUM	PANCARDITIS
CARIES DENTAL	TOOTH CARIES
CARPEL TUNNEL SYNDROME	TENOSYNOVITIS
CASTS URINARY	URIN CASTS
CASTS URINARY CELLULAR	URIN CASTS
CASTS URINARY GRANULAR	URIN CASTS
CASTS URINARY HYALINE	URIN CASTS
CATABOLISM EXTREME	CACHEXIA
CATABOLISM INCREASED	WEIGHT DEC
CATALEPSY	CATATON REACT
CATAPLEXY	CONVULS
CATARACT	CATARACT

CATARACT CONGENITAL	CATARACT
CATARACT LENTICULAR	CATARACT
CATARACT NOS	CATARACT NOS
CATARACT SPECIFIED	CATARACT
CATARACT SUBCAPSULAR	CATARACT
CATARACT UNSPECIFIED	CATARACT
CATATONIA	CATATON REACT
CATATONIC REACTION	CATATON REACT
CATATONIC STATE	CATATON REACT
CATECHOLAMINES URINARY ELEVATED	LAB TEST ABNORM
CELL MEDIATED IMMUNOLOGICAL REACTION	IMMUNE SYSTEM DIS
CELL-MEDIATED IMMUNOLOGICAL REACT	IMMUNE SYSTEM DIS
CELLULITIS	CELLULITIS
CELLULITIS BREAST	MASTITIS
CENTRAL NERVOUS SYSTEM DISORDER	CNS DEPRESS
CEPHALALGIA	HEADACHE
CEPHALGIA	HEADACHE
CEPHALIN FLOCCULATION ABNORMAL	CEPH FLOC ABNORM
CEPHALIN FLOCCULATION TEST ABNORMAL	CEPH FLOC ABNORM
CEREBELLAR SYNDROME	CEREBELL SYND
CEREBRAL ATROPHY	CEREBROVASC DIS
CEREBRAL DYSFUNCTION	THINKING ABNORM
CEREBRAL HAEMORRHAGE	HEM CEREBR
CEREBRAL HAEMORRHAGE NEONATAL	HEM CEREBR
CEREBRAL HEMORRHAGE	HEM CEREBR
CEREBRAL HEMORRHAGE NEONATAL	HEM CEREBR
CEREBRAL INFARCTION	INFARCT CEREBR
CEREBRAL ISCHEMIA	ISCHEMIA CEREBR
CEREBRAL PALSY	ANOMALY CONGEN CNS
CEREBRAL VASCULAR DISTURBANCE (NOS)	CEREBROVASC DIS
CEREBRAL VASCULAR LESION (NOS)	CEREBROVASC DIS
CEREBRATION IMPAIRED	THINKING ABNORM
CEREBROSPINAL FLUID ABNORMAL	CSF ABNORM
CEREBROVASCULAR ACCIDENT	CEREBROVASC ACCID
CEREBROVASCULAR DISORDER	CEREBROVASC DIS
CEREBROVASCULAR DISORDER (NOS)	CEREBROVASC DIS
CERVICAL DISCHARGE	LEUKORRHEA
CERVICAL DYSPLASIA	CERVIX DIS
CERVICAL HYPERSECRETION	CERVIX DIS
CERVICAL SMEAR POS CLASS III TO V	PAP SMEAR SUSP
CERVICAL SMEAR TEST POSITIVE	PAP SMEAR SUSP
CERVICAL UTERINE POLYP	NEOPL CERVIX
CERVICITIS	CERVICITIS
CERVICITIS CYSTIC	CERVICITIS
CERVIX CARCINOMA	CARCINOMA CERVIX
CERVIX CARCINOMA IN SITU	CARCINOMA CERVIX SITU
CERVIX LESION	CERVIX DIS
CERVIX UTERINE DISORDER (NOS)	CERVIX DIS
CFT ABNORMAL	CEPH FLOC ABNORM
CHARACTER CHANGE IN	PERSON DIS
CHEILITIS	CHEILITIS
CHEILOSIS	CHEILITIS
CHEMOSIS	CONJUNCTIVITIS
CHEST ACHE	PAIN CHEST
CHEST ACHING OF	PAIN CHEST
CHEST BURNING PAIN OF	PAIN CHEST
CHEST DISCOMFORT	PAIN CHEST

CHEST DISTRESSED FEELING OF	PAIN CHEST
CHEST FULLNESS OF	PAIN CHEST
CHEST PAIN	PAIN CHEST
CHEST PAIN PRECORDIAL	PAIN CHEST SUBSTERN
CHEST PAIN SUBSTERNAL	PAIN CHEST SUBSTERN
CHEST PAIN-L ARM	PAIN CHEST
CHEST PRESSURE SENSATION OF	PAIN CHEST
CHEST TENDERNESS OF	PAIN CHEST
CHEST TIGHTNESS OF	PAIN CHEST
CHEST X-RAY ABNORMAL	LUNG DIS
CHEYNE-STOKES RESPIRATION	APNEA
CHILLINESS	CHILLS
CHILLS	CHILLS
CHILLS AND FEVER	CHILLS FEVER
CHLOASMA	CHLOASMA
CHLORIDES BLOOD DECREASED	HYPOCHLOREM
CHLORIDES BLOOD INCREASED	HYPERCHLOREM
CHLOROPSIA	CHROMATOPSIA
CHOKING	DYSPHAGIA
CHOLANGIOLITIS TOXIC	JAUNDICE CHOLESTAT
CHOLANGITIS	CHOLANGITIS
CHOLANGITIS SCLEROSING	CHOLANGITIS SCLERO
CHOLANGITIS SUPPURATIVE	CHOLANGITIS
CHOLECYSTITIS	CHOLECYST
CHOLELITHIASIS	CHOLELITH
CHOLESTASIS INTRAHEPATIC	JAUNDICE CHOLESTAT
CHOLESTEROL BLOOD DECREASED	HYPOCHOLESTEREM
CHOLESTEROL BLOOD INCREASED	HYPERCHOLESTEREM
CHOLINERGIC SYNDROME	CHOLINERG SYND
CHOLINESTERASE BLOOD DECREASED	CHOLINESTERASE DEC
CHOLINESTERASE BLOOD INCREASED	CHOLINESTERASE INC
CHOLINESTERASE INCREASED	CHOLINESTERASE INC
CHOLURIA	URIN ABNORM
CHONDRODYSTROPHY	CHONDRODYST
CHOREA	CHOREOATHETOSIS
CHOREIFORM	CHOREOATHETOSIS
CHOREOATHETOID MOVEMENTS	CHOREOATHETOSIS
CHOREOATHETOSIS	CHOREOATHETOSIS
CHORIODORETINITIS	CHORIORETINITIS
CHOROIDAL DETACHMENT	RETINAL DETACH
CHOROIDITIS	CHOROIDITIS
CHROMATOPSIA	CHROMATOPSIA
CHROMATURIA	URIN ABNORM
CHROMOSOME ABNORMALITY	CHROMOSOME ABNORM
CHROMOSOME DISORDER	CHROMOSOME ABNORM
CICATRIX CORNEAL	CORNEAL OPACITY
CICATRIX SKIN	ATROPHY SKIN
CILIARY MUSCLE PARALYSIS	ACCOMMODATION ABNORM
CILIARY SPASM	MIOSIS
CINCHONISM	CINCHONISM
CIRCULATORY COLLAPSE	SHOCK
CIRCULATORY FAILURE	SHOCK
CIRCULATORY FAILURE NEONATAL	SHOCK
CIRCULATORY SYSTEM DISORDER (NOS)	CARDIOVASC DIS
CIRRHOSIS BILARY	LIVER CIRRHO
CIRRHOSIS BILIARY	LIVER CIRRHO
CIRRHOSIS LIVER	LIVER CIRRHO

CIRRHOSIS LIVER POSTNECROTIC	LIVER CIRRHO
CLAMMINESS	SWEAT
CLAUDICATION INTERMITTENT	VASC DIS PERIPH
CLEARANCE CREATININE DECREASED	CREATININE CLEAR DEC
CLEARANCE RENAL DECREASED (NOS)	KIDNEY FUNC ABNORM
CLEARANCE UREA DECREASED	UREA CLEAR DEC
CLEFT LIP	CLEFT LIP
CLEFT LIP AND PALATE	CLEFT PALATE
CLEFT PALATE	CLEFT PALATE
CLITORIS ENLARGED	CLITORIS ENLARGE
CLOSURE DELAYED EPIPHYSIS	EPIPHYS CLOS DELAY
CLOSURE PREMATURE EPIPHYSIS	EPIPHYS CLOS PREMAT
CLOT BLOOD	THROM
CLOT RETRACTION ACCELERATED	CLOT RETRACT ACCEL
CLOT RETRACTION RETARDED	CLOT RETRACT RETARD
CLOTTING	COAGUL DIS
CLOTTING TIME DECREASED	COAGUL TIME DEC
CLOTTING TIME INCREASED	COAGUL TIME INC
CLOTTING TIME LENGTHENED	COAGUL TIME INC
CLOTTING TIME PROLONGED	COAGUL TIME INC
CLUBBING OF NAILS	NAIL DIS
CLUBFOOT	CLUBFOOT
CLUMSINESS	COORDINAT ABNORM
CNS CONGENITAL ANOMALY	ANOMALY CONGEN CNS
CNS DEPRESSION	CNS DEPRESS
CNS DISORDER (NOS)	CNS DEPRESS
CNS STIMULATION	CNS STIMULAT
COAGULATION DISORDER	COAGUL DIS
COAGULATION DISORDER (NOS)	COAGUL DIS
COAGULATION DISORDER NEONATAL	COAGUL DIS
COAGULATION DISORDER NEONATAL (NOS)	COAGUL DIS
COAGULATION FACTOR DECREASED	COAGUL DIS
COAGULATION TIME DECREASED	COAGUL TIME DEC
COAGULATION TIME INCREASED	COAGUL TIME INC
COAGULATION TIME PROLONGED	COAGUL TIME INC
COAGULATION TIME SHORTENED	COAGUL TIME DEC
COCHLEAR NERVE DAMAGE	DEAF
COCHLEAR NERVE DEAFNESS	DEAF
COGNITIVE DISTURBANCE	THINKING ABNORM
COGWHEEL RIGIDITY	COGWHEEL RIGID
COITUS PAINFUL	DYSPAREUNIA
COLD AGGLUTININS POSITIVE	LAB TEST ABNORM
COLD EXTREMITIES	VASC DIS PERIPH
COLD URTICARIA	URTICARIA
COLDNESS GENERAL	CHILLS
COLDNESS LOCAL	PARESTHESIA
COLIC	PAIN
COLIC ABDOMINAL	PAIN ABDO
COLIC BILIARY	PAIN BIL
COLIC RENAL	PAIN KIDNEY
COLITIS	COLITIS
COLITIS (NOS)	COLITIS
COLITIS HAEMORRHAGIC	COLITIS HEM
COLITIS HEMORRHAGIC	COLITIS HEM
COLITIS MUCOUS	COLITIS
COLITIS PSEUDOMEMBRANOUS	COLITIS PSEUDOMEM
COLITIS ULCERATIVE	COLITIS ULCER

COLITIS ULCERATIVE AGGRAVATED	COLITIS ULCER
COLLAGEN DISORDER (NOS)	COLLAGEN DIS
COLLAGENOSIS	COLLAGEN DIS
COLLAPSE CARDIOVASCULAR	SHOCK
COLLAPSE CIRCULATORY	SHOCK
COLLAPSE FLEETING	SYNCOPE
COLLAPSE PERIPHERAL CIRCULATORY	SHOCK
COLLAPSE PERIPHERAL VASCULAR	SHOCK
COLLAPSE TRANSIENT	SYNCOPE
COLLAPSE VASCULAR	SHOCK
COLLAPSE VASOMOTOR	SYNCOPE
COLON ATONIC	ILEUS
COLON CARCINOMA	CARCINOMA GI
COLON OBSTRUCTION	OBSTRUCT INTEST
COLON PERFORATION	INTEST LARGE PER
COLON SPASTIC	COLITIS
COLON ULCER	ULCER INTEST
COMA	COMA
COMA (NOS)	COMA
COMA DIABETIC	COMA DIABET
COMA HEPATIC	COMA HEPATIC
COMA HYPERGLYCEMIC	COMA DIABET
COMA HYPOGLYCEMIC	HYPOGLYCEM REACT
COMA UREMIC	COMA UREMIC
COMBATIVE REACTION	HOSTILITY
COMEDOME	ACNE
COMMON COLD	INFECT
COMPLEMENT FACTOR ABNORMALITY	LAB TEST ABNORM
COMPULSIVE REACTION	NEUROSIS
CONCENTRATION (MENTAL) ABNORMAL	THINKING ABNORM
CONCENTRATION IMPAIRED	THINKING ABNORM
CONDITION AGGRAVATED	REACT AGGRAV
CONDUCTION DISORDER	ECG ABNORM
CONFABULATION	CONFUS
CONFUSION	CONFUS
CONFUSION STATE	CONFUS
CONGENITAL	ANOMALY CONGEN
CONGENITAL ANOMALY NOS	ANOMALY CONGEN
CONGESTION CONJUNCTIVAL	CONJUNCTIVITIS
CONGESTION NASAL	RHINITIS
CONGESTION PULMONARY	LUNG DIS
CONGESTIVE HEART FAILURE	HEART FAIL RIGHT
CONJUNCTIVAL DEPOSIT	CONJUNCTIVITIS
CONJUNCTIVAL DISCOLORATION	CONJUNCTIVITIS
CONJUNCTIVAL DISCOLOURATION	CONJUNCTIVITIS
CONJUNCTIVAL HAEMORRHAGE	HEM EYE
CONJUNCTIVAL HEMORRHAGE	HEM EYE
CONJUNCTIVITIS	CONJUNCTIVITIS
CONSCIOUSNESS LOSS OF	SYNCOPE
CONSTIPATION	CONSTIP
CONSTRICTION CHEST	PAIN CHEST
CONSTRICTION THROAT	LARYNGISMUS
CONTACT LENS INTOLERANCE	CORNEAL LESION
CONTRACEPTIVE WITHDRAWAL BLEEDING	WITHDRAW BLEED
CONTRACTION SKELETAL MUSCLE	MYOCLONUS
CONTRACTIONS UTERINE IMPAIRED	UTER ATONY
CONTRACTIONS UTERINE INCREASED	LABOR ABNORM

CONTRACTURE DUPYTREN'S	FIBRO TENDON
CONTRACTURE TENDINOUS	FIBRO TENDON
CONVERSION REACTION	HYSTERIA
CONVULSION (NOS)	CONVULS
CONVULSION DISORDER	CONVULS
CONVULSION GRAND MAL	CONVULS GRAND MAL
CONVULSION JACKSONIAN	CONVULS
CONVULSION PETIT MAL	CONVULS
CONVULSION PSYCHOMOTOR	CONVULS
CONVULSIONS	CONVULS
CONVULSIONS AGGRAVATED	CONVULS
CONVULSIONS GRAND MAL	CONVULS GRAND MAL
CONVULSIONS LOCAL	CONVULS
CONVULSIONS NEONATAL	CONVULS
COOMBS DIRECT TEST POSITIVE	COOMBS DIR TEST POS
COOMBS TEST DIRECT POSITIVE	COOMBS DIR TEST POS
COOMBS TEST INDIRECT POSITIVE	COOMBS INDIR TEST POS
COORDINATION ABNORMAL	COORDINAT ABNORM
COORDINATION IMPAIRED	COORDINAT ABNORM
COR PULMONALE	COR PULM
CORNEAL DEPOSITS	CORNEAL OPACITY
CORNEAL DISORDER (NOS)	CORNEAL LESION
CORNEAL EDEMA	KERATITIS
CORNEAL EROSION	CORNEAL LESION
CORNEAL INFLAMMATION	KERATITIS
CORNEAL LESION	CORNEAL LESION
CORNEAL OEDEMA	CORNEAL LESION
CORNEAL OPACITY	CORNEAL OPACITY
CORNEAL REFLEX DECREASED ABSENT	CORNEAL REFLEX DEC
CORNEAL ULCERATION	ULCER CORNEAL
CORONARY ARTERY DISORDER	CORONARY ART DIS
CORONARY ARTERY DISORDER (NOS)	CORONARY ART DIS
CORONARY ARTERY OCCLUSION	OCCLUS CORONARY
CORONARY ATHEROMA	CORONARY ART DIS
CORONARY DISEASE	CORONARY ART DIS
CORONARY INSUFFICIENCY	ANGINA PECTORIS
CORONARY SCLEROSIS	CORONARY ART DIS
CORONARY SPASM	ANGINA PECTORIS
CORPORAL DISASSOCIATION	DEPERSONAL
CORPUS UTERI CARCINOMA	CARCINOMA ENDOMETR
CORTICOSTEROID WITHDRAWAL SYNDROME	ADDISON CRISIS
CORTISOL INCREASED	GLUCOCORT INC
CORYZA-LIKE	RHINITIS
COUGH DECRESED	COUGH DEC
COUGH INCREASED	COUGH INC
COUGH NONPRODUCTIVE	COUGH INC
COUGHING	COUGH INC
COUGHING BLOOD	HEMOPTYSIS
COUPLED HEART BEATS	EXTRASYSTOLES BIGEM
CPK INCREASED	CREATINE PK INC
CRAMP	PAIN
CRAMP ABDOMINAL	PAIN ABDO
CRAMP LEGS	CRAMPS LEG
CRAMP MUSCLE	HYPERTONIA
CRAMPS IN THE CALVES	CRAMPS LEG
CRAMPS MENSTRUAL	DYSMENORRHEA
CRANIAL NERVE LESION	NEUROPATHY

CRANIAL THIRD NERVE PARESIS	PARALYSIS EXTRAOCUL
CRANIOPHARYNGIOMA	NEOPL CNS
CRAWLING SENSATION	PARESTHESIA
CREATINE KINASE INCREASED	CREATINE PK INC
CREATINE PHOSPHOKINASE INCREASED	CREATINE PK INC
CREATINE PHOSPHOKINASE SERUM INC	CREATINE PK INC
CREATININE CLEARANCE DECREASED	CREATININE CLEAR DEC
CREATININE SERUM INCREASED	CREATININE INC
CRETINISM	CRETIN
CRISIS ADDISONIAN	ADDISON CRISIS
CRISIS ADRENAL	ADDISON CRISIS
CRISIS HYPERTENSIVE	HYPERTENS
CRISIS OCULOGYRIC	OCULOGYRIC CRISIS
CRISIS THYROID	HYPERTHYR
CROSS INFECTION	INFECT
CROSS SENSITIVITY REACT	ALLERG REACT
CROUP	LARYNGITIS
CRYING ABNORMAL	SCREAMING SYND
CRYING DPT VACCINE RELATED	SCREAMING SYND
CRYING UNCONTROLLABLE	EMOTION LABIL
CRYPTOCOCCOSIS	CRYPTOCOCCOSIS
CRYPTORCHISM	ANOMALY CONGEN UG
CRYSTALLIZATION KIDNEY	CRYSTALLURIA
CRYSTALLURIA	CRYSTALLURIA
CRYSTALLURIA CALCIUM	CRYSTALLURIA CA
CRYSTALLURIA SULFONAMIDE	CRYSTALLURIA SULFA
CRYSTALLURIA URATE	CRYSTALLURIA URIC
CSF ABNORMAL	CSF ABNORM
CUSHING'S DISEASE	CUSHINGS SYND
CUSHING'S SYNDROME	CUSHINGS SYND
CUSHINGOID	CUSHINGS SYND
CUSHINGOID FACIES	CUSHINGS SYND
CVA	CEREBROVASC ACCID
CYANOSIS	CYANOSIS
CYANOSIS NEONATAL	CYANOSIS
CYANOSIS PERIPHERAL	CYANOSIS
CYCLOPLEGIA	ACCOMMODATION ABNORM
CYCLOTHYMIC REACTION	PERSON DIS
CYLINDRURIA	URIN CASTS
CYST	CYST
CYST EPIDERMAL	CYST
CYST INJECTION SITE	CYST INJECT SITE
CYST OVARY	CYST
CYST SEBACEOUS	CYST
CYSTIC FIBROSIS LUNG	LUNG DIS
CYSTIC FIBROSIS PANCREAS	PANCREAS DIS
CYSTITIS	CYSTITIS
CYSTITIS (NOS)	CYSTITIS
CYSTITIS HAEMORRHAGIC	HEM CYSTITIS
CYSTITIS HEMORRHAGIC	HEM CYSTITIS
CYSTITIS INTERSTITIAL	CYSTITIS
CYSTITIS PSEUDOMONAL	CYSTITIS
CYSTITIS ULCERATIVE	CYSTITIS
DAMAGE LIVER	LIVER DAMAGE
DARK ACCOMMODATION DISORDER	BLIND NIGHT
DAYTIME SLEEPINESS	SOMNOLENCE
DEAFNESS	DEAF

DEAFNESS (NOS)	DEAF
DEAFNESS CONGENITAL	DEAF
DEAFNESS MIDDLE EAR TYPE	DEAF
DEAFNESS NERVE	DEAF
DEAFNESS NERVE TYPE	DEAF
DEAFNESS PERMANENT	DEAF PERM
DEAFNESS PERMANENT PARTIAL	DEAF PERM PART
DEAFNESS PERMANENT TOTAL	DEAF PERM TOTAL
DEAFNESS TRANSITORY	DEAF TRANS
DEAFNESS TRANSITORY PARTIAL	DEAF TRANS PART
DEAFNESS TRANSITORY TOTAL	DEAF TRANS TOTAL
DEATH	DEATH
DEATH FETAL	STILLBIRTH
DEATH FOETAL	STILLBIRTH
DEATH INFANT SUDDEN	SIDS
DEATH INTRAUTERINE	STILLBIRTH
DEATH NEONATAL	DEATH
DEATH NEONATAL (NOS)	DEATH
DEATH SUDDEN (NOS)	SUDDEN DEATH
DEATH SUDDEN INFANT	SIDS
DEATH UNEXPLAINED (NOS)	DEATH
DEBILITY	MALAISE
DEBILITY MARKED	ASTHENIA
DECAY DENTAL	TOOTH CARIES
DECOLORATION SKIN	LEUKODERMA
DECOMPENSATION CARDIAC	HEART FAIL
DECOMPENSATION MYOCARDIAL	HEART FAIL
DECREASED TSH	ALTERED HORMONE LEVEL
DEFECATION URGE PAINFUL	TENESMUS
DEFECT ARTRIAL SEPTUM	ATR SEPT DEF
DEFECT COAGULATION (NOS)	COAGUL DIS
DEFECT CONDUCTION (NOS)	ARRHYTHMIA
DEFECT CONDUCTION INTRAVENTRICULAR	BUNDLE BRANCH BLOCK
DEFECT INTERVENTRICULAR SEPTUM	VENT SEPT DEF
DEFECT SPEECH (NOS)	SPEECH DIS
DEFECT VISUAL FIELD (NOS)	VISUAL FIELD DEFECT
DEFECTS CARDIAC MULTIPLE	ANOMALY HEART
DEFICIENCY FACTOR I	FIBRINOGEN DEC
DEFICIENCY MENTAL	MENTAL RETARD
DEFICIENCY VITAMIN	AVITAMINOSIS
DEGENERATION FATTY LIVER	LIVER FATTY
DEGENERATION MACULAR	RETINAL DIS
DEGENERATION MUSCLE	MYOPATHY
DEGENERATION MYOCARDIAL	MYOCARDITIS
DEGENERATION RETINAL	RETINAL DEGENERAT
DEGENERATION TUBULAR KIDNEY	NECRO KIDNEY TUBUL
DEGLUTITION DISORDER	DYSPHAGIA
DEHYDRATION	DEHYDRAT
DEHYDROGENASE LACTIC BLOOD URINE INCREASED	LDH INC
DEJA-VU	DEPERSONAL
DEJECTION EMOTIONAL	DEPRESSION
DELIRIUM	DELIRIUM
DELIRIUM TOXIC	DELIRIUM
DELIRIUM TREMENS	DELIRIUM
DELIVERY DELAYED	LABOR ABNORM
DELUSION	DELUSIONS
DELUSION SOMATIC	DEPERSONAL

DELUSION UNSYSTEMATIZED	DELUSIONS
DELUSIONS	DELUSIONS
DEMENTIA	DEMENTIA
DEMENTIA ACQUIRED	DEMENTIA
DEMYELINATION	NEUROPATHY
DENTAL CARIES	TOOTH CARIES
DENTAL DEVELOPMENT IMPAIRED	ANOMALY TOOTH
DEPENDENCE ADDICTIVE	DRUG DEPEND ADDICT
DEPENDENCE DRUG (NOS)	DRUG DEPEND
DEPENDENCE NON-ADDICTIVE	DRUG DEPEND
DEPENDENCE PHYSIOLOGICAL	DRUG DEPEND ADDICT
DEPENDENCE PSYCHOLOGICAL	DRUG DEPEND
DEPERSONALIZATION	DEPERSONAL
DEPIGMENTATION RETINAL	RETINAL DEPIGMENT
DEPIGMENTATION SKIN	LEUKODERMA
DEPILATION	ALOPECIA
DEPLETION BLOOD ELECTROLYTE (NOS)	ELECTROLYTE DEPLET
DEPOSIT BONE ABNORMAL	BONE DIS
DEPOSIT CALCIUM	CALCIUM DIS
DEPOSIT CORNEAL	CORNEAL OPACITY
DEPOSIT EYE	EYE DIS
DEPOSIT JOINT	JOINT DIS
DEPOSIT LENS	CATARACT
DEPOSITS TOOTH	TOOTH DIS
DEPRESSED REACTION	DEPRESSION
DEPRESSED STATE	DEPRESSION
DEPRESSION	DEPRESSION
DEPRESSION AGGRAVATED	DEPRESSION
DEPRESSION AGITATED	DEPRESSION
DEPRESSION BONE MARROW (NOS)	MARROW DEPRESS
DEPRESSION CARDIOVASCULAR (NOS)	CARDIOVASC DIS
DEPRESSION CENTRAL NERVOUS SYSTEM	CNS DEPRESS
DEPRESSION ENDOGENOUS	DEPRESSION PSYCHOTIC
DEPRESSION FUNCTIONAL	DEPRESSION
DEPRESSION MENTAL	DEPRESSION
DEPRESSION NEUROTIC	DEPRESSION
DEPRESSION PSYCHIC	DEPRESSION
DEPRESSION PSYCHOTIC	DEPRESSION PSYCHOTIC
DEPRESSION REACTIVE	DEPRESSION
DEPRESSION RESPIRATORY	HYPOVENTIL
DEPRESSION SUICIDAL	DEPRESSION PSYCHOTIC
DEPRESSION WORSENED	DEPRESSION
DERMATITIS	RASH
DERMATITIS (NOS)	RASH
DERMATITIS ALLERGIC	RASH
DERMATITIS ATOPIC	RASH
DERMATITIS CONTACT	DERM CONTACT
DERMATITIS COSMETIC	DERM CONTACT
DERMATITIS ECZEMATOID	ECZEMA
DERMATITIS EXFOLIATIVE	DERM EXFOL
DERMATITIS EXTRINSIC	DERM CONTACT
DERMATITIS EYELID	BLEPHARITIS
DERMATITIS FUNGAL	DERM FUNG
DERMATITIS FUNGOID	DERM FUNG
DERMATITIS HAEMORRHAGIC	RASH PURPUR
DERMATITIS HERPETIFORMIS	RASH VESIC BULL
DERMATITIS LICHENOID	DERM LICHEN

DERMATITIS LUPOID	RASH LE
DERMATITIS MEDICAMENTOSA	RASH
DERMATITIS MYCOID	DERM FUNG
DERMATITIS NECROTIZING	EPIDERM NECRO
DERMATITIS PAPULAR	RASH MAC PAP
DERMATITIS PYOGENIC	RASH PUST
DERMATITIS SEBORRHEIC	SEBORRHEA
DERMATITIS SIMPLEX ERYTHEMATOSA	RASH
DERMATITIS VENENATA	DERM CONTACT
DERMATOGRAPHIA	URTICARIA
DERMATOMYOSITIS	DERMATOMYOSITIS
DERMOGRAPHIA	URTICARIA
DESQUAMATION	DERM EXFOL
DESTRUCTION JOINT	ARTHROSIS
DESTRUCTION PLATELET INCREASED	THROMBOCYTOPENIA
DETACHMENT CHORIDAL	RETINAL DETACH
DETACHMENT CORPOREAL	DEPERSONAL
DETACHMENT EMOTIONAL	APATHY
DETACHMENT PSYCHOLOGICAL	APATHY
DETACHMENT RETINAL	RETINAL DETACH
DETERIORATION MENTAL (NOS)	DEMENTIA
DETRUSOR MUSCLE WEAKNESS	INCONTIN URIN
DEVELOPMENT DENTAL IMPAIRED	ANOMALY TOOTH
DEVELOPMENT PSYCHOMOTOR IMPAIRED	MENTAL RETARD
DEVICE DIFFICULT TO REMOVE	DEVICE MIGRATION
DEVICE MOVED	DEVICE MIGRATION
DI GUGLIELMO'S SYNDROME	MARROW HYPERPLASIA
DIABETES INSIPIDUS	DIABETES INSIPID
DIABETES INSIPIDUS NEPHROGENIC	DIABETES INSIPID
DIABETES MELLITUS	DIABETES MELL
DIABETES MELLITUS AGGRAVATED	DIABETES MELL
DIABETES MELLITUS PRECIPITATED	DIABETES MELL
DIABETES MELLITUS REACTIVATED	DIABETES MELL
DIABETES NEPHROGENIC (EXCLUDES GLYCOSURIA)	DIABETES INSIPID
DIABETIC COMA	COMA DIABET
DIABETIC TYPE CURVE	GLUCOSE TOLER DEC
DIAPHORESIS	SWEAT
DIAPHRAGM APLASIA	ANOMALY CONGEN
DIARRHEA	DIARRHEA
DIARRHEA BLOODY	DIARRHEA BLOODY
DIARRHEA NEONATAL	DIARRHEA
DIARRHOEA	DIARRHEA
DIARRHOEA NEONATAL	DIARRHEA
DIARRHOEA, CLOSTRIDIUM DIFFICILE	DIARRHEA
DIC	DIC
DIFFICULTY FOCUSING EYES	VISION ABNORM
DIFFICULTY THINKING	THINKING ABNORM
DIGESTION IMPAIRED	DYSPEPSIA
DIGITALIS INTOXICATION (NOS)	DIGITALIS INTOX
DILATATION PERIPORTAL SINUS	LIVER DAMAGE
DILATATION PUPILLARY	MYDRIASIS
DILATATION STOMACH	STOMACH DILAT
DILATATION URETERAL	HYDROURETER
DILATATION VASCULAR RETINAL	RETINAL VASC DIS
DIPLOPIA	DIPLOPIA
DISASSOCIATION/ASSOCIATION	DEPERSONAL
DISCHARGE BREAST FEMALE	LACTATION FEM

DISCHARGE BREAST MALE	LACTATION MALE
DISCHARGE EYE	CONJUNCTIVITIS
DISCHARGE UTERINE CERVIX	LEUKORRHEA
DISCHARGE VAGINAL	LEUKORRHEA
DISCOLORATION FECAL	STOOL ABNORM
DISCOLORATION NAIL	NAIL DIS
DISCOLORATION SKIN	SKIN DISCOLOR
DISCOLORATION STOOL	STOOL ABNORM
DISCOLORATION TONGUE	DISCOLOR TONGUE
DISCOLORATION TOOTH	DISCOLOR TOOTH
DISCOLORATION URINE	URIN ABNORM
DISCOMFORT	PAIN
DISCOMFORT ABDOMINAL	PAIN ABDO
DISCOMFORT BODILY	PAIN
DISCOMFORT EPIGASTRIC	PAIN ABDO
DISCOMFORT RECTAL	PAIN
DISCOMPOSURE MARKED	AGITATION
DISEASE ADDISON'S	ADREN INSUFFIC
DISEASE AGGRAVATION	REACT AGGRAV
DISEASE CORONARY ARTERY	CORONARY ART DIS
DISEASE CROHNS	ILEITIS
DISEASE CYSTIC BREAST	BREAST FIBROCYST
DISEASE FIBROCYSTIC BREAST	BREAST FIBROCYST
DISEASE FIBROCYSTIC PANCREAS	PANCREAS DIS
DISEASE GALLBLADDER	CHOLECYST
DISEASE GRAVES'	HYPERTHYR
DISEASE HEART CONGENITAL (NOS)	ANOMALY HEART
DISEASE HEART PULMONARY	COR PULM
DISEASE HEPATOCELLULAR	LIVER DAMAGE
DISEASE OBSTRUCTIVE LUNG	LUNG DIS
DISEASE PARKINSON'S	EXTRAPYR SYND
DISEASE PELVIC INFLAMMATORY	SALPINGITIS
DISEASE PINK	ACRODYNIA
DISEASES OF OESOPHAGUS	ESOPHAGITIS
DISORDER ACCOMMODATION	ACCOMMODATION ABNORM
DISORDER ADRENAL (NOS)	ADREN DIS
DISORDER AGGRAVATION	REACT AGGRAV
DISORDER ANORECTAL (NOS)	RECTAL DIS
DISORDER ANUS	RECTAL DIS
DISORDER BEHAVIOR	PERSON DIS
DISORDER BIRTH	PERINATAL DIS
DISORDER BLOOD (NOS)	BLOOD DYSCRASIA
DISORDER BODY IMAGE	DEPERSONAL
DISORDER BONE (NOS)	BONE DIS
DISORDER BRAIN (ACUTE)	BRAIN SYND ACUTE
DISORDER BRAIN (CHRONIC)	BRAIN SYND CHRON
DISORDER BRAIN STEM	BRAIN STEM DIS
DISORDER CALCIUM (NOS)	CALCIUM DIS
DISORDER CARDIAC (NOS)	CARDIOVASC DIS
DISORDER CARDIOVASCULAR (NOS)	CARDIOVASC DIS
DISORDER CARTILAGE DEVELOPMENT (NOS)	CHONDRODYST
DISORDER CENTRAL NERVOUS SYSTEM	CNS DEPRESS
DISORDER CEREBROVASCULAR	CEREBROVASC DIS
DISORDER CERVIX	CERVIX DIS
DISORDER CIRCULATORY SYSTEM	CARDIOVASC DIS
DISORDER COAGULATION	COAGUL DIS
DISORDER COLLAGEN (NOS)	COLLAGEN DIS

DISORDER CONVULSIVE	CONVULS
DISORDER CORNEAL	CORNEAL LESION
DISORDER CORONARY ARTERY	CORONARY ART DIS
DISORDER DARK ACCOMMODATION	BLIND NIGHT
DISORDER DEGLUTITION	DYSPHAGIA
DISORDER EAR	EAR DIS
DISORDER ECG/EKG (NOS)	ECG ABNORM
DISORDER EEG (NOS)	EEG ABNORM
DISORDER ENDOCRINE	ENDO DIS
DISORDER ENDOCRINE POLYGLANDULAR	ENDO DIS
DISORDER ENDOMETRIAL	ENDOMETR DIS
DISORDER EQUILIBRIUM	COORDINAT ABNORM
DISORDER EYE	EYE DIS
DISORDER FETAL	FETAL DIS
DISORDER GAIT	GAIT ABNORM
DISORDER GASTROINTESTINAL	GI DIS
DISORDER HAIR	HAIR DIS
DISORDER HEMATOLOGIC	BLOOD DYSCRASIA
DISORDER HEPATIC	LIVER DAMAGE
DISORDER IMMUNE SYSTEM (NOS)	IMMUNE SYSTEM DIS
DISORDER JOINT	JOINT DIS
DISORDER KIDNEY	URIN TRACT DIS
DISORDER LABYRINTHINE	VESTIBUL DIS
DISORDER LACRIMATION	LACRIMATION DIS
DISORDER LIVER	LIVER DAMAGE
DISORDER LUNG	LUNG DIS
DISORDER MENSTRUAL	MENS DIS
DISORDER MUSCLE	MYOPATHY
DISORDER MYELOPROLIFERATIVE	MYELOPROLIF DIS
DISORDER NAIL	NAIL DIS
DISORDER NEONATAL	PERINATAL DIS
DISORDER NERVOUS SYSTEM	NEUROPATHY
DISORDER OVARIAN	OVAR DIS
DISORDER PANCREAS	PANCREAS DIS
DISORDER PARATHYROID	PARATHYR DIS
DISORDER PENIS	PENIS DIS
DISORDER PERINATAL	PERINATAL DIS
DISORDER PERIOSTEAL	PERIOST DIS
DISORDER PERIPHERAL VASCULAR	VASC DIS PERIPH
DISORDER PERSONALITY	PERSON DIS
DISORDER PLACENTAL	PLACENTA DIS
DISORDER PLATELET	PLAT ABNORM
DISORDER PULMONARY	LUNG DIS
DISORDER RADIATION	RADIAT INJ
DISORDER RECTAL	RECTAL DIS
DISORDER REFRACTION	REFRACT DIS
DISORDER RENAL	URIN TRACT DIS
DISORDER RESPIRATORY SYSTEM	RESPIRAT DIS
DISORDER RETINAL	RETINAL DIS
DISORDER SIGHT	VISION ABNORM
DISORDER SKIN (NOS)	SKIN DIS
DISORDER SLEEP	SLEEP DIS
DISORDER SPEECH	SPEECH DIS
DISORDER SPERM	TESTIS DIS
DISORDER SPLEEN	SPLEEN DIS
DISORDER TENDON	TENDON DIS
DISORDER TESTICLE	TESTIS DIS

DISORDER THYROID	THYR DIS
DISORDER TONGUE	TONGUE DIS
DISORDER TOOTH	TOOTH DIS
DISORDER TUBULAR KIDNEY	KIDNEY TUBUL DIS
DISORDER URINARY TRACT	URIN TRACT DIS
DISORDER UROGENITAL	UG DIS
DISORDER UTERINE (NOS)	UTER DIS
DISORDER UTERINE CERVIX	CERVIX DIS
DISORDER VASCULAR	VASC DIS
DISORDER VASCULAR PERIPHERAL	VASC DIS PERIPH
DISORDER VASCULAR RETINAL	RETINAL VASC DIS
DISORDER VESTIBULAR	VESTIBUL DIS
DISORDER VITREOUS	VITREOUS DIS
DISORDER VULVA	VULVOVAGINAL DIS
DISORDER VULVOVAGINAL	VULVOVAGINAL DIS
DISORIENTATION	CONFUS
DISSEM. INTRAVASC. COAGULATION	DIC
DISSEMINATED INTRAVASCULAR COAGULATION	DIC
DISSEMINATED LUPUS ERYTHEMATOSUS	LE SYND
DISSOCIATION AURICULOVENTRICULAR	AV BLOCK COMP
DISSOCIATION CORPOREAL	DEPERSONAL
DISSOCIATIVE REACTION	DEPERSONAL
DISTANCE ACCOMMODATION DISORDER	ACCOMMODATION ABNORM
DISTENTION	FLATUL
DISTORTION CORPOREAL	DEPERSONAL
DISTORTION PERSONAL	DEPERSONAL
DISTRESS ABDOMINAL	DYSPEPSIA
DISTRESS EPIGASTRIC	DYSPEPSIA
DISTRESS GASTROINTESTINAL	DYSPEPSIA
DISTRESS RESPIRATORY	DYSPNEA
DISTRESS RESPIRATORY SYNDROME ADULTS	RESPIRAT DIS
DISTRESS RESPIRATORY SYNDROME NEWBORN	PERINATAL DIS
DISULFIRAM LIKE REACTION	ALCOHOL INTOLER
DIVERTICULITIS	COLITIS
DIZZINESS	DIZZINESS
DIZZINESS EXERTIONAL	DIZZINESS
DIZZINESS POSTURAL	HYPOTENS POST
DIZZINESS UPON STANDING	HYPOTENS POST
DIZZY ON STANDING	HYPOTENS POST
DLE	LE SYND
DOPINESS	SOMNOLENCE
DORSAL PAIN	PAIN BACK
DOWN'S SYNDROME	MENTAL RETARD
DRAWING NECK	TORTICOLLIS
DREAM DELIRIUM	DREAM ABNORM
DREAMING ABNORMAL	DREAM ABNORM
DREAMS ABNORMAL	DREAM ABNORM
DREAMS BIZARRE UNUSUAL OR FRIGHTENING	DREAM ABNORM
DROOLING	SALIVA INC
DROWSINESS	SOMNOLENCE
DROWSY ON AWAKENING	SOMNOLENCE
DRUG ABUSE	DRUG DEPEND
DRUG ADDICTION	DRUG DEPEND ADDICT
DRUG DEPENDENCE	DRUG DEPEND
DRUG DEPENDENCE PHYSICAL	DRUG DEPEND ADDICT
DRUG DEPENDENCE PSYCHIC	DRUG DEPEND ADDICT
DRUG EFFECT DEMINISHED	NO DRUG EFFECT

DRUG EFFECT GOOD UNEXPECTED BENEFICIAL	UNEXPECTED BENEFIT
DRUG EFFECT INCOMPLETE	NO DRUG EFFECT
DRUG EFFECT INCREASED	INCREASED EFFECT
DRUG EFFECT LACK OF	NO DRUG EFFECT
DRUG EFFECT PROLONGED	INCREASED EFFECT
DRUG ERUPTION	RASH
DRUG FEVER	FEVER
DRUG HABIT	DRUG DEPEND
DRUG HABITUATING	DRUG DEPEND
DRUG INTERACTION (NOS)	DRUG INTERACTION
DRUG INTOXICATION	OVERDOSE
DRUG LEVEL DECREASED	DRUG LEVEL DEC
DRUG LEVEL IN BLOOD DECEASED	DRUG LEVEL DEC
DRUG LEVEL IN BLOOD INCREASED	DRUG LEVEL INC
DRUG LEVEL INCREASED	DRUG LEVEL INC
DRUG MALADMINISTRATION	DRUG DEPEND
DRUG TOXICITY (NOS)	OVERDOSE
DRUG WITHDRAWAL SYNDROME	WITHDRAW SYND
DRUGGEDNESS	SOMNOLENCE
DRUNKENNESS	STUPOR
DRY AND SORE THROAT	PHARYNGITIS
DRY EYES	DRY EYE
DRY MOUTH	DRY MOUTH
DRY SKIN	SKIN DRY
DRYING	SKIN DRY
DRYNESS ORAL	DRY MOUTH
DRYNESS VAGINAL	VAGINITIS
DUCTUS ARTERIOSUS PATENT	DUCT ART PAT
DULLNESS	SOMNOLENCE
DUODENAL ATRESIA CONGENITAL	ANOMALY GI
DUODENAL CARCINOMA	CARCINOMA GI
DUODENAL ULCER	ULCER DUODEN
DUODENAL ULCER AGGRAVATED	ULCER DUODEN
DUODENAL ULCER HAEMORRHAGIC	ULCER DUODEN HEM
DUODENAL ULCER HAEMPER	ULCER DUODEN PERHEM
DUODENAL ULCER HEMORRHAGE PERFORATED	ULCER DUODEN PERHEM
DUODENAL ULCER HEMORRHAGIC	ULCER DUODEN HEM
DUODENAL ULCER PERFORATED	ULCER DUODEN PER
DUODENAL ULCER REACTIVATED	ULCER DUODEN REACT
DUODENITIS	DUODENITIS
DUODENITIS HEMORRHAGIC	DUODENITIS
DUPUYTREN'S CONTRACTURE	FIBRO TENDON
DWARFISM	DWARFISM
DYSARTHRIA	DYSARTHRIA
DYSARTHROSIS	CHONDRODYST
DYSAUTONOMIA	DYSAUTONOMIA
DYSBASIA	GAIT ABNORM
DYSCHONDROPLASIA	CHONDRODYST
DYSCRASIA BLOOD (NOS)	BLOOD DYSCRASIA
DYSDIADOCHOKINESIS	COORDINAT ABNORM
DYSEQUILIBRIUM	COORDINAT ABNORM
DYSFUNCTION ADRENAL	ADREN DIS
DYSFUNCTION HEPATIC NONICTERIC	LIVER FUNC ABNORM
DYSFUNCTION KIDNEY	KIDNEY FUNC ABNORM
DYSFUNCTION OVARIAN	OVAR DIS
DYSFUNCTION PARATHYROID	PARATHYR DIS
DYSFUNCTION TESTICULAR	TESTIS DIS

DYSFUNCTION THYROID	THYR DIS
DYSGENSIA	TASTE LOSS
DYSKINESIA	DYSKINESIA
DYSKINESIA BUCCOGLOSSAL	BUCCOGLOSSAL SYND
DYSKINESIA NEONATAL	DYSKINESIA
DYSKINESIA OCULOMOTOR	OCULOGYRIC CRISIS
DYSKINESIA SYNDROME	DYSKINESIA
DYSKINESIA TARDIVE	DYSKINESIA TARDIVE
DYSMENORRHEA	DYSMENORRHEA
DYSMENORRHOEA	DYSMENORRHEA
DYSMETRIA	COORDINAT ABNORM
DYSOMIA	PAROSMIA
DYSPAREUNIA	DYSPAREUNIA
DYSPEPSIA	DYSPEPSIA
DYSPHAGIA	DYSPHAGIA
DYSPHASIA	SPEECH DIS
DYSPHONIA	VOICE ALTERAT
DYSPHORIA	DEPRESSION
DYSPLASIA ADRENAL CORTEX	ADREN DIS
DYSPLASIA EPIPHYSEAL MULTIPLE	CHONDRODYST
DYSPLASIA TOOTH	ANOMALY TOOTH
DYSPNEA	DYSPNEA
DYSPNOEA	DYSPNEA
DYSTONIA	DYSTONIA
DYSTONIC REACTION	DYSTONIA
DYSURIA	DYSURIA
EAR BUZZING	TINNITUS
EAR CRACKLING	TINNITUS
EAR DISORDER (NOS)	EAR DIS
EAR DISORDER NOS	EAR DIS
EAR DRUM PERFORATION	EAR DIS
EAR FEELS CLOGGED	EAR DIS
EAR HISSING	TINNITUS
EAR MALFORMATION	ANOMALY CONGEN
EAR NOISES	TINNITUS
EAR PAIN	PAIN EAR
EAR RINGING	TINNITUS
EAR ROARING	TINNITUS
EARACHE	PAIN EAR
ECCHYMOSIS	ECCHYMOSIS
ECCHYMOSIS INJECTION SITE	ECCHYMOSIS
ECG ABNORMAL	ECG ABNORM
ECG ABNORMAL SPECIFIC	ECG ABNORM
ECG EKG ABNORMAL (NOS)	ECG ABNORM
ECG/EKG CHANGES NON-SPECIFIC	ECG ABNORM
ECHOLALIA	SPEECH DIS
ECLAMPSIA	PREGN DIS
ECTOPIA CORDIS	ECTOPIA CORDIS
ECTOPIC BEATS	EXTRASYSTOLES
ECTROMELIA	ECTROMELIA
ECTROMELIA FOUR LIMBS	ECTROMELIA
ECTROMELIA ONE LIMB	ECTROMELIA
ECTROMELIA THREE LIMBS	ECTROMELIA
ECTROMELIA TWO LIMBS	ECTROMELIA
ECZEMA	ECZEMA
ECZEMA ALLERGIC ATOPIC	ECZEMA
ECZEMA ATOPIC	ECZEMA

ECZEMA NUMMULAR	ECZEMA
ECZEMA PAPULAR	ECZEMA
EDEMA	EDEMA
EDEMA (NOS)	EDEMA
EDEMA ANGIONEUROTIC	ANGIOEDEMA
EDEMA APPLICATION SITE	APPLICAT SITE REACT
EDEMA BRAIN	EDEMA BRAIN
EDEMA CEREBRAL	EDEMA BRAIN
EDEMA CONJUNCTIVAL	EDEMA CONJUNCT
EDEMA DEPENDENT	EDEMA PERIPH
EDEMA EXTREMITIES	EDEMA PERIPH
EDEMA EYELID	EDEMA FACE
EDEMA FACE	EDEMA FACE
EDEMA GENERALIZED	EDEMA GENERAL
EDEMA GENITAL	EDEMA GENITAL
EDEMA GLOTTIS	EDEMA LARYNX
EDEMA INJECTION SITE	EDEMA INJECT SITE
EDEMA LABIAL GENITAL	EDEMA LABIA
EDEMA LARYNGOTRACHEAL	EDEMA LARYNX
EDEMA LARYNX	EDEMA LARYNX
EDEMA LEGS	EDEMA PERIPH
EDEMA LIP	EDEMA FACE
EDEMA LUNG	EDEMA LUNG
EDEMA OF EXTREMITIES	EDEMA PERIPH
EDEMA PERIORBITAL	EDEMA FACE
EDEMA PERIPHERAL	EDEMA PERIPH
EDEMA PHARYNX	PHARYNGITIS
EDEMA PULMONARY	EDEMA LUNG
EDEMA QUINCKE'S	ANGIOEDEMA
EDEMA RETINAL	EDEMA RETINAL
EDEMA SCROTAL	EDEMA SCROTUM
EDEMA TONGUE	EDEMA TONGUE
EDEMA TRACHEAL	EDEMA LARYNX
EDEMA VOCAL CORD	EDEMA LARYNX
EDEMA VULVA	VULVOVAGINITIS
EEG ABNORMAL	EEG ABNORM
EFFECT INCREASED	INCREASED EFFECT
EFFICACY LACK OF	NO DRUG EFFECT
EFFORT ANGINA	ANGINA PECTORIS
EFFORT SYNDROME	NEUROSIS
EFFUSION PERICARDIAL	EFFUS PERICARD
EFFUSION PERICARDIAL BLOODY	EFFUS PERICARD
EFFUSION PLEURAL	EFFUS PLEURAL
EFFUSION PLEURAL BLOODY	EFFUS PLEURAL
EIGHTH NERVE LESION (NOS)	EAR DIS
EJACULATION ABNORMAL	EJACULAT ABNORM
EJACULATION DECREASED	EJACULAT ABNORM
EJACULATION DELAYED	EJACULAT ABNORM
EJACULATION DISORDER	EJACULAT ABNORM
EJACULATION FAILURE	EJACULAT ABNORM
EJACULATION INHIBITED	EJACULAT ABNORM
EJACULATION PREMATURE	EJACULAT ABNORM
EKG ABNORMAL NON-SPECIFIC	ECG ABNORM
EKG/ECG ABNORMALITIES NON-SPECIFIC	ECG ABNORM
ELATION INAPPROPRIATE	EUPHORIA
ELECTROCARDIOGRAM ABNORMAL (NOS)	ECG ABNORM
ELECTROENCEPHALOGRAM ABNORMAL	EEG ABNORM

ELECTROLYTE ABNORMALITY	ELECTROLYTE ABNORM
ELECTROLYTE ABNORMALITY SERUM (NOS)	ELECTROLYTE ABNORM
ELECTROLYTE DEPLETION (NOS)	ELECTROLYTE DEPLET
ELECTROLYTES SERUM INCREASED (NOS)	ELECTROLYTE ABNORM
ELECTROLYTES SERUM LOW (NOS)	ELECTROLYTE DEPLET
EMACIATION	CACHEXIA
EMBEDDED IUD	UTER DIS
EMBOLISM - BLOOD CLOT	EMB
EMBOLISM ARTERIAL	EMB
EMBOLISM CEREBRAL	EMB CEREBR
EMBOLISM EMBOLUS	EMB
EMBOLISM LIMB	EMB
EMBOLISM MESENTERIC	EMB
EMBOLISM PULMONARY	EMB PULM
EMBOLUS AMNIOTIC FLUID	EMB
EMBOLUS ARM	EMB ARM
EMBOLUS CAROTID	EMB CAROTID
EMBOLUS CEREBRAL	EMB CEREBR
EMBOLUS CEREBRAL FAT GAS OIL ETC.	EMB CEREBR
EMBOLUS CORONARY ARTERY	EMB CORONARY
EMBOLUS LEG	EMB LEG
EMBOLUS LOWER EXTREMITY	EMB LEG
EMBOLUS MESENTERIC	OCCLUS MESENTER ART
EMBOLUS PULMONARY	EMB PULM
EMBOLUS RETINAL ARTERY	OCCLUS RETINAL ART
EMBOLUS UPPER EXTREMITY	EMB ARM
EMESIS	VOMIT
EMESIS BLOODY	HEMATEMESIS
EMOTIONAL LABILITY	EMOTION LABIL
EMOTIONAL POVERTY	APATHY
EMOTIONAL REACTION	EMOTION LABIL
EMOTIONAL WITHDRAWAL	APATHY
EMPHYSEMA	EMPHYSEMA
EMPHYSEMA PULMONARY	EMPHYSEMA
EMPROSTHOTONUS	DYSTONIA
ENAMEL ANOMALY	ANOMALY TOOTH
ENAMEL HYPOPLASIA	ANOMALY TOOTH
ENAMEL MOTTLING	DISCOLOR TOOTH
ENANTHEMA	RASH
ENCEPHALITIS	ENCEPHALITIS
ENCEPHALITIS TOXIC ACUTE	BRAIN SYND ACUTE
ENCEPHALITIS TOXIC CHRONIC	BRAIN SYND CHRON
ENCEPHALOCELE	ENCEPHALOCELE
ENCEPHALOMYELITIS	ENCEPHALITIS
ENCEPHALOPATHY	ENCEPHALOPATHY
ENCEPHALOPATHY ACUTE	ENCEPHALOPATHY
ENCEPHALOPATHY ALLERGIC	ENCEPHALOPATHY
ENCEPHALOPATHY CHRONIC	ENCEPHALOPATHY
ENCEPHALOPATHY HEPATIC	ENCEPHALOPATHY
ENCEPHALOPATHY HYPERTENSIVE	ENCEPHALOP HYPERTENS
ENCEPHALOPATHY NEONATAL	ENCEPHALOPATHY
ENCEPHALOPATHY NEONATAL ACUTE	ENCEPHALOPATHY
ENCEPHALOPATHY NEONATAL CHRONIC	ENCEPHALOPATHY
ENCEPHALOPATHY PULMONARY	ACIDOSIS RESP
ENCEPHALOPATHY TOXIC ACUTE	ENCEPHALOPATHY
ENCEPHALOPATHY TOXIC CHRONIC	ENCEPHALOPATHY
ENDARTERITIS	ARTERITIS

ENDOCARDITIS	ENDOCARD
ENDOCERVICITIS	CERVICITIS
ENDOCRINE DISORDER (NOS)	ENDO DIS
ENDOCRINE DISORDER NOS	ENDO DIS
ENDOMETRIAL CARCINOMA (NOS)	CARCINOMA ENDOMETR
ENDOMETRIAL DISORDER (NOS)	ENDOMETR DIS
ENDOMETRIAL HYPERPLASIA	HYPERPLASIA ENDOMETR
ENDOMETRIAL HYPOPLASIA	ENDOMETR DIS
ENDOMETRIAL NEOPLASM MALIGNANT	CARCINOMA ENDOMETR
ENDOMETRIOSIS	ENDOMETR DIS
ENDOMETRITIS	ENDOMETR DIS
ENDOMETRITIS DECIDUAL	ENDOMETR DIS
ENDOMETRIUM ARRESTED STAGE	ENDOMETR DIS
ENDOMETRIUM CYSTIC	ENDOMETR DIS
ENDOMETRIUM PSEUDODECIDUAL	ENDOMETR DIS
ENGORGEMENT BREAST	BREAST ENGORGE
ENLARGEMENT ABDOMEN	ABDO ENLARGE
ENLARGEMENT BREAST FEMALE	BREAST ENLARGE
ENLARGEMENT BREAST MALE	GYNECOMASTIA
ENLARGEMENT CLITORIS	CLITORIS ENLARGE
ENLARGEMENT HEART	CARDIOMEGALY
ENLARGEMENT OVARY	OVAR DIS
ENLARGEMENT PAROTID GLAND	PAROTID ENLARGE
ENLARGEMENT SALIVARY GLAND	SALIV GLAND ENLARGE
ENLARGEMENT UTERINE	UTER ENLARGE
ENTERITIS	ENTERITIS
ENTERITIS HEMORRHAGIC	ENTERITIS
ENTERITIS PSEUDOMEMBRANOUS	ENTERITIS
ENTERITIS ULCERATIVE	ENTERITIS
ENTEROCOLITIS	ENTEROCOL
ENTEROCOLITIS HEMORRHAGIC	ENTEROCOL HEM
ENTEROCOLITIS PSEUDOMEMBRANOUS	ENTEROCOL PSEUDOMEM
ENTEROCOLITIS ULCERATIVE	ENTEROCOL ULCER
ENURESIS	INCONTIN URIN
ENZYME ABNORMALITY	ENZYME ABNORM
ENZYME ABNORMALITY (NOS)	ENZYME ABNORM
ENZYME(S) ERYTHROCYTE ABNORMAL	RBC ABNORM
EOSINOPHILIA	EOSINOPHILIA
EOSINOPHILIC GRANULOMA	GRANULOMA
EPENDYMITIS	EPENDYMITIS
EPIDERMAL NECROLYSIS	EPIDERM NECRO
EPIDIDYMITIS	EPIDIDYMITIS
EPIGASTRIC BURNING	DYSPEPSIA
EPIGASTRIC DISTRESS	DYSPEPSIA
EPIGASTRIC FOOD-RELATED PAIN	PAIN ABDO
EPIGASTRIC PAIN NOT FOOD-RELATED	PAIN ABDO
EPILEPSY	CONVULS
EPILEPSY GRAND MAL	CONVULS GRAND MAL
EPILEPSY PETIT MAL	CONVULS
EPILEPSY SENSORY	CONVULS
EPILEPSY TEMPORAL LOBE	CONVULS
EPILEPTIC EQUIVALENT	CONVULS
EPILEPTIFORM ATTACKS (NOS)	CONVULS
EPIPHORA	LACRIMATION DIS
EPIPHYSIS CLOSURE DELAYED	EPIPHYS CLOS DELAY
EPIPHYSIS CLOSURE PREMATURE	EPIPHYS CLOS PREMAT
EPISCLERITIS	SCLERITIS

EPISTAXIS	EPISTAXIS
EQUILIBRIUM DISORDER OF (NOS)	COORDINAT ABNORM
ERECTION DECREASED	IMPOTENCE
ERECTION INADEQUATE	IMPOTENCE
ERECTION INCREASED	LIBIDO INC
ERECTION NOCTURNAL	PENIS DIS
ERETHISM	CNS STIMULAT
EROSION UTERINE CERVIX	CERVIX DIS
ERROR REFRACTION	REFRACT DIS
ERUCTATION	ERUCTAT
ERUPTION	RASH
ERUPTION FIXED	ERUPT FIXED
ERYSIPELAS	CELLULITIS
ERYTHEMA	RASH
ERYTHEMA BULLOSUM	ERYTHEMA MULT
ERYTHEMA EXUDATIVUM	ERYTHEMA MULT
ERYTHEMA INDURATUM	ERYTHEMA MULT
ERYTHEMA MARGINATUM	ERYTHEMA MULT
ERYTHEMA MULTIFORME	ERYTHEMA MULT
ERYTHEMA MULTIFORME EXUDATIVUM	STEVENS JOHNSON SYND
ERYTHEMA MULTIFORME SEVERE	ERYTHEMA MULT
ERYTHEMA NODOSUM	ERYTHEMA NOD
ERYTHREMIC MYELOSIS	MARROW HYPERPLASIA
ERYTHROBLASTOSIS FETALIS	JAUNDICE NEONAT
ERYTHROCYTE SEDIMENTATION INCREASED	ESR INC
ERYTHROCYTES ABNORMAL	RBC ABNORM
ERYTHROCYTES ABNORMAL (NOS)	RBC ABNORM
ERYTHROCYTES AGGLUTINATION	RBC ABNORM
ERYTHROCYTES MATURATION ARREST	ERYTHRO MATUR ARREST
ERYTHROCYTES SEDIMENTATION RATE DECREASED	ESR DEC
ERYTHROCYTES SEDIMENTATION RATE INCREASED	ESR INC
ERYTHROCYTES VACUOLIZATION OF	ERYTHRO VACUOL
ERYTHRODERMA	RASH
ERYTHROLEUKEMIA	LEUKEMIA
ESCAPE NODAL	ARRHYTHMIA NOD
ESOPHAGALGIA	ESOPHAGITIS
ESOPHAGEAL CARCINOMA	CARCINOMA GI
ESOPHAGEAL DISORDER	ESOPHAGITIS
ESOPHAGEAL HEMORRHAGE	HEM ESOPH
ESOPHAGEAL PAIN	ESOPHAGITIS
ESOPHAGEAL SPASM	CARDIOSPASM
ESOPHAGEAL VARICES	HEM ESOPH
ESOPHAGITIS	ESOPHAGITIS
ESOPHAGITIS CHEMICAL	ESOPHAGITIS
ESOPHAGOSPASM	CARDIOSPASM
ESOPHAGUS BURN	ESOPHAGITIS
ESOPHAGUS ULCERATION	ULCER ESOPH
ESOPHAGUS ULCERATION HEMORRHAGE	ULCER ESOPH
ESR DECREASED	ESR DEC
ESR INCREASED	ESR INC
ESTROGEN INCREASED	ALTERED HORMONE LEVEL
EUNUCHOIDISM	HYPOGONAD MALE
EUPHORIA	EUPHORIA
EXAGGERATED WELL-BEING	EUPHORIA
EXANTHEM	RASH
EXCITABILITY	NERVOUSNESS
EXCITATION CEREBRAL	CNS STIMULAT

EXCITEMENT EXCESSIVE	EUPHORIA
EXENCEPHALY	ENCEPHALOCELE
EXFOLIATION	DERM EXFOL
EXHAUSTION	ASTHENIA
EXHILIRATION INAPPROPRIATE	EUPHORIA
EXOMPHALOS	ANOMALY GI
EXOPHTHALMIC GOITRE	HYPERTHYR
EXOPHTHALMOS	EXOPHTHALMOS
EXPULSION OF DEVICE	DEVICE MIGRATION
EXSANGUINATION	HEM
EXTRACELLULAR FLUID INCREASED	EDEMA GENERAL
EXTRAOCULAR MUSCLE PARESIS	PARALYSIS EXTRAOCUL
EXTRAPYRAMIDAL DISORDER	EXTRAPYR SYND
EXTRAPYRAMIDAL DISORDER (NOS)	EXTRAPYR SYND
EXTRAPYRAMIDAL SYNDROME (NOS)	EXTRAPYR SYND
EXTRASYSTOLES	EXTRASYSTOLES
EXTRASYSTOLES (NOS)	EXTRASYSTOLES
EXTRASYSTOLES ATRIAL	EXTRASYSTOLES SUPVENT
EXTRASYSTOLES BIGEMINAL	EXTRASYSTOLES BIGEM
EXTRASYSTOLES MULTIFOCAL	EXTRASYSTOLES MF
EXTRASYSTOLES NODAL	EXTRASYSTOLES SUPVENT
EXTRASYSTOLES SUPRAVENTRICULAR	EXTRASYSTOLES SUPVENT
EXTRASYSTOLES VENTRICULAR	EXTRASYSTOLES VENT
EXTRAVASATION BLOOD	HEM
EXUDATE NIPPLES BLOODY	HEM
EXUDATE NIPPLES FEMALE	LACTATION FEM
EXUDATE NIPPLES MALE	LACTATION MALE
EYE ABNORMALITY	EYE DIS
EYE ABNORMALITY (NOS)	EYE DIS
EYE BLOOD SHOT	CONJUNCTIVITIS
EYE DISCHARGE	CONJUNCTIVITIS
EYE DISORDER (NOS)	EYE DIS
EYE FLOATERS	VITREOUS DIS
EYE HEMORRHAGE	HEM EYE
EYE INFLAMED	CONJUNCTIVITIS
EYE IRRITATION	CONJUNCTIVITIS
EYE MALFORMATION	ANOMALY CONGEN SS
EYE MUSCLE PARALYSIS	OPHTHALMOPLEGIA
EYE PAIN	PAIN EYE
EYE SCRATCH	CORNEAL LESION
EYELID EDEMA	EDEMA FACE
EYELID RETRACTION	EYE DIS
EYES DRY	DRY EYE
EYES GAZE UPWARD	OCULOGYRIC CRISIS
EYES SWOLLEN	EDEMA FACE
EYES TEARING	LACRIMATION DIS
FACE EDEMA	EDEMA FACE
FACE MALFORMATION	ANOMALY CONGEN MS
FACE OEDEMA	EDEMA FACE
FACIAL DROOP	PARALYSIS FACIAL
FACIAL SWELLING	EDEMA FACE
FACIES MASKED	FACIES MASK
FACTOR RHEUMATOID	LAB TEST ABNORM
FAECAL INCONTINENCE	INCONTIN FECAL
FAECES DISCOLOURED	STOOL ABNORM
FAILURE CIRCULATORY	SHOCK
FAILURE HEART	HEART FAIL

FAILURE HEART CONGESTIVE	HEART FAIL RIGHT
FAILURE HEART LEFT	HEART FAIL LEFT
FAILURE HEPATORENAL	HEPATORENAL SYND
FAILURE KIDNEY	KIDNEY FAIL
FAILURE KIDNEY ACUTE	KIDNEY FAIL ACUTE
FAILURE LEFT HEART	HEART FAIL LEFT
FAILURE LIVER	LIVER FAIL
FAILURE PERIPHERAL CIRCULATORY	SHOCK
FAILURE RESPIRATORY	APNEA
FAILURE RIGHT HEART	HEART FAIL RIGHT
FAINT	SYNCOPE
FAINTNESS	DIZZINESS
FALLING DOWN	INJURY ACCID
FALLING OUT	SYNCOPE
FALLOT TETRALOGY OF	TETRAL FALLOT
FALSE PREGNANCY	ABDO ENLARGE
FALSE SENSATION	PERSON DIS
FANCONI-LIKE SYNDROME	FANCONI SYND
FASCICULATION SKELETAL MUSCLE	TWITCH
FASCITIS	FIBRO TENDON
FAT TISSUE INCREASED	OBESITY
FATIGABILITY	ASTHENIA
FATIGUE	ASTHENIA
FATTY LIVER	LIVER FATTY
FATTY STOOLS	MALABSORP SYND
FEBRILE CONVULSION SEIZURE	CONVULS
FEBRILE REACTION	FEVER
FECAL FAT INCREASED	MALABSORP SYND
FECAL IMPACTION	IMPACT FECAL
FECES ABNORMAL	STOOL ABNORM
FECES BLOODSTAINED	MELENA
FECES CLAY-COLORED	STOOL ABNORM
FECES DISCOLORED	STOOL ABNORM
FECES INCONTINENCE OF	INCONTIN FECAL
FECES PALE	STOOL ABNORM
FECES TABLET IN STOOL	NO DRUG EFFECT
FECTOR HEPATICUS	LIVER DAMAGE
FEEDING DISORDER NEONATAL	PERINATAL DIS
FEELING "COOL"	EUPHORIA
FEELING BAD	MALAISE
FEELING DETACHED	DEPERSONAL
FEELING FLOATING	DEPERSONAL
FEELING HAPPY INAPPROPRIATELY	EUPHORIA
FEELING HIGH	EUPHORIA
FEELING LACK OF	APATHY
FEELING OF WARMTH	VASODILAT
FEELING QUEASY	NAUSEA
FEELING REMOTE	DEPERSONAL
FEELING STRANGE	DEPERSONAL
FEELING TENSE	ANXIETY
FEELING UNREAL	DEPERSONAL
FEELING UNWELL	MALAISE
FEELING WEIGHTLESS	DEPERSONAL
FEMALE SEX MATURATION ACCELERATED	SEX MAT FEM ACCEL
FEMINIZATION	FEMININE
FEMORAL ARTERY THROMBOSIS	THROM ART
FERTILITY DECREASED FEMALE	FERTIL DEC FEM

FERTILITY DECREASED MALE	FERTIL DEC MALE
FERTILITY FEMALE DECREASED	FERTIL DEC FEM
FERTILITY FEMALE INCREASED	FERTIL INC FEM
FERTILITY MALE DECREASED	FERTIL DEC MALE
FESTINATING GAIT	GAIT ABNORM
FETAL DEATH	STILLBIRTH
FETAL DISORDER	FETAL DIS
FETAL DISTRESS	FETAL DIS
FETAL MATURATION IMPAIRED	FETAL DIS
FETUS MACERATED	DEATH
FEVER	FEVER
FEVER CHILLS	CHILLS FEVER
FEVER CONVULSIONS	CONVULS
FEVER MALIGNANT	FEVER MALIGNANT
FEVER NEONATAL	FEVER
FEVER SORE	ULCER MOUTH
FIBRILLATION	FIBRILLAT VENT
FIBRILLATION ATRIAL	FIBRILLAT ATR
FIBRILLATION CARDIAC	FIBRILLAT VENT
FIBRILLATION PAROXYSMAL ATRIAL	FIBRILLAT ATR
FIBRILLATION PAROXYSMAL VENT	FIBRILLAT VENT
FIBRILLATION SKELETAL MUSCLE	TWITCH
FIBRILLATION VENTRICULAR	FIBRILLAT VENT
FIBRIN DECREASED	FIBRIN DEC
FIBRIN INCREASED	FIBRIN INC
FIBRINOGEN PLASMA DECREASED	FIBRINOGEN DEC
FIBRINOGEN PLASMA INCREASED	FIBRINOGEN INC
FIBRINOGENOPENIA	FIBRINOGEN DEC
FIBRINOLYSIN DECREASED	FIBRINOLYSIS DEC
FIBRINOLYSIN INCREASED	FIBRINOLYSIS INC
FIBRINOLYSIS DECREASED	FIBRINOLYSIS DEC
FIBRINOLYSIS INCREASED	FIBRINOLYSIS INC
FIBRINOLYTIC ACTIVITY INCREASED	FIBRINOLYSIS INC
FIBRINOPENIA	FIBRIN DEC
FIBROADENOSIS BREAST	BREAST FIBROCYST
FIBROCYSTIC BREAST	BREAST FIBROCYST
FIBROCYSTIC DISEASE OF PANCREAS	PANCREAS DIS
FIBROID UTERINE DEGENERATED	UTER FIBROID DEGEN
FIBROID UTERINE ENLARGED	UTER FIBROID ENLARGE
FIBROIDS	UTER FIBROID ENLARGE
FIBROSIS BILIARY	CHOLANGITIS SCLERO
FIBROSIS BREAST	BREAST FIBROCYST
FIBROSIS ENDOCARDIAL	FIBRO MYOCARD
FIBROSIS INJECTION SITE	FIBRO INJECT SITE
FIBROSIS KIDNEY	FIBRO KIDNEY
FIBROSIS LIVER	LIVER CIRRHO
FIBROSIS LUNG	FIBRO LUNG
FIBROSIS LYMPH NODE	LYMPHADENO
FIBROSIS MEDIASTINAL	FIBRO MEDIAST
FIBROSIS MESENTERIC	FIBRO MESENTER
FIBROSIS MYOCARDIAL	FIBRO MYOCARD
FIBROSIS OTOSCLEROSIS	EAR DIS
FIBROSIS PULMONARY	FIBRO LUNG
FIBROSIS RETROPERITONEAL	FIBRO RETROPERIT
FIBROSIS TENDINOUS	FIBRO TENDON
FINGERS WEBBED	SYNDACTYLY
FISTULA ARTERIOVENOUS	ANOMALY ART

FIT UNCINATE	CONVULS
FIXED ERUPTION	ERUPT FIXED
FLACCIDITY MUSCLE	HYPOTONIA
FLANK PAIN	PAIN BACK
FLASH HOT	VASODILAT
FLATULENCE	FLATUL
FLATUS	FLATUL
FLOATERS IN EYE	VITREOUS DIS
FLOATING CORPOREAL	DEPERSONAL
FLU	FLU SYND
FLU SYNDROME	FLU SYND
FLU-LIKE SYMPTOMS	FLU SYND
FLUID LOSS	DEHYDRAT
FLUID OVERLOAD	HYPERVOLEM
FLUID RETENTION IN TISSUES	EDEMA GENERAL
FLUOR	LEUKORRHEA
FLUORESCENCE TOOTH	DISCOLOR TOOTH
FLUORIDE INTOXICATION	FLUOROSIS
FLUOROSIS	FLUOROSIS
FLUSH HOT	VASODILAT
FLUSHING	VASODILAT
FLUTTER ATRIAL	FLUTTER ATR
FOETAL DISTRESS	FETAL DIS
FOETAL MATURATION IMPAIRED	FETAL DIS
FOLATE SERUM TEST ABNORMAL	LAB TEST ABNORM
FOLLICLE-STIMULATING HORMONE DECREASED	GONADOTR DEC FSH
FOLLICLE-STIMULATING HORMONE INCREASED	GONADOTR INC FSH
FOLLICULITIS	ACNE
FONTANEL BULGING	INTRACRAN HYPERTENS
FOOT CRAMPS	CRAMPS LEG
FOOTDROP	FOOT DROP
FORAMEN OVALE PATENT	ATR SEPT DEF
FORGETFULNESS	AMNESIA
FORMATION BONE INCREASED	BONE DIS
FORMICATION	PARESTHESIA
FORUNCULOSIS	FURUNCULOSIS
FRACTURE BONE	BONE FRACT SPONTAN
FRACTURE DUE TO OSTEOPOROSIS	OSTEOPOROSIS FRACT
FRACTURE PATHOLOGICAL	BONE FRACT SPONTAN
FRAGILITY CAPILLARY INCREASED	CAPILL FRAGIL INC
FRAGILITY UTERINE CERVIX	CERVIX DIS
FRECKLES	MELANOSIS
FREQUENCY URINARY	URIN FREQUENCY
FSH ELEVATED	GONADOTR INC FSH
FULLNESS ABDOMINAL	FLATUL
FULLNESS HEAD	HEADACHE
FUMBLING	COORDINAT ABNORM
FUNCTION KIDNEY ABNORMAL	KIDNEY FUNC ABNORM
FUNCTION KIDNEY DECREASED	KIDNEY FUNC ABNORM
FUNCTION LIVER ABNORMAL	LIVER FUNC ABNORM
FUNCTION LIVER DECREASED	LIVER FUNC ABNORM
FUNCTION PULMONARY DECREASED	LUNG FUNC DEC
FUNCTION TESTS MULTIPLE KIDNEY ABNORMAL	KIDNEY FUNC ABNORM
FUNCTION TESTS MULTIPLE LIVER ABNORMAL	LIVER FUNC ABNORM
FUNCTION TESTS RESPIRATORY ABNORMAL	LUNG FUNC DEC
FURUNCULOSIS	FURUNCULOSIS
FUZZY	SOMNOLENCE

GAGGING	VOMIT
GAIT ABNORMAL	GAIT ABNORM
GAIT BROADENED	GAIT ABNORM
GAIT DISORDER	GAIT ABNORM
GAIT DISTURBANCE	GAIT ABNORM
GAIT FESTINATING	GAIT ABNORM
GAIT RIGID	GAIT ABNORM
GAIT SHUFFLING	GAIT ABNORM
GAIT STUMBLING	GAIT ABNORM
GAIT TRIPPING	GAIT ABNORM
GAIT UNSTEADY	GAIT ABNORM
GALACTORRHEA FEMALE	LACTATION FEM
GALL BLADDER DISORDER	CHOLECYST
GALL BLADDER INFLAMMATION	CHOLECYST
GALL BLADDER PAIN	PAIN BIL
GALL BLADDER STONES	CHOLELITH
GAMMA GLUTAMYL TRANSPEPTIDASE INCREASED	GGTP INC
GAMMA GT INCREASED	GGTP INC
GAMMA-GT INCREASED	GGTP INC
GAMMAGLOBULINS DECREASED	GLOBULIN DEC GAMMA
GANGRENE	GANGRENE
GANGRENE ILEUM	GANGRENE ILEUM
GANGRENE INTESTINE	GANGRENE INTEST
GANGRENE JEJUNUM	GANGRENE JEJUNUM
GANGRENE NEONATAL	GANGRENE
GANGRENE PERIPHERAL	GANGRENE PERIPH
GANGRENE SKIN	NECRO SKIN
GARRULOUSNESS	PERSON DIS
GAS IN STOMACH	ERUCTAT
GAS PAIN	PAIN ABDO
GAS RAISING	ERUCTAT
GASEOUS REGURGITATION	ERUCTAT
GASES BLOOD ABNORM	HYPOXIA
GASPING	DYSPNEA
GASTRIC ACID DECREASED	ACHLORHYDRIA
GASTRIC ATONY	STOMACH ATONY
GASTRIC BLEEDING	HEM GI
GASTRIC CARCINOMA	CARCINOMA GI
GASTRIC DILATATION	STOMACH DILAT
GASTRIC HEMORRHAGE	HEM GI
GASTRIC INFLAMMATION	GASTRITIS
GASTRIC IRRITATION	GASTRITIS
GASTRIC PAIN	PAIN ABDO
GASTRIC ULCER	ULCER STOMACH
GASTRIC ULCER HAEMORRHAGIC	ULCER STOMACH HEM
GASTRIC ULCER HAEMPER	ULCER STOMACH PERHEM
GASTRIC ULCER HEMORRHAGE AND PERFORATION	ULCER STOMACH PERHEM
GASTRIC ULCER HEMORRHAGIC	ULCER STOMACH HEM
GASTRIC ULCER PERFORATED	ULCER STOMACH PER
GASTRIN INCREASED	DYSPEPSIA
GASTRITIS	GASTRITIS
GASTRITIS ATROPHIC	GASTRITIS
GASTRITIS EROSIVE	GASTRITIS HEM
GASTRITIS HAEMORRHAGIC	GASTRITIS HEM
GASTRITIS HEMORRHAGIC	GASTRITIS HEM
GASTRITIS HYPERTROPHIC	GASTRITIS
GASTRO-INTESTINAL DISORDER NOS	GI DIS

GASTROENTERITIS	GASTROENTERITIS
GASTROESOPHAGEAL REFLUX	GI DIS
GASTROINTESTINAL BLEEDING	HEM GI
GASTROINTESTINAL CARCINOMA	CARCINOMA GI
GASTROINTESTINAL DISORDER (NOS)	GI DIS
GASTROINTESTINAL PERFORATION (NOS)	GI PER
GASTROINTESTINAL TRACT BLEED (NOS)	HEM GI
GASTROPARESIS	STOMACH ATONY
GASTROSCHISIS	ANOMALY CONGEN
GENE GENETIC ABNORMALITY	CHROMOSOME ABNORM
GENITALIA EXTERNAL AMBIGUOUS	ANOMALY CONGEN
GENITALIA EXTERNAL PAINFUL	PAIN PELVIC
GGTP ABNORMAL	LIVER FUNC ABNORM
GGTP INC	GGTP INC
GGTP INCREASE	GGTP INC
GI HAEMORRHAGE	HEM GI
GI HEMORRHAGE	HEM GI
GI IRRITATION	GASTROENTERITIS
GI MALFORMATION	ANOMALY GI
GI MUCOSAL NECROSIS GENERAL	GI DIS
GI NEOPLASIA	NEOPL GI
GI NEOPLASM MALIGNANT	CARCINOMA GI
GI PAIN	PAIN ABDO
GI TRACT OBSTRUCTION	OBSTRUCT INTEST
GI TRACT STENOSIS ANY SITE	STENO INTEST
GI UPSET	DYSPEPSIA
GIANT HIVES	ANGIOEDEMA
GIANT URTICARIA	ANGIOEDEMA
GIDDINESS	DIZZINESS
GIGANTISM	GIGANTISM
GILLES DE LA TOURETTE	TWITCH
GINGIVAL ATROPHY	GINGIVITIS
GINGIVAL BLEEDING	HEM GUM
GINGIVAL DISCOLORATION	GINGIVITIS
GINGIVAL DISCOLOURATION	GINGIVITIS
GINGIVAL HYPERTROPHY	HYPER GUM
GINGIVAL REACTION	GINGIVITIS
GINGIVAL RECESSION	GINGIVITIS
GINGIVAL SWELLING	GINGIVITIS
GINGIVITIS	GINGIVITIS
GINGIVITIS HEMORRHAGIC	HEM GUM
GLANDS SWOLLEN	LYMPHADENO
GLAUCOMA	GLAUCOMA
GLOBULIN BENCE JONES PRESENT	GLOBULIN INC BJ
GLOBULIN GAMMA SERUM PLASMA DEC	GLOBULIN DEC GAMMA
GLOBULIN GAMMA SERUM PLASMA INC	GLOBULIN INC GAMMA
GLOBULIN SERUM PLASMA DEC	GLOBULIN DEC
GLOBULIN SERUM PLASMA INC	GLOBULIN INC
GLOBULINS INCREASED	GLOBULIN INC
GLOBULINURIA	ALBUMINURIA
GLOMERULITIS	GLOMERULITIS
GLOMERULONEPHRITIS	GLOMERULITIS
GLOMERULONEPHRITIS FOCAL	GLOMERULITIS
GLOSSITIS	GLOSSITIS
GLOTTIC EDEMA	EDEMA LARYNX
GLOTTIC SPASM	LARYNGISMUS
GLOTTIS CARCINOMA	CARCINOMA LARYNX

GLUCOCORTICOIDS INCREASED	GLUCOCORT INC
GLUCOCORTICOSTEROID ACTIVITY INCR	GLUCOCORT INC
GLUCOSE BLOOD DECREASED	HYPOGLYCEM
GLUCOSE BLOOD INCREASED	HYPERGLYCEM
GLUCOSE TOLERANCE ABNORMAL	GLUCOSE TOLER DEC
GLUCOSE TOLERANCE CURVE ABNORMAL	GLUCOSE TOLER DEC
GLUCOSE TOLERANCE DECREASED	GLUCOSE TOLER DEC
GLUCOSE URINE FALSE POSITIVE TEST	GLYCOSURIA FALSE POS
GLUTAMIC-OXALOACETIC TRANSAM INCR	SGOT INC
GLUTAMIC-PYRUVIC TRANSAM INCR	SGPT INC
GLYCOLYSIS INCREASED	ACIDOSIS LACTIC
GLYCOSURIA	GLYCOSURIA
GLYCOSURIA FALSE POSITIVE TEST	GLYCOSURIA FALSE POS
GLYCOSURIA RENAL	GLYCOSURIA
GNASHING TOOTH	TOOTH DIS
GOITER	GOITER
GOITER CONGENITAL	GOITER
GOITER DIFFUSE	GOITER
GOITER EXOPHTHALMIC	HYPERTHYR
GOITER NODULAR	GOITER
GOITRE	GOITER
GOITRE CONGENITAL	GOITER
GONADOTROPIC FSH DECREASED	GONADOTR DEC FSH
GONADOTROPIC FSH INCREASED	GONADOTR INC FSH
GONADOTROPIC LUTEINIZING HORMONE DEC	GONADOTR DEC LH
GONADOTROPIC LUTEINIZING HORMONE INC	GONADOTR INC LH
GONADOTROPIN PITUITARY DECREASED	GONADOTR DEC PIT
GONADOTROPIN PITUITARY INCREASED	GONADOTR INC PIT
GONADOTROPIN PLACENTAL DECREASED	GONADOTR DEC PLAC
GONADOTROPIN PLACENTAL INCREASED	GONADOTR INC PLAC
GONADOTROPINS DECREASED	GONADOTR DEC
GONADOTROPINS INCREASED	GONADOTR INC
GOOD EFFECT	UNEXPECTED BENEFIT
GOODPASTURE'S SYNDROME	GLOMERULITIS
GOUT	GOUT
GOUTY ARTHRITIS	GOUT
GRANULATION TOXIC LEUCOCYTES	WBC ABNORM
GRANULOCYTOPENIA	LEUKOPENIA
GRANULOCYTOPENIA SEVERE	AGRANULOCYTOSIS
GRANULOCYTOSIS	GRANULOCYTOSIS
GRANULOCYTOSIS	LEUKOCYTOSIS
GRANULOMA	GRANULOMA
GRANULOMA INJECTION SITE	GRANULOMA INJECT SITE
GRANULOMA SKIN	GRANULOMA SKIN
GRANULOMATOUS LESION	GRANULOMA
GRAVES' DISEASE	HYPERTHYR
GRAY BABY SYNDROME	PERINATAL DIS
GRAY SYNDROME NEONATAL	PERINATAL DIS
GRINDING TOOTH	TOOTH DIS
GRIPING ABDOMINAL	GASTROENTERITIS
GROGGY	SOMNOLENCE
GROGGY AND SLUGGISH	SOMNOLENCE
GROGGY ON AWAKENING	SOMNOLENCE
GROWTH ACCELERATED	GROWTH ACCELER
GROWTH INTERUTERINE RETARD	BIRTH WEIGHT SUBNORM
GROWTH RETARDED	GROWTH RETARD
GTT ABNORMAL	GLUCOSE TOLER DEC

GUILLAIN BARRE SYNDROME	GUILLAIN BARRE SYND
GUM BLUE LINE	GUM BLUE LINE
GUM HYPERPLASIA	HYPER GUM
GUM HYPERTROPHY	HYPER GUM
GUSTATORY SENSE DIMINISHED	TASTE LOSS
GYNAECOMASTIA	GYNECOMASTIA
GYNECOMASTIA	GYNECOMASTIA
HABITUATION	DRUG DEPEND
HAEMANGIOMA AQUIRED	ANOMALY VASCUL
HAEMARTHROSIS	JOINT DIS
HAEMATEMESIS	HEMATEMESIS
HAEMATOMA	HEM
HAEMATURIA	HEMATURIA
HAEMOLYSIS	HEMOLYSIS
HAEMOPERITONEUM	HEMOPERITON
HAEMOPTYSIS	HEMOPTYSIS
HAEMORRHAGE ANT CHAMBER EYE	HEM EYE
HAEMORRHAGE IN PREGNANCY	HEM PREGN
HAEMORRHAGE INTRACRANIAL	HEM INTRACRAN
HAEMORRHAGE NOS	HEM
HAEMORRHAGE NOS NEONATAL	HEM
HAEMORRHAGE RECTUM	HEM RECTAL
HAEMORRHAGE RETROPERITONEAL	HEM RETROPERIT
HAEMORRHOIDS	RECTAL DIS
HAEMORRHOIDS THROMBOSED	RECTAL DIS
HAIR DARKENED	HAIR DISCOLOR
HAIR DEPIGMENTED	HAIR DISCOLOR
HAIR DISCOLORED	HAIR DISCOLOR
HAIR DISCOLOURATION	HAIR DISCOLOR
HAIR DISORDER	HAIR DIS
HAIR LOSS	ALOPECIA
HAIR TEXTURE ABNORMAL	HAIR DIS
HAIR THINNING	ALOPECIA
HAIRINESS	HIRSUTISM
HALITOSIS	HALITOSIS
HALLUCINATION	HALLUCIN
HALLUCINATION AUDITORY	HALLUCIN
HALLUCINATION GUSTATORY	HALLUCIN
HALLUCINATION OLFACTORY	HALLUCIN
HALLUCINATION VISUAL	HALLUCIN
HANGOVER	HANGOVER
HANGOVER EFFECT	HANGOVER
HAPATITIS B SURFACE ANTIGEN POSTIVE	HEPATITIS HBSAG
HARD TO AWAKEN	SOMNOLENCE
HARELIP	CLEFT LIP
HCV	HEPATITIS C
HEAD DISCOMFORT	HEADACHE
HEAD FULLNESS	HEADACHE
HEAD PAIN	HEADACHE
HEAD PRESSURE	HEADACHE
HEAD REVOLVING AROUND	VERTIGO
HEAD SPINNING	VERTIGO
HEAD TIGHTNESS	HEADACHE
HEAD-FACE-NECK-SYNDROME	DYSKINESIA
HEADACHE	HEADACHE
HEADACHE HISTAMINE	HEADACHE VASC
HEADACHE VASCULAR	HEADACHE VASC

HEADACHE VASOMOTOR	HEADACHE VASC
HEALING ABNORMAL	HEALING ABNORM
HEALING DELAYED	HEALING ABNORM
HEALING IMPAIRED	HEALING ABNORM
HEARING ABNORMALLY ACUTE	HYPERACUSIS
HEARING DECREASED	DEAF
HEARING IMPAIRED	DEAF
HEARING REDUCED	DEAF
HEART ARREST	HEART ARREST
HEART ATTACK	INFARCT MYOCARD
HEART BLOCK	HEART BLOCK
HEART BLOCK (NOS)	HEART BLOCK
HEART BLOCK ATRIOVENTRICULAR	AV BLOCK
HEART BLOCK AV COMPLETE	AV BLOCK COMP
HEART BLOCK AV COMPLETE WITH ASYSTOLE	ADAMS STOKES SYND
HEART BLOCK AV FIRST DEGREE	AV BLOCK FD
HEART BLOCK AV SECOND DEGREE	AV BLOCK SD
HEART BLOCK AV THIRD DEGREE	AV BLOCK COMP
HEART BLOCK BUNDLE BRANCH	BUNDLE BRANCH BLOCK
HEART BLOCK INTRA-ATRIAL	HEART BLOCK
HEART BLOCK INTRAVENTRICULAR	BUNDLE BRANCH BLOCK
HEART BLOCK SINOAURICULAR	HEART BLOCK
HEART DISEASE CONGENITAL	ANOMALY HEART
HEART DISEASE PULMONARY	COR PULM
HEART DISORDER	CARDIOVASC DIS
HEART ENLARGED	CARDIOMEGALY
HEART FAILURE (NOS)	HEART FAIL
HEART FLUTTERING	PALPITAT
HEART INSUFFIENCY	HEART FAIL
HEART IRREGULAR	ARRHYTHMIA
HEART MALFORMATION	ANOMALY HEART
HEART POUNDING	PALPITAT
HEART RATE INCREASED	TACHYCARDIA
HEART SEPTAL DEFECT ATRIAL	ATR SEPT DEF
HEART THROBBING	PALPITAT
HEART VALVE DISORDERS	CARDIOVASC DIS
HEARTBEATS COUPLED	EXTRASYSTOLES BIGEM
HEARTBEATS ECTOPIC	EXTRASYSTOLES
HEARTBEATS INCREASED	TACHYCARDIA
HEARTBEATS IRREGULAR	ARRHYTHMIA
HEARTBEATS PREMATURE	EXTRASYSTOLES
HEARTBEATS SKIPPED	ARRHYTHMIA
HEARTBURN	DYSPEPSIA
HEAT EXHAUSTION	HEAT STROKE
HEAT PRODUCTION INCREASED	FEVER
HEAT STROKE	HEAT STROKE
HEAT SYNCOPE	HEAT STROKE
HEAVINESS IN LIMBS	ASTHENIA
HEBEPHRENIA	SCHIZOPHRENIC REACT
HEINZ BODIES	HEINZ BODIES
HEM	HEM
HEMANGIOMA	ANOMALY VASCUL
HEMARTHROSIS	JOINT DIS
HEMATEMESIS	HEMATEMESIS
HEMATEMESIS GASTRIC ULCER	HEMATEMESIS
HEMATOCRIT DECREASED	ANEMIA
HEMATOLOGIC DISORDER	BLOOD DYSCRASIA

HEMATOMA	HEM
HEMATOMA CEREBRAL	HEM CEREBR
HEMATOMA INJECTION SITE	HEM INJECT SITE
HEMATOMA MUSCLE	HEM MUSCLE
HEMATOMA SUBDURAL	HEMATOMA SUBDURAL
HEMATOMETRA	HEM UTER
HEMATOPOIESIS DEPRESSED	MARROW DEPRESS
HEMATOPOIESIS IMPAIRED	MARROW DEPRESS
HEMATOPOIESIS INCREASED	MARROW HYPERPLASIA
HEMATOPOIESIS SUPPRESSED	MARROW DEPRESS
HEMATURIA	HEMATURIA
HEMERALOPIA	BLIND
HEMIANOPIA	VISUAL FIELD DEFECT
HEMIANOPIA HEMIANOPSIA	VISUAL FIELD DEFECT
HEMICEPHALGIA	MIGRAINE
HEMICRANIA	MIGRAINE
HEMIHYPERTROPHY	HYPERTROPHY
HEMIMELIA	ECTROMELIA
HEMIPARESIS	HEMIPLEGIA
HEMIPLEGIA	HEMIPLEGIA
HEMOCHROMATOSIS	HEMOCHROMATO
HEMOGLOBIN DECREASED	ANEMIA HYPOCHROM
HEMOGLOBINEMIA	HEMOLYSIS
HEMOGLOBINURIA	HEMOLYSIS
HEMOLYSIS	HEMOLYSIS
HEMOLYSIS INTRAVASCULAR	HEMOLYSIS
HEMOLYTIC ANEMIA (NOS)	ANEMIA HEMOL
HEMOLYTIC AUTOIMMUNE ANEMIA DCN	ANEMIA HEMOL DCN
HEMOLYTIC AUTOIMMUNE ANEMIA DCP	ANEMIA HEMOL DCP
HEMOLYTIC AUTOIMMUNE ANEMIA ICP	ANEMIA HEMOL ICP
HEMOLYTIC REACTION	HEMOLYSIS
HEMOLYTIC UREMIC SYNDROME	UREMIA
HEMOPERICARDIUM	HEMOPERICARD
HEMOPERITONEUM	HEMOPERITON
HEMOPTYSIS	HEMOPTYSIS
HEMORRHAGE (NOS)	HEM
HEMORRHAGE ADRENAL	HEM ADREN
HEMORRHAGE ANT CHAMBER EYE	HEM EYE
HEMORRHAGE BRAIN	HEM INTRACRAN
HEMORRHAGE BREAST	HEM
HEMORRHAGE CEREBRAL	HEM CEREBR
HEMORRHAGE COLON	HEM COLON
HEMORRHAGE CORONARY ARTERY	OCCLUS CORONARY
HEMORRHAGE DUODENUM	ULCER DUODEN HEM
HEMORRHAGE ESOPHAGEAL	HEM ESOPH
HEMORRHAGE EYE	HEM EYE
HEMORRHAGE GASTRIC	HEM GI
HEMORRHAGE GASTROINTESTINAL	HEM GI
HEMORRHAGE GINGIVAL	HEM GUM
HEMORRHAGE GUM	HEM GUM
HEMORRHAGE ILEUM	HEM ILEUM
HEMORRHAGE INJECTION SITE	HEM INJECT SITE
HEMORRHAGE INTRACEREBRAL	HEM CEREBR
HEMORRHAGE INTRACRANIAL	HEM INTRACRAN
HEMORRHAGE INTRAOCULAR	HEM EYE
HEMORRHAGE INTRAPERICARDIAL	HEMOPERICARD
HEMORRHAGE INTRAPERITONEAL	HEMOPERITON

HEMORRHAGE JEJUNUM	HEM JEJUNUM
HEMORRHAGE KIDNEY	HEM
HEMORRHAGE LUNG	HEM LUNG
HEMORRHAGE MOUTH	HEM
HEMORRHAGE MUSCLE	HEM MUSCLE
HEMORRHAGE NASAL	EPISTAXIS
HEMORRHAGE NEONATAL (NOS)	HEM
HEMORRHAGE ORAL	HEM
HEMORRHAGE PERICARDIAL	HEMOPERICARD
HEMORRHAGE PERITONEAL	HEMOPERITON
HEMORRHAGE PLACENTAL	HEM
HEMORRHAGE PLEURAL	HEMOTHORAX
HEMORRHAGE POSTMENOPAUSAL	HEM UTER
HEMORRHAGE POSTPARTUM	HEM POSTPARTUM
HEMORRHAGE PREGNANCY	HEM PREGN
HEMORRHAGE PULMONARY	HEM LUNG
HEMORRHAGE RECTAL	HEM RECTAL
HEMORRHAGE RETINAL	HEM RETINAL
HEMORRHAGE RETROPERITONEAL	HEM RETROPERIT
HEMORRHAGE STOMACH	HEM GI
HEMORRHAGE SUBARACHNOID	HEM SUBARACHNOID
HEMORRHAGE TERM	HEM POSTPARTUM
HEMORRHAGE URINARY BLADDER	HEM
HEMORRHAGE URINARY TRACT	HEMATURIA
HEMORRHAGE UTERINE	HEM UTER
HEMORRHAGE VAGINAL	HEM VAGINAL
HEMORRHAGE WITHDRAWAL (CONTRACEPTIVE)	WITHDRAW BLEED
HEMORRHAGIC CYSTITIS	HEM CYSTITIS
HEMORRHAGIC PROCTITIS	PROCTITIS HEM
HEMORRHOIDS	RECTAL DIS
HEMORRHOIDS THROMBOSED	RECTAL DIS
HEMOSIDEROSIS	HEMOSIDERO
HEMOTHORAX	HEMOTHORAX
HEPATIC CIRRHOSIS	LIVER CIRRHO
HEPATIC DAMAGE (NOS)	LIVER DAMAGE
HEPATIC DISEASE (NOS)	LIVER DAMAGE
HEPATIC DISORDER (NOS)	LIVER DAMAGE
HEPATIC DYSFUNCTION NONICTERIC	LIVER FUNC ABNORM
HEPATIC ENCEPHALOPATHY	ENCEPHALOPATHY
HEPATIC ENZYMES INCREASED	LIVER FUNC ABNORM
HEPATIC FAILURE	LIVER FAIL
HEPATIC FUNCTION ABNORMAL	LIVER FUNC ABNORM
HEPATIC HAEMORRHAGE	HEM
HEPATIC INFARCTION	INFARCT LIVER
HEPATIC NECROSIS	NECRO LIVER
HEPATIC NEOPLASM	NEOPL LIVER
HEPATIC NEOPLASM BENIGN	NEOPL LIVER
HEPATIC NEOPLASM MALIGNANT	HEPATOMA
HEPATIS PELIOSIS	HEPATITIS
HEPATITIS	HEPATITIS
HEPATITIS A	HEPATITIS
HEPATITIS C VIRUS	HEPATITIS C
HEPATITIS CHOLESTATIC	JAUNDICE CHOLESTAT
HEPATITIS HOMOLOGOUS SERUM-LIKE	HEPATITIS
HEPATITIS INFECTIOUS	HEPATITIS
HEPATITIS NECROTIZING	NECRO LIVER
HEPATITIS NEONATAL	HEPATITIS

HEPATITIS NONICTERIC	HEPATITIS
HEPATITIS NONSPECIFIC	HEPATITIS NONSPECIFIC
HEPATITIS TOXIC	HEPATITIS
HEPATITIS TOXIC OBSTRUCTIVE	JAUNDICE CHOLESTAT
HEPATITIS VIRAL-LIKE	HEPATITIS
HEPATOCELLULAR DAMAGE	LIVER DAMAGE
HEPATOCELLULAR DAMAGE NEONATAL	LIVER DAMAGE
HEPATOMA	HEPATOMA
HEPATOMEGALY	HEPATOMEGALY
HEPATORENAL SYNDROME	HEPATORENAL SYND
HEPATOSPLENOMEGALY	HEPATOSPLENOMEGALY
HEPATOSPLENOMEGALY NEONATAL	HEPATOSPLENOMEGALY
HEPATOTOXIC EFFECT	LIVER DAMAGE
HERMAPHRODITISM	HERMAPHRODIT
HERNIA	HERNIA
HERNIA CONGENITAL	ANOMALY CONGEN
HERNIA HIATAL	HERNIA
HERPES SIMPLEX	HERPES SIMPLEX
HERPES ZOSTER	HERPES ZOSTER
HERPETIFORM LESION	RASH VESIC BULL
HESITANCY URINATION	URIN IMPAIRED
HETEROTROPIA	STRABISMUS
HICCOUGH	HICCUP
HICCUP	HICCUP
HIGH DENSITY LIPOPROTEIN DECREASE	HDL DEC
HIGH DENSITY LIPOPROTEIN DECREASED	HDL DEC
HIGH FEELING	EUPHORIA
HIRSUTISM	HIRSUTISM
HIV DISEASE	HIV SYND
HIV TEST POSITIVE	HIV TEST POS
HIV TEST POSITVE	HIV TEST POS
HIVES	URTICARIA
HIVES GIANT	ANGIOEDEMA
HOARSENESS	VOICE ALTERAT
HODGINS	LYMPHOMA LIKE REACT
HODGKIN'S-LIKE	LYMPHOMA LIKE REACT
HORMONAL IMBALANCE	ENDO DIS
HOSTILITY	HOSTILITY
HOT FLASHES	VASODILAT
HOT FLUSHES	VASODILAT
HUNGER ABNORMAL	APPETITE INC
HUNGER AIR	HYPERVENTIL
HYALINE MEMBRANE DISEASE	PERINATAL DIS
HYDATIDIFORM MOLE	NEOPL UTER
HYDRALAZINE LE TYPE REACTION	LE SYND
HYDRAMNIOS	PREGN DIS
HYDRARTHROSIS	ARTHROSIS
HYDROCEPHALUS	HYDROCEPHALUS
HYDROCEPHALUS CONGENITAL	HYDROCEPHALUS
HYDRONEPHROSIS	HYDRONEPHROSIS
HYDROPS FETALIS	ANOMALY CONGEN
HYDROURETER	HYDROURETER
HYDROXYCORTICOSTEROIDS INCREASED	GLUCOCORT INC
HYDROXYSTEROID ACTIVITY INCREASED	GLUCOCORT INC
HYPALGESIA	HYPALGESIA
HYPER	NERVOUSNESS
HYPERACIDITY	DYSPEPSIA

HYPERACTIVITY	HYPERKINESIA
HYPERACUSIS	HYPERACUSIS
HYPERADRENALISM	CUSHINGS SYND
HYPERADRENOCORTICISM	CUSHINGS SYND
HYPERAESTHESIA	HYPERESTHESIA
HYPERALDOSTERONISM	ALDOSTERONE INC
HYPERALGESIA	HYPERALGESIA
HYPERAMMONAEMIA	NPN INC
HYPERAMMONEMIA	NPN INC
HYPERBILIRUBINEMIA	BILIRUBINEM
HYPERCALCAEMIA	HYPERCALCEM
HYPERCALCEMIA	HYPERCALCEM
HYPERCALCINURIA	HYPERCALCINURIA
HYPERCAPNIA	ACIDOSIS RESP
HYPERCARBIA	ACIDOSIS RESP
HYPERCHLORAEMIA	HYPERCHLOREM
HYPERCHLOREMIA	HYPERCHLOREM
HYPERCHLORHYDRIA	HYPERCHLORHYDRIA
HYPERCHOLESTEREMIA	HYPERCHOLESTEREM
HYPERCHOLESTEROLAEMIA	HYPERCHOLESTEREM
HYPERCHOLESTEROLEMIA	HYPERCHOLESTEREM
HYPERCOAGULATION	COAGUL DIS
HYPERCORTICISM ADRENAL	CUSHINGS SYND
HYPERCORTISONISM	GLUCOCORT INC
HYPEREMESIS	VOMIT
HYPEREMIA	VASODILAT
HYPEREMIA CEREBRAL	CEREBROVASC DIS
HYPERESTHESIA	HYPERESTHESIA
HYPERESTHESIA SKIN	HYPERESTHESIA
HYPEREXCITABILITY EXTREME	CNS STIMULAT
HYPEREXCITATION	AGITATION
HYPERGASTRINEMIA	DYSPEPSIA
HYPERGLOBULINEMIA	GLOBULIN INC
HYPERGLYCAEMIA	HYPERGLYCEM
HYPERGLYCEMIA	HYPERGLYCEM
HYPERHAEMOGLOBINAEMIA	RBC ABNORM
HYPERHEMOGLOBINEMIA	RBC ABNORM
HYPERHIDROSIS	SWEAT
HYPERKALAEMIA	HYPERKALEM
HYPERKALEMIA	HYPERKALEM
HYPERKERATOSIS	HYPERTROPHY SKIN
HYPERKINESIA	HYPERKINESIA
HYPERKINESIA NEONATAL	HYPERKINESIA
HYPERKINETIC REACTION	HYPERKINESIA
HYPERKINETIC SYNDROME	HYPERKINESIA
HYPERLIPAEMIA	HYPERLIPEM
HYPERLIPEMIA	HYPERLIPEM
HYPERLIPIDEMIA	HYPERLIPEM
HYPERLIPOPROTEINEMIA	HYPERLIPEM
HYPERMAGNESAEMIA	HYPERMAGNESEM
HYPERMAGNESEMIA	HYPERMAGNESEM
HYPERMOTILITY INTESTINAL	GI DIS
HYPERNATRAEMIA	HYPERNATREM
HYPERNATREMIA	HYPERNATREM
HYPERNEPHROMA	NEOPL
HYPEROPIA	REFRACT DIS
HYPEROREXIA	APPETITE INC

HYPEROSTOSIS	BONE DIS
HYPERPARATHYROIDISM	PARATHYR DIS
HYPERPHAGIA	APPETITE INC
HYPERPHOSPHATAEMIA	HYPERPHOSPHATEM
HYPERPHOSPHATEMIA	HYPERPHOSPHATEM
HYPERPIGMENTATION SKIN	SKIN DISCOLOR
HYPERPITUITARISM	PIT ACTIV INC
HYPERPLASIA	NEOPL
HYPERPLASIA ADRENAL	HYPERPLASIA ADREN
HYPERPLASIA ADRENAL CORTEX	HYPERPLASIA ADREN
HYPERPLASIA BONE MARROW	MARROW HYPERPLASIA
HYPERPLASIA BREAST	BREAST ENLARGE
HYPERPLASIA ENDOMETRIAL	HYPERPLASIA ENDOMETR
HYPERPLASIA ERYTHROID	MARROW HYPERPLASIA
HYPERPLASIA GUM	HYPER GUM
HYPERPNEA	HYPERVENTIL
HYPERPOTASSEMIA	HYPERKALEM
HYPERPROLACTINAEMIA	PROLACTIN INC
HYPERPROLACTINEMIA	PROLACTIN INC
HYPERPYREXIA	FEVER
HYPERPYREXIA MALIGNANT	FEVER MALIGNANT
HYPERREFLEXIA	REFLEXES INC
HYPERSALIVATION	SALIVA INC
HYPERSECRETION GASTRIC	HYPERCHLORHYDRIA
HYPERSENSATION SKIN	HYPERESTHESIA
HYPERSENSITIVITY INJECTION SITE	HYSN INJECT SITE
HYPERSENSITIVITY REACTION (NOS)	ALLERG REACT
HYPERSPLENISM	SPLENOMEGALY
HYPERTENSION	HYPERTENS
HYPERTENSION AGGRAVATED	HYPERTENS
HYPERTENSION ARTERIAL	HYPERTENS
HYPERTENSION DIASTOLIC	HYPERTENS
HYPERTENSION INTRACRANIAL	INTRACRAN HYPERTENS
HYPERTENSION MALIGNANT	HYPERTENS
HYPERTENSION OCULAR	GLAUCOMA
HYPERTENSION PORTAL	HYPERTENS
HYPERTENSION PULMONARY	HYPERTENS PULM
HYPERTENSION RENAL	HYPERTENS RENAL
HYPERTHERMIA	FEVER
HYPERTHERMIA MALIGNANT	FEVER MALIGNANT
HYPERTHYROIDISM	HYPERTHYR
HYPERTHYROIDISM AGGRAVATED	HYPERTHYR
HYPERTONIA	HYPERTONIA
HYPERTONICITY	DEHYDRAT
HYPERTONICITY BLOOD	DEHYDRAT
HYPERTONUS	HYPERTONIA
HYPERTRICHOSIS	HIRSUTISM
HYPERTRICHOSIS AGGRAVATED	HIRSUTISM
HYPERTRICHOSIS CONGENITAL	HIRSUTISM
HYPERTRIGLYCERIDAEMIA	HYPERLIPEM
HYPERTRIGLYCERIDEMIA	HYPERLIPEM
HYPERTROPHY	HYPERTROPHY
HYPERTROPHY BREAST	BREAST ENLARGE
HYPERTROPHY GINGIVAL	HYPER GUM
HYPERTROPHY SKIN	HYPERTROPHY SKIN
HYPERTROPHY THYMUS	ENDO DIS
HYPERTROPHY UTERINE CERVIX	HYPERTROPHY

HYPERURICAEMIA	HYPERURICEM
HYPERURICAEMIC NEPHROPATHY	CRYSTALLURIA URIC
HYPERURICEMIA	HYPERURICEM
HYPERURICEMIC ARTHRITIS	GOUT
HYPERURICEMIC NEPHROPATHY	CRYSTALLURIA URIC
HYPERVENTILATION	HYPERVENTIL
HYPERVITAMINOSIS	VITAMIN TOX
HYPERVOLAEMIA	HYPERVOLEM
HYPERVOLEMIA	HYPERVOLEM
HYPESTHESIA	HYPESTHESIA
HYPHIDROSIS	SWEAT DEC
HYPOACTIVITY	HYPOKINESIA
HYPOACUITY AUDITORY	DEAF
HYPOADRENALISM	ADREN INSUFFIC
HYPOAESTHESIA	HYPESTHESIA
HYPOALBUMINEMIA	HYPOPROTEINEM
HYPOALGESIA	HYPALGESIA
HYPOCALCAEMIA	HYPOCALCEM
HYPOCALCEMIA	HYPOCALCEM
HYPOCAPNIA	ALKALOSIS RESP
HYPOCHLORAEMIA	HYPOCHLOREM
HYPOCHLOREMIA	HYPOCHLOREM
HYPOCHLORHYDRIA	ACHLORHYDRIA
HYPOCHOLESTEREMIA	HYPOCHOLESTEREM
HYPOCHOLESTEROLAEMIA	HYPOCHOLESTEREM
HYPOCHOLESTEROLEMIA	HYPOCHOLESTEREM
HYPOCHONDRIASIS	NEUROSIS
HYPOCOAGULABLE STATE	COAGUL TIME INC
HYPOESTHESIA	HYPESTHESIA
HYPOFIBRINOGENEMIA	FIBRINOGEN DEC
HYPOFUNCTION ADRENAL	ADREN INSUFFIC
HYPOFUNCTION OVARIAN	HYPOGONAD FEM
HYPOFUNCTION TESTICLE	HYPOGONAD MALE
HYPOGALACTIA	LACTATION DEC
HYPOGENSIA	TASTE LOSS
HYPOGLOBULINEMIA	GLOBULIN DEC
HYPOGLYCAEMIA	HYPOGLYCEM
HYPOGLYCAEMIA NEONATAL	HYPOGLYCEM
HYPOGLYCAEMIC REACTION	HYPOGLYCEM REACT
HYPOGLYCEMIA	HYPOGLYCEM
HYPOGLYCEMIA NEONATAL	HYPOGLYCEM
HYPOGLYCEMIC REACTION	HYPOGLYCEM REACT
HYPOGONADISM FEMALE	HYPOGONAD FEM
HYPOGONADISM MALE	HYPOGONAD MALE
HYPOKALAEMIA	HYPOKALEM
HYPOKALEMIA	HYPOKALEM
HYPOKALEMIC SYNDROME	HYPOKALEM
HYPOKINESIA	HYPOKINESIA
HYPOKINESIA NEONATAL	HYPOKINESIA
HYPOLIPEMIA	HYPOLIPEM
HYPOLIPOPROTEINEMIA	HYPOLIPEM
HYPOMAGNESAEMIA	HYPOMAGNESEM
HYPOMAGNESEMIA	HYPOMAGNESEM
HYPOMENORRHEA	HYPOMENORRHEA
HYPONATRAEMIA	HYPONATREM
HYPONATREMIA	HYPONATREM
HYPOPARATHYROIDISM	PARATHYR DIS

HYPOPHOSPHATAEMIA	HYPOPHOSPHATEM
HYPOPHOSPHATEMIA	HYPOPHOSPHATEM
HYPOPITUITARISM	PIT ACTIV DEC
HYPOPLASIA BONE MARROW	MARROW DEPRESS
HYPOPLASIA ENAMEL	ANOMALY TOOTH
HYPOPLASIA ERYTHROID	ERYTHRO MATUR ARREST
HYPOPLASIA TOOTH	ANOMALY TOOTH
HYPOPNEA	HYPOVENTIL
HYPOPOTASSEMIA	HYPOKALEM
HYPOPROTEINAEMIA	HYPOPROTEINEM
HYPOPROTEINEMIA	HYPOPROTEINEM
HYPOPYON	OPHTHALMITIS
HYPOPYREXIA	HYPOTHERMIA
HYPOREFLEXIA	REFLEXES DEC
HYPOSPADIAS	ANOMALY CONGEN
HYPOSTHENURIA	KIDNEY FUNC ABNORM
HYPOTENSION	HYPOTENS
HYPOTENSION ORTHOSTATIC	HYPOTENS POST
HYPOTENSION POSTURAL	HYPOTENS POST
HYPOTHERMIA	HYPOTHERMIA
HYPOTHYROIDISM	HYPOTHYR
HYPOTHYROIDISM CONGENITAL	CRETIN
HYPOTONIA	HYPOTONIA
HYPOTONIA NEONATAL	HYPOTONIA
HYPOTONICITY SERUM PLASMA	WATER INTOX
HYPOTRICHOSIS	ALOPECIA
HYPOTRIGLYCERIDEMIA	HYPOLIPEM
HYPOVENTILATION	HYPOVENTIL
HYPOVITAMINOSIS	AVITAMINOSIS
HYPOVOLAEMIA	HYPOVOLEM
HYPOVOLEMIA	HYPOVOLEM
HYPOXEMIA	HYPOXIA
HYPOXIA	HYPOXIA
HYSN	ALLERG REACT
HYSTERIA	HYSTERIA
HYSTERIA CONVERSION TYPE	HYSTERIA
HYSTERICAL EXCITEMENT	HYSTERIA
IA SEPTAL DEFECT	ATR SEPT DEF
ICHTHYOSIS	ICHTHYOSIS
ICSH	GONADOTR DEC LH
ICTERUS	JAUNDICE
ICTERUS NEONATORUM	JAUNDICE NEONAT
IDENITY LOSS OF	DEPERSONAL
IDIOCY	MENTAL RETARD
ILEITIS	ILEITIS
ILEITIS AGGRAVATED	ILEITIS
ILEITIS REGIONAL	ILEITIS
ILEUS	ILEUS
ILEUS PARALYTIC	ILEUS
ILEUS PARALYTIC NEONATAL	ILEUS
ILEUS SPASTIC	ILEUS
ILL FEELING	MALAISE
ILLIAC ARTERY THROMBOSIS	THROM ART
ILLUSION	PERSON DIS
IMBALANCE AUTONOMIC NERVOUS SYSTEM	DYSAUTONOMIA
IMBALANCE BLOOD ELECTROLYTE	ELECTROLYTE ABNORM
IMBALANCE HORMONAL	ENDO DIS

IMBECILITY	MENTAL RETARD
IMMUNE DISORDER (NOS)	IMMUNE SYSTEM DIS
IMMUNE IMBALANCE	IMMUNE SYSTEM DIS
IMMUNE SYSTEM DISORDER (NOS)	IMMUNE SYSTEM DIS
IMMUNOGLOBINS DECREASED	IMMUNOGLOBUL DEC
IMMUNOGLOBINS INCREASED	IMMUNOGLOBUL INC
IMMUNOGLOBULINS DECREASED	IMMUNOGLOBUL DEC
IMPACTION FECAL	IMPACT FECAL
IMPERFORATE ANUS	ANUS IMPERFOR
IMPLANTATION COMPLICATION	APPLICAT SITE REACT
IMPLANTATION COMPLICATION IUD	UTER DIS
IMPOTENCE	IMPOTENCE
IMPOTENTIA ERIGENDI	IMPOTENCE
INANITION	CACHEXIA
INAPPROPRIATE ADH	ADH INAPPROP
INCOHERENT	THINKING ABNORM
INCOMPLETE URINATION	URIN RETENT
INCONTINENCE FECAL	INCONTIN FECAL
INCONTINENCE URINARY	INCONTIN URIN
INCOORDINATION	COORDINAT ABNORM
INCREASED EFFECT	INCREASED EFFECT
INCREASED THIRST	THIRST
INCREASED TSH	ALTERED HORMONE LEVEL
INDIFFERENCE	APATHY
INDIGESTION	DYSPEPSIA
INDIGESTION ACID	DYSPEPSIA
INDIGESTION NERVOUS	DYSPEPSIA
INERTIA UTERI	UTER ATONY
INFANT DEATH SUDDEN	SIDS
INFARCT	OCCLUS
INFARCT CEREBRAL	INFARCT CEREBR
INFARCT INFARCTION	OCCLUS
INFARCT LIVER	INFARCT LIVER
INFARCT MYOCARDIAL	INFARCT MYOCARD
INFARCT PULMONARY	INFARCT PULM
INFARCTION MESENTERIC	OCCLUS MESENTER
INFECTION	INFECT
INFECTION AGGRAVATED	INFECT
INFECTION BACTERIAL	INFECT BACT
INFECTION BLADDER	CYSTITIS
INFECTION BREAST	MASTITIS
INFECTION FUNGAL	INFECT FUNG
INFECTION INJECTION SITE	INJECT SITE REACT
INFECTION MASKED	INFECT MASKED
INFECTION MYCOTIC	INFECT FUNG
INFECTION PARASITIC	INFECT PARA
INFECTION PRECIPITATED	INFECT
INFECTION PROTOZOAL	INFECT
INFECTION RESPIRATORY	INFECT
INFECTION SUPERIMPOSED	INFECT SUPER
INFECTION SUSCEPTIBILITY INCR	IMMUNE SYSTEM DIS
INFECTION SYSTEMIC	SEPSIS
INFECTION TBC	TUBERCUL REACT
INFECTION TUBERCULOSIS	INFECT
INFECTION UPPER RESPIRATORY	INFECT
INFECTION URINARY TRACT	INFECT URIN TRACT
INFECTION VIRAL	INFECT VIRAL

INFERTILITY MALE	FERTIL DEC MALE
INFILTRATION ANESTHESIA	INJECT SITE REACT
INFILTRATION FATTY LIVER	LIVER FATTY
INFILTRATION INTRAVENOUS INJECTION	INJECT SITE REACT
INFLAMMATION BILE DUCT	CHOLECYST
INFLAMMATION CORNEAL	KERATITIS
INFLAMMATION GALL BLADDER	CHOLECYST
INFLAMMATION GUM	GINGIVITIS
INFLAMMATION INJECTION SITE	INFLAM INJECT SITE
INFLAMMATION LOCALIZED	INFLAM INJECT SITE
INFLAMMATION MUCOUS MEMBRANE	MUCOUS MEM DIS
INFLAMMATION PELVIC	SALPINGITIS
INFLAMMATION STOMACH	GASTRITIS
INFLAMMATION TONGUE	GLOSSITIS
INFLAMMATORY ARTERY REACTION	ARTERITIS
INFLAMMATORY EDEMA REACTION	EDEMA
INFLAMMATORY SWELLING	EDEMA
INFLUENZA-LIKE SYMPTOMS	FLU SYND
INITIATIVE LOSS OF	APATHY
INJECTION SITE ABSCESS	ABSCESS INJECT SITE
INJECTION SITE ABSCESS STERILE	ABSCESS INJECT SITE
INJECTION SITE ANESTHESIA	HYPESTHESIA
INJECTION SITE ATROPHY	ATROPHY INJECT SITE
INJECTION SITE EDEMA	EDEMA INJECT SITE
INJECTION SITE FIBROSIS	FIBRO INJECT SITE
INJECTION SITE HYPERSENSITIVITY	HYSN INJECT SITE
INJECTION SITE INFECTION	INJECT SITE REACT
INJECTION SITE INFLAMMATION	INFLAM INJECT SITE
INJECTION SITE MASS	MASS INJECT SITE
INJECTION SITE NECROSIS	NECRO INJECT SITE
INJECTION SITE PAIN	PAIN INJECT SITE
INJECTION SITE REACTION	INJECT SITE REACT
INJECTION SITE REACTION (NOS)	INJECT SITE REACT
INJURY	INJURY ACCID
INJURY CORNEAL	CORNEAL LESION
INJURY RADIATION	RADIAT INJ
INSOMNIA	INSOMNIA
INSTABILITY CARDIOVASCULAR	CARDIOVASC DIS
INSTABILITY EMOTIONAL	EMOTION LABIL
INSTABILITY GAIT	ATAXIA
INSTABILITY STATION	COORDINAT ABNORM
INSTABILITY VASOMOTOR	CARDIOVASC DIS
INSUFFICIENCY ADRENAL	ADREN INSUFFIC
INSUFFICIENCY ADRENAL CORTEX	ADREN INSUFFIC
INSUFFICIENCY CARDIAC	HEART FAIL
INSUFFICIENCY CEREBROVASCULAR	ISCHEMIA CEREBR
INSUFFICIENCY CORONARY ARTERY	CORONARY ART DIS
INSUFFICIENCY PANCREATIC	PANCREAS DIS
INSUFFICIENCY PITUITARY	PIT ACTIV DEC
INSUFFICIENCY RENAL	KIDNEY FUNC ABNORM
INSULIN SHOCK	HYPOGLYCEM REACT
INTELLECT IMPAIRED	THINKING ABNORM
INTELLIGENCE DECREASED	THINKING ABNORM
INTELLIGENCE INCREASED	UNEXPECTED BENEFIT
INTENTION TREMOR	TREMOR
INTERACTION DRUG (NOS)	DRUG INTERACTION
INTERFERENCE LABORATORY TEST	LAB TEST INTERFER

INTERMENSTRUAL BLEEDING	METRORRHAGIA
INTERMITTENT CLAUDICATION	VASC DIS PERIPH
INTERSTITIAL CELL-STIMULATING HORMONE	GONADOTR DEC LH
INTERSTITIAL FLUID INCREASED	EDEMA GENERAL
INTERSTITIAL LUNG DISEASE	PNEUMONIA INTERSTIT
INTERSTITIAL NEPHRITIS ACUTE	NEPHRITIS
INTERSTITIAL NEPHRITIS CHRONIC	FIBRO KIDNEY
INTERSTITIAL PNEUMONIA	PNEUMONIA INTERSTIT
INTERSTITIAL PNEUMONITIS	PNEUMONIA INTERSTIT
INTERUTERINE GROWTH RETARD	BIRTH WEIGHT SUBNORM
INTESTINAL CARCINOMA	CARCINOMA GI
INTESTINAL DILATATION TOXIC SEVERE	ILEUS
INTESTINAL GANGRENE	GANGRENE INTEST
INTESTINAL HYPERMOTILITY	GI DIS
INTESTINAL ISCHAEMIA	OCCLUS MESENTER ART
INTESTINAL ISCHEMIA	OCCLUS MESENTER
INTESTINAL LARGE ULCER	ULCER INTEST
INTESTINAL NECROSIS	NECRO INTEST
INTESTINAL OBSTRUCTION	OBSTRUCT INTEST
INTESTINAL PERFORATION	INTEST PER
INTESTINAL PERFORATION LARGE	INTEST LARGE PER
INTESTINAL PERFORATION SMALL	INTEST SMALL PER
INTESTINAL STENOSIS	STENO INTEST
INTESTINAL ULCERATION	ULCER INTEST
INTESTINAL ULCERATION PERFORATED	ULCER INTEST PER
INTOLERANCE ALCOHOLIC	ALCOHOL INTOLER
INTOLERANCE CONTACT LENS	CORNEAL LESION
INTOLERANCE INDUCED	TOLER DEC
INTOXICATION	OVERDOSE
INTRACEREBRAL HEMORRHAGE	HEM CEREBR
INTRACRANIAL HYPERTENSION	INTRACRAN HYPERTENS
INTRACRANIAL PRESSURE INCREASED	INTRACRAN HYPERTENS
INTRAOCULAR PRESSURE INCREASED	GLAUCOMA
INTRAUTERINE DEVICE DISORDER	UTER DIS
INTRAVENTRICULAR BLOCK	BUNDLE BRANCH BLOCK
INVOLUNTARY MOVEMENT (NOS)	MOVEMENT DIS
INVOLUNTARY MUSCLE MOVEMENT	TWITCH
IODIDE INTOXICATION	IODISM
IODINE BUTANOL-EXTRACTABLE SERUM DEC	BEI DEC
IODINE BUTANOL-EXTRACTABLE SERUM INC	BEI INC
IODINE ISOTOPE THYROID UPTAKE DEC	IOD ISOTOPE UPT DEC
IODINE ISOTOPE THYROID UPTAKE INC	IOD ISOTOPE UPT INC
IODINE ISOTOPE UPTAKE DECREASED	IOD ISOTOPE UPT DEC
IODINE ISOTOPE UPTAKE INCREASED	IOD ISOTOPE UPT INC
IODINE L3L UPTAKE DECREASED	IOD ISOTOPE UPT DEC
IODINE L3L UPTAKE INCREASED	IOD ISOTOPE UPT INC
IODINE PROTEIN-BOUND DECREASED	PBI DEC
IODINE PROTEIN-BOUND INCREASED	PBI INC
IODINE RADIOACTIVE UPTAKE DEC	IOD ISOTOPE UPT DEC
IODINE RADIOACTIVE UPTAKE INC	IOD ISOTOPE UPT INC
IODISM	IODISM
IRIDOCYCLITIS	UVEITIS
IRITIS	IRITIS
IRON SERUM DECREASED	ANEMIA HYPOCHROM
IRON SERUM INCREASED	SERUM IRON INC
IRRATIONAL	THINKING ABNORM
IRRESPONSIBILITY	PERSON DIS

IRRITABILITY	NERVOUSNESS
IRRITABILITY POST VAC	AGITATION
IRRITABLE COLON	COLITIS
IRRITATION EYE	CONJUNCTIVITIS
IRRITATION GASTRIC	GASTRITIS
IRRITATION GASTROINTESTINAL	GASTROENTERITIS
IRRITATION SKIN	RASH
ISCHEMIA BOWEL	GI DIS
ISCHEMIA CEREBRAL	ISCHEMIA CEREBR
ISCHEMIA CEREBROVASCULAR	ISCHEMIA CEREBR
ISCHEMIA CORONARY ARTERY ORIGIN	ISCHEMIA MYOCARD
ISCHEMIA INTEST	NECRO INTEST
ISCHEMIA MYOCARDIAL	ISCHEMIA MYOCARD
ISCHEMIA PERIPHERAL	VASC DIS PERIPH
ISCHEMIA PLACENTAL	PLACENTA DIS
ISCHEMIA RETINAL	RETINAL VASC DIS
ISOSTHENURIA	KIDNEY FUNC ABNORM
IUD COMPLICATION	UTER DIS
IUD EMBEDDED	UTER DIS
JACKSONIAN EPILEPSY	CONVULS
JACKSONIAN SEIZURES	CONVULS
JAUNDICE	JAUNDICE
JAUNDICE ACHOLURIC	ANEMIA HEMOL
JAUNDICE CHOLESTATIC	JAUNDICE CHOLESTAT
JAUNDICE HEMATOGENOUS	ANEMIA HEMOL
JAUNDICE HEMOLOGOUS SERUM-LIKE	HEPATITIS
JAUNDICE HEMOLYTIC	ANEMIA HEMOL
JAUNDICE HEPATOCELLULAR	HEPATITIS
JAUNDICE NEONATAL	JAUNDICE NEONAT
JAW BONE PAIN	PAIN BONE
JAW MALFORMATION	ANOMALY CONGEN MS
JAW PAIN	PAIN
JITTERINESS	NERVOUSNESS
JOINT ACHE	ARTHRALGIA
JOINT DISLOCATION TEMPOROMANDIB	JOINT DIS
JOINT DISORDER	JOINT DIS
JOINT EFFUSION	ARTHROSIS
JOINT INFLAMMATION	ARTHRITIS
JOINT MALFORMATION	ANOMALY CONGEN MS
JOINT PAIN	ARTHRALGIA
JOINT STIFFNESS	JOINT DIS
JOINT SWELLING NON-INFLAMMATORY	ARTHROSIS
JUDGEMENT IMPAIRED	THINKING ABNORM
JUMPINESS	NERVOUSNESS
KARYOTYPE ABNORMAL	CHROMOSOME ABNORM
KELOID	HYPERTROPHY SKIN
KERATITIS	KERATITIS
KERATOCONJUNCTIVITIS	KERATOCONJUNCTIVITIS
KERATOCONUS	EYE DIS
KERATOSIS	HYPERTROPHY SKIN
KERNICTERUS	JAUNDICE NEONAT
KETOACIDOSIS	KETOSIS
KETOSIS	KETOSIS
KIDNEY ABSCESS	ABSCESS KIDNEY
KIDNEY ATROPHIC	URIN TRACT DIS
KIDNEY CALCULUS	KIDNEY CALCULUS
KIDNEY CARCINOMA	CARCINOMA

KIDNEY CONTRACTED	URIN TRACT DIS
KIDNEY DYSFUNCTION	KIDNEY FUNC ABNORM
KIDNEY FAILURE	KIDNEY FAIL
KIDNEY FAILURE ACUTE	KIDNEY FAIL ACUTE
KIDNEY FAILURE CHRONIC	UREMIA
KIDNEY FUNCTION ABNORMAL	KIDNEY FUNC ABNORM
KIDNEY POLYCYSTIC	KIDNEY POLYCYSTIC
KIDNEY STONE	KIDNEY CALCULUS
KIDNEY TUBULE DISORDER	KIDNEY TUBUL DIS
KIDNEY TUBULE NECROSIS	NECRO KIDNEY TUBUL
KNEE PAIN	PAIN
KUPPFER CELL DECREASE	RE BLOCK
LAB TEST ABNORMALITY	LAB TEST ABNORM
LABIA ENLARGED	EDEMA LABIA
LABILITY EMOTIONAL	EMOTION LABIL
LABOR ABNORMAL	LABOR ABNORM
LABOR INDUCED	LABOR ABNORM
LABOR INTERRUPTED	UTER ATONY
LABOR ONSET DELAYTED	LABOR ABNORM
LABOR PAINS STOPPED	UTER ATONY
LABOR PRECIPITOUS	LABOR ABNORM
LABOR PREMATURE	LABOR ABNORM
LABOR PROLONGED	LABOR ABNORM
LABORATORY TEST ABNORMALITY	LAB TEST ABNORM
LABORATORY TEST INTERFERENCE	LAB TEST INTERFER
LABOUR PREMATURE	LABOR ABNORM
LABYRINTHINE DISORDER	VESTIBUL DIS
LABYRINTHITIS	VESTIBUL DIS
LACRIMAL DUCT OBSTRUCTION	LACRIMATION DIS
LACRIMAL GLAND DISORDER	LACRIMATION DIS
LACRIMATION ABNORMAL	LACRIMATION DIS
LACRIMATION DISORDER	LACRIMATION DIS
LACTATE BLOOD INCREASED	ACIDOSIS LACTIC
LACTATION DECREASED	LACTATION DEC
LACTATION FEMALE	LACTATION FEM
LACTATION INDUCED	LACTATION FEM
LACTATION MALE	LACTATION MALE
LACTATION NONPUERPERAL	LACTATION FEM
LACTATION PUERPERAL DECREASED	LACTATION DEC
LACTATION PUERPERAL INCREASED	LACTATION FEM
LACTIC ACID BLOOD INCREASED	ACIDOSIS LACTIC
LACTIC DEHYDROGENASE ACTIVITY INC	LDH INC
LACTOSE INTOLERANCE	GI DIS
LARGE ARM SWELLING	EDEMA PERIPH
LARGE FOR GESTATIONAL AGE	BIRTH POSTMAT
LARGE INTESTINE ULCER	ULCER INTEST
LARNYX CARCINOMA	CARCINOMA LARYNX
LARYNGEAL EDEMA	EDEMA LARYNX
LARYNGISMUS	LARYNGISMUS
LARYNGITIS	LARYNGITIS
LARYNGOPARALYSIS	PARALYSIS VOCAL CORD
LARYNGOSPASM	LARYNGISMUS
LARYNGOTRACHEAL EDEMA	EDEMA LARYNX
LARYNX EDEMA	EDEMA LARYNX
LARYNX NEOPLASM BENIGN	NEOPL LARYNX
LARYNX NEOPLASM MALIGNANT	CARCINOMA LARYNX
LARYNX OEDEMA	EDEMA LARYNX

LASSITUDE	ASTHENIA
LAUGHTER	EMOTION LABIL
LDH BLOOD URINE INCREASED	LDH INC
LDH INCREASED	LDH INC
LDL INC	HYPERCHOLESTEREM
LE ARTHRITIS	LE SYND
LE CELLS PRESENT	LE TEST ABNORM
LE RASH	RASH LE
LE REACTION SYSTEMIC	LE SYND
LE SYNDROME	LE SYND
LE SYNDROME AGGRAVATED	LE SYND
LE TEST ABNORMAL	LE TEST ABNORM
LE TEST ABNORMALITY	LE TEST ABNORM
LE TYPE REACTION	LE SYND
LE-LIKE RASH	RASH LE
LEE-WHITE CLOTTING TIME PROLONGED	COAGUL TIME INC
LEG CRAMPS	CRAMPS LEG
LEGS RESTLESS	HYPERKINESIA
LEIOMYOMA UTERINE DEGENERATED	UTER FIBROID DEGEN
LEIOMYOMAUTERINE INCREASE	UTER FIBROID ENLARGE
LENTICULAR DEPOSIT	CATARACT
LENTICULAR OPACITY	CATARACT
LESION CORNEAL	CORNEAL LESION
LESS ALERT ON ARISING	SOMNOLENCE
LETHARGY	SOMNOLENCE
LEUCOPENIA	LEUKOPENIA
LEUCOPENIA NEONATAL	LEUKOPENIA
LEUKAEMIA	LEUKEMIA
LEUKAEMIA ACUTE	LEUKEMIA ACUTE
LEUKAEMIA GRANULOCYTIC	LEUKEMIA CHRON MYELO
LEUKAEMIA LYMPHOCYTIC	LEUKEMIA CHRON LYMPHO
LEUKAEMIA MONOCYTIC	LEUKEMIA CHRON MONO
LEUKAEMIA NEONATAL	LEUKEMIA
LEUKAEMOID REACTION	LEUKEMOID REACT
LEUKEMIA	LEUKEMIA
LEUKEMIA ACUTE	LEUKEMIA ACUTE
LEUKEMIA ALEUKEMIC	LEUKEMIA
LEUKEMIA BASOPHILIC	LEUKEMIA CHRON MYELO
LEUKEMIA CHRONIC	LEUKEMIA CHRON
LEUKEMIA EOSINOPHILIC	LEUKEMIA CHRON MYELO
LEUKEMIA GRANULOCYTIC	LEUKEMIA CHRON MYELO
LEUKEMIA LYMPHATIC	LEUKEMIA CHRON LYMPHO
LEUKEMIA LYMPHOBLASTIC ACUTE	LEUKEMIA ACUTE LYMPHO
LEUKEMIA LYMPHOCYTIC CHRONIC	LEUKEMIA CHRON LYMPHO
LEUKEMIA LYMPHOID	LEUKEMIA CHRON LYMPHO
LEUKEMIA MONOBLASTIC ACUTE	LEUKEMIA ACUTE MONO
LEUKEMIA MONOCYTIC CHRONIC	LEUKEMIA CHRON MONO
LEUKEMIA MYELOBLASTIC ACUTE	LEUKEMIA ACUTE MYELO
LEUKEMIA MYELOCYTIC CHRONIC	LEUKEMIA CHRON MYELO
LEUKEMIA MYELOGENOUS	LEUKEMIA CHRON MYELO
LEUKEMIA MYELOID	LEUKEMIA CHRON MYELO
LEUKEMIA NEONATAL	LEUKEMIA ACUTE
LEUKEMIA PLASMACYTIC	LEUKEMIA
LEUKEMIA STEM CELL	LEUKEMIA ACUTE
LEUKEMOID REACTION	LEUKEMOID REACT
LEUKOCYTES ABNORMAL (NOS)	WBC ABNORM
LEUKOCYTOSIS	LEUKOCYTOSIS

LEUKODERMA	LEUKODERMA
LEUKOERYTHROBLASTOSIS	MARROW HYPERPLASIA
LEUKOPENIA	LEUKOPENIA
LEUKOPLAKIA GENITAL	LEUKOPLAKIA GENIT
LEUKOPLAKIA ORAL	LEUKOPLAKIA ORAL
LEUKORRHEA	LEUKORRHEA
LEUKORRHOEA	LEUKORRHEA
LIBIDO DECREASED	LIBIDO DEC
LIBIDO INCREASED	LIBIDO INC
LIBIDO LOSS OF	LIBIDO DEC
LICHEN PLANUS-LIKE DERMATITIS	DERM LICHEN
LIGHT-HEADED	DIZZINESS
LIMB MALFORMATION	ANOMALY CONGEN MS
LIP AND PALATE CLEFT	CLEFT PALATE
LIP CLEFT	CLEFT LIP
LIP SMACKING	BUCCOGLOSSAL SYND
LIP ULCER	ULCER MOUTH
LIPASE INCREASED	LIPASE INC
LIPID PNEUMONIA	PNEUMONIA LIPID
LIPIDOSIS	ANOMALY CONGEN
LIPIDS BLOOD DECREASED	HYPOLIPEM
LIPIDS BLOOD INCREASED	HYPERLIPEM
LIPIDURIA	HYPERLIPEM
LIPOATROPHY INJECTION SITE	ATROPHY INJECT SITE
LIPODYSTROPHY	LIPODYSTROPHY
LIPOMA	NEOPL
LISTLESSNESS	MALAISE
LIVEDO RETICULARIS	VASC DIS
LIVER CARCINOMA	CARCINOMA LIVER
LIVER CELL DAMAGE	LIVER DAMAGE
LIVER CIRRHOSIS	LIVER CIRRHO
LIVER DAMAGE	LIVER DAMAGE
LIVER DAMAGE AGGRAVATED	LIVER DAMAGE AGGRAV
LIVER DISORDER	LIVER DAMAGE
LIVER ENLARGEMENT	HEPATOMEGALY
LIVER ENZYME ABNORMAL	LIVER FUNC ABNORM
LIVER FAILURE	LIVER FAIL
LIVER FATTY	LIVER FATTY
LIVER FATTY CHANGE	LIVER FATTY
LIVER FATTY DEGENERATION	LIVER FATTY
LIVER FATTY DEPOSITION	LIVER FATTY
LIVER FATTY INFILTRATION	LIVER FATTY
LIVER FATTY METAMORPHOSIS	LIVER FATTY
LIVER FATTY PHANEROSIS	LIVER FATTY
LIVER FUNCTION TESTS MULTIPLE ABNORM	LIVER FUNC ABNORM
LIVER TENDER	LIVER TENDER
LIVER TENDERNESS OF	LIVER TENDER
LIVER TUMOR	NEOPL LIVER
LOCAL THROAT IRRITATION	PHARYNGITIS
LOIN PAIN	PAIN BACK
LOOSE STOOLS	DIARRHEA
LOSS OF CONSIOUSNESS	SYNCOPE
LOW DENSITY LIPOPROTEIN	HYPERCHOLESTEREM
LOW POTASSIUM SYNDROME	HYPOKALEM
LOW SALT SYNDROME	HYPONATREM
LOW SODIUM SYNDROME	HYPONATREM
LOWER NEPHRON NEPHROSIS	KIDNEY TUBUL DIS

LUMBAGO	PAIN BACK
LUMBAR CUSHION	EDEMA
LUMBO-SACRAL PAIN	PAIN BACK
LUNATISM	CARCINOMA LUNG
LUNG CARCINOMA	CARCINOMA LUNG
LUNG DISEASE OBSTRUCTIVE	LUNG DIS
LUNG DISORDER (NOS)	LUNG DIS
LUNG EDEMA	EDEMA LUNG
LUNG FIBROSIS INTERSTITIAL	FIBRO LUNG
LUNG FUNCTION DECREASED (NOS)	LUNG FUNC DEC
LUPOID DERMATITIS	RASH LE
LUPUS ERYTHEMATOSIS (NOS)	LE SYND
LUPUS ERYTHEMATOSIS DISCOID	RASH LE
LUPUS ERYTHEMATOSIS DISSEMINATED	LE SYND
LUPUS ERYTHEMATOSUS SYSTEMIC	LE SYND
LUPUS SYNDROME	LE SYND
LUTEINIZING HORMONE DECREASED	GONADOTR DEC LH
LUTEINIZING HORMONE INCREASED	GONADOTR INC LH
LYELL'S SYNDROME	EPIDERM NECRO
LYMPH NODES ENLARGED	LYMPHADENO
LYMPHADENITIS	LYMPHADENO
LYMPHADENOPATHY	LYMPHADENO
LYMPHADENOPATHY CERVICAL	LYMPHADENO
LYMPHADENOPATHY FIBROTIC	LYMPHADENO
LYMPHADENOPATHY MASSIVE	LYMPHOMA LIKE REACT
LYMPHADENOPATHY THORACIC	LYMPHADENO
LYMPHANGITIS	LYMPHANGITIS
LYMPHEDEMA	LYMPHEDEMA
LYMPHOCYTES ATYPICAL	WBC ABNORM
LYMPHOCYTOPENIA	LEUKOPENIA
LYMPHOCYTOSIS	LYMPHOCYTOSIS
LYMPHOEDEMA	LYMPHEDEMA
LYMPHOMA	LYMPHOMA LIKE REACT
LYMPHOMA MALIGNANT	LYMPHOMA LIKE REACT
LYMPHOMA-LIKE DISORDER	LYMPHOMA LIKE REACT
LYMPHOMA-LIKE REACTION	LYMPHOMA LIKE REACT
LYMPHOMOID	LYMPHOMA LIKE REACT
LYMPHOPENIA	LEUKOPENIA
LYMPHOSARCOMOID	LYMPHOMA LIKE REACT
LYSIS BONE IMPLANT	BONE IMPLANT LYSIS
MACROCYTOSIS	RBC ABNORM
MACROGLOBULIN PRESENT	GLOBULIN INC
MACROPHAGES DECREASED	RE BLOCK
MACULA LUTEA DEGENERATION	RETINAL DIS
MACULAR RASH	RASH MAC PAP
MACULOPATHY	RETINAL DIS
MALABSORPTION	MALABSORP SYND
MALABSORPTION SYNDROME	MALABSORP SYND
MALAISE	MALAISE
MALE HORMONE IMBALANCE	ENDO DIS
MALE SEX MATURATION ACCELERATED	SEX MAT MALE ACCEL
MALFORMATION BILIARY	BIL ATRESIA
MALFORMATION FOOT	ANOMALY CONGEN MS
MALFORMATION HAND	ANOMALY CONGEN MS
MALFORMATION HEART (NOS)	ANOMALY HEART
MALFORMATION SKULL	ANOMALY CONGEN MS
MALFORMATION TOOTH	ANOMALY TOOTH

MALFORMATION VENOUS	ANOMALY VASCUL
MALFORMATIONS MULTIPLE	ANOMALY CONGEN MULT
MALIGNANT HYPERTHEMIA	FEVER MALIGNANT
MALIGNANT MELANOMA	MELANOMA SKIN
MANIA ACUTE	MANIC REACT
MANIC DEPRESSIVE REACTION	MANIC DEPRESS REACT
MANIC EXCITEMENT	MANIC REACT
MANIC PSYCHOSIS	MANIC REACT
MANIC REACTION	MANIC REACT
MARROW DEPRESSION	MARROW DEPRESS
MARROW DEPRESSION OF	MARROW DEPRESS
MARROW HYPERCELLULAR	MARROW HYPERPLASIA
MARROW HYPERPLASIA	MARROW HYPERPLASIA
MARROW HYPERPLASIA OF	MARROW HYPERPLASIA
MARROW HYPOPLASIA	MARROW DEPRESS
MASCERATION	EPIDERM NECRO
MASCULINIZATION	VIRILISM
MASS BREAST (NOS)	NEOPL BREAST
MASS BREAST FIBROCYSTIC	BREAST FIBROCYST
MASS INJECTION SITE	MASS INJECT SITE
MASTALGIA	PAIN BREAST
MASTATROPHY	ATROPHY BREAST
MASTITIS	MASTITIS
MASTITIS ACUTE FEMALE	MASTITIS
MASTITIS CHRONIC	BREAST FIBROCYST
MASTITIS MALE	MASTITIS
MATURATION ARREST ERYTHROID	ERYTHRO MATUR ARREST
MATURATION ARREST MARROW	MARROW DEPRESS
MATURATION ARREST MYELOID	MYELOID MATUR ARREST
MATURATION ARREST PLATELET	THROMBOCYTOPENIA
MATURATION SEX ACCELERATED	SEX MAT ACCEL
MEASLY RASH	RASH MAC PAP
MECODIUM INCREASED	FETAL DIS
MECONIUM INCREASED	FETAL DIS
MEDICATION ERROR	MED ERROR
MEDICATION TAMPERING	MED ERROR
MEGACOLON ACQUIRED	MEGACOLON
MEGACOLON AQUIRED	MEGACOLON
MEGACOLON CONGENITAL	ANOMALY GI
MEGACOLON TOXIC	GI DIS
MEGAKARYOCYTES ABNORMAL	MEGAKARYO ABNORM
MEGAKARYOCYTES DECREASED	MEGAKARYO DEC
MEGAKARYOCYTES INCREASED	MEGAKARYO INC
MEGALOCARDIA	CARDIOMEGALY
MELAENA	MELENA
MELANCHOLIA	DEPRESSION
MELANODERMA	MELANOSIS
MELANOMA MALIGNANT	MELANOMA SKIN
MELANOMA SKIN	MELANOMA SKIN
MELANOSIS	MELANOSIS
MELANOSIS COLI	MELANOSIS
MELANOSIS CONGENITAL	MELANOSIS
MELASMA	MELANOSIS
MELENA	MELENA
MELENA GASTRIC ULCER	MELENA
MEMBRANE MUCOUS DISORDER (NOS)	MUCOUS MEM DIS
MEMORY DISTURBANCE	AMNESIA

MEMORY IMPAIRED	AMNESIA
MEMORY LOSS OF	AMNESIA
MENIERE'S SYNDROME	VESTIBUL DIS
MENINGEAL IRRITATION	MENINGISM
MENINGISM	MENINGISM
MENINGISMUS	MENINGISM
MENINGITIS	MENINGITIS
MENINGITIS CRYPTOCOCCAL	CRYPTOCOCCOSIS
MENINGITIS TORULA	CRYPTOCOCCOSIS
MENINGITIS-LIKE	MENINGISM
MENINGOCELE	MENINGOMYELOCELE
MENINGOENCEPHALITIS	ENCEPHALITIS
MENINGOMYELOCELE	MENINGOMYELOCELE
MENOMETRORRHAGIA	METRORRHAGIA
MENOPAUSAL SYNDROME	MENOPAUSE
MENOPAUSE	MENOPAUSE
MENOPAUSE DELAYED	MENOPAUSE
MENOPAUSE PREMATURE	MENOPAUSE
MENORRHAGIA	MENORRHAGIA
MENSES INFREQUENT	HYPOMENORRHEA
MENSES IRREGULAR	METRORRHAGIA
MENSES IRREGULAR WITH EXCESSIVE BLEEDING	METRORRHAGIA
MENSES LACK OF	AMENORRHEA
MENSES ONSET DELAYED	MENS DIS
MENSES PAINFUL	DYSMENORRHEA
MENSES REGULAR WITH EXCESSIVE BLEEDING	MENORRHAGIA
MENSTRUAL CRAMP	DYSMENORRHEA
MENSTRUAL DISORDER	MENS DIS
MENSTRUAL FLOODING	MENORRHAGIA
MENSTRUAL FLOW EXCESSIVE	MENORRHAGIA
MENSTRUAL IRREGULARITY	METRORRHAGIA
MENTAL ACTIVITY DECREASED	THINKING ABNORM
MENTAL CONCENTRATION DIFFICULTY	THINKING ABNORM
MENTAL DEFICIENCY	MENTAL RETARD
MENTAL DETERIORATION	THINKING ABNORM
MENTAL DISTRESS	ANXIETY
MENTAL DULLNESS	THINKING ABNORM
MENTAL RETARDATION	MENTAL RETARD
MENTAL TORPOR	THINKING ABNORM
MENTATION IMPAIRED	THINKING ABNORM
METAMEPHRINE URINARY ELEVATED	URIN ABNORM
METAMORPHOSIS FATTY LIVER	LIVER FATTY
METAPLASIA MYELOID	MYELOID METAPLASIA
METEORISM	FLATUL
METHAEMOGLOBINAEMIA	METHEMOGLOBIN
METHAEMOGLOBINURIA	METHEMOGLOBINURIA
METHEMOGLOBINEMIA	METHEMOGLOBIN
METHEMOGLOBINURIA	METHEMOGLOBINURIA
METRORRHAGIA	METRORRHAGIA
MICROCEPHALY	ANOMALY CONGEN CNS
MICROCYTIC ANEMIA	ANEMIA MICROCYT
MICROGNATHIA	ANOMALY CONGEN MS
MICTRUITION FREQUENT	URIN FREQUENCY
MICTRUITION URGENT	URIN URGENCY
MICTURITION BURNING	DYSURIA
MICTURITION DISORDER	URIN TRACT DIS
MICTURITION FREQUENCY	URIN FREQUENCY

MICTURITION PAINFUL	DYSURIA
MIGRAINE	MIGRAINE
MIGRAINE AGGRAVATED	MIGRAINE
MILIARIA	MILIARIA
MILK OVERPRODUCTION	BREAST ENGORGE
MILK-ALKALI SYNDROME	CALCIUM DIS
MIOSIS	MIOSIS
MISCARRIAGE	ABORTION
MITRAL INSUFFICIENCY	CARDIOVASC DIS
MITTELSCHMERZ	OVAR DIS
MONARTHRITIS	ARTHRITIS
MONGOLISM	MENTAL RETARD
MONILIASIS	MONILIA
MONILIASIS AXILLARY	MONILIA AXILLA
MONILIASIS CUTANEOUS	MONILIA SKIN
MONILIASIS GASTROINTESTINAL	MONILIA GI
MONILIASIS GENITAL	MONILIA VAGINA
MONILIASIS GENITAL FEMALE	MONILIA VAGINA
MONILIASIS GI	MONILIA GI
MONILIASIS MONILIA	MONILIA
MONILIASIS ORAL	MONILIA ORAL
MONILIASIS PULMONARY	MONILIA RESP
MONILIASIS RESPIRATORY SYSTEM	MONILIA RESP
MONILIASIS SKIN	MONILIA SKIN
MONILIASIS VAGINAL	MONILIA VAGINA
MONOCYTOSIS	MONOCYTOSIS
MONONCULEOID REACTION	LYMPHOCYTOSIS
MONONEURITIS	NEURITIS
MONOPLEGIA	MONOPLEGIA
MOOD ALTERED	EMOTION LABIL
MOOD CHANGE	EMOTION LABIL
MOOD ELEVATED	EUPHORIA
MOOD ELEVATION INAPPROPRIATE	EUPHORIA
MOOD SWINGS	EMOTION LABIL
MOOD VARIABLE	EMOTION LABIL
MOON FACE	CUSHINGS SYND
MORBILLIFORM RASH	RASH MAC PAP
MORONITY	MENTAL RETARD
MOROSENESS	DEPRESSION
MOTOR ACTIVITY EXAGGERATED	HYPERKINESIA
MOTOR ACTIVITY RETARDED	HYPOKINESIA
MOTOR UNREST COMPULSIVE	AKATHISIA
MOTTLING ENAMEL	DISCOLOR TOOTH
MOUTH CARCINOMA	CARCINOMA MOUTH
MOUTH DRY	DRY MOUTH
MOUTH HEMORRHAGE	HEM
MOUTH IRRITATION	STOMATITIS
MOUTH NECROSIS	ULCER MOUTH
MOUTH PARESTHESIA	PARESTH CIRCUMORAL
MOUTH PLAQUE	LEUKOPLAKIA ORAL
MOUTH ULCERATION	ULCER MOUTH
MOVEMENT DISORDER (NOS)	MOVEMENT DIS
MOVEMENTS INVOLUNTARY (NOS)	MOVEMENT DIS
MOVEMENTS REDUCED	HYPOKINESIA
MOVEMENTS SPASTIC INVOLUNTARY	DYSKINESIA
MS AGGRAVATED	SCLEROSIS MULT
MS-LIKE SYNDROME	SCLEROSIS MULT

MUCOSAL DISCOLORATION GI	GI DIS
MUCOSAL DISCOLOURATION GI	GI DIS
MUCOSAL SORES	MUCOUS MEM DIS
MUCOSITIS NOS	MUCOUS MEM DIS
MUCOSITIS ORAL	STOMATITIS
MUCOUS HYPERPLASIA	MUCOUS MEM DIS
MUCOUS MEMBRANE DISORDER (NOS)	MUCOUS MEM DIS
MUCOUS NASAL INCREASED	RHINITIS
MUCOVISCIDOSIS	PANCREAS DIS
MULTIPLE MYELOMA	MYELOMA
MULTIPLE MYELOMA MYELOMATOSIS	MYELOMA
MULTIPLE ORGAN FAILURE	REACT UNEVAL
MULTIPLE SCLEROSIS	SCLEROSIS MULT
MULTIPLE SCLEROSIS-LIKE SYNDROME	SCLEROSIS MULT
MULTIPLE TELANGIETASES	VASC DIS
MURDER	INJURY INTENT
MUSCLE ACHE	MYALGIA
MUSCLE ATROPHY	ATROPHY MUSCLE
MUSCLE CONTRACTIONS INVOLUNTARY	TWITCH
MUSCLE CRAMP	HYPERTONIA
MUSCLE DEGENERATION	MYOPATHY
MUSCLE DISCOMFORT	MYALGIA
MUSCLE DISORDER	MYOPATHY
MUSCLE FASCICULATION	TWITCH
MUSCLE FIBRILLATION	TWITCH
MUSCLE HAEMORRHAGE	HEM MUSCLE
MUSCLE MALFORMATION	ANOMALY CONGEN MS
MUSCLE MOVEMENT INVOLUNTARY	TWITCH
MUSCLE NECROSIS	MYOPATHY
MUSCLE PAIN	MYALGIA
MUSCLE PARALYSIS EYE	OPHTHALMOPLEGIA
MUSCLE RIGIDITY	HYPERTONIA
MUSCLE SORENESS	MYALGIA
MUSCLE SPASM	HYPERTONIA
MUSCLE SPASTICITY	HYPERTONIA
MUSCLE STIFFNESS	HYPERTONIA
MUSCLE TENDERNESS ANY SITE	MYALGIA
MUSCLE TONE FLACCID	HYPOTONIA
MUSCLE TWITCH	TWITCH
MUSCLE WEAKNESS	MYASTHENIA
MUSCULAR HYPERACTIVITY	HYPERKINESIA
MUSCULAR TONE EXCESSIVE	HYPERTONIA
MUSCULAR TONE INCREASED	HYPERTONIA
MUSCULAR UNREST	HYPERKINESIA
MUSCULAR WEAKNESS	MYASTHENIA
MUTAGENIC EFFECT FEMALE	CHROMOSOME ABNORM
MUTAGENIC EFFECT MALE	CHROMOSOME ABNORM
MYALGIA	MYALGIA
MYASTHENIA	MYASTHENIA
MYASTHENIA GRAVIS-LIKE PARALYSIS	MYASTHENIA
MYASTHENIA GRAVIS-LIKE REACTION	MYASTHENIA
MYASTHENIA GRAVIS-LIKE SYNDROME	MYASTHENIA
MYDRIASIS	MYDRIASIS
MYELITIS	MYELITIS
MYELITIS TRANSVERSE	MYELITIS
MYELOFIBROSIS	MYELOFIBROSIS
MYELOID MATURATION ARREST	MYELOID MATUR ARREST

MYELOID METAPLASIA	MYELOID METAPLASIA
MYELOMA	MYELOMA
MYELOMATOSIS MULTIPLE	MYELOMA
MYELOPATHY	MYELITIS
MYELOPROLIFERATIVE DISORDER	MYELOPROLIF DIS
MYELOSIS ERYTHREMIC	MARROW HYPERPLASIA
MYELOSIS NONLEUKEMIC	MARROW HYPERPLASIA
MYELOSUPPRESSION ADULT	MARROW DEPRESS
MYOCARDIAL DECOMPENSATION	HEART FAIL
MYOCARDIAL INFARCTION	INFARCT MYOCARD
MYOCARDIAL ISCHAEMIA	ISCHEMIA MYOCARD
MYOCARDIAL ISCHEMIA	ISCHEMIA MYOCARD
MYOCARDIAL RUPTURE	INFARCT MYOCARD
MYOCARDIAL RUPTURE (POST INFARCT)	INFARCT MYOCARD
MYOCARDITIS	MYOCARDITIS
MYOCARDITIS ALLERGIC	MYOCARDITIS ALLERG
MYOCARDITIS EOSINOPHILIC	MYOCARDITIS ALLERG
MYOCARDITIS INTERSTITIAL	MYOCARDITIS
MYOCARDOSIS	MYOCARDITIS
MYOCLONUS	MYOCLONUS
MYOGLOBINURIA	MYOPATHY
MYOMETRIAL INCREASE	ENDOMETR DIS
MYOPATHY	MYOPATHY
MYOPIA	REFRACT DIS
MYOSITIS	MYOSITIS
MYXEDEMA	HYPOTHYR
MYXEDEMA JUVENILE	CRETIN
MYXOEDEMA	HYPOTHYR
NAEVUS	NEOPL SKIN
NAIL DISCOLORATION	NAIL DIS
NAIL DISORDER	NAIL DIS
NAIL DISORDER CONGENITAL	NAIL DIS
NANISM	DWARFISM
NARCOLEPSY	SOMNOLENCE
NARCOSIS CARBON DIOXIDE	ACIDOSIS RESP
NASAL BURNING	RHINITIS
NASAL CONGESTION	RHINITIS
NASAL DISCHARGE	RHINITIS
NASAL INFLAMMATION	RHINITIS
NASAL MUCOUS INCREASED	RHINITIS
NASAL POLYP	NEOPL
NASAL SEPTUM PERFORATION	NASAL SEPTUM DIS
NASAL SEPTUM ULCERATION	NASAL SEPTUM DIS
NASAL STUFFINESS	RHINITIS
NASOPHARYNGITIS	PHARYNGITIS
NAUSEA	NAUSEA
NAUSEA AND VOMITING	NAUSEA VOMIT
NAUSEA VOMITING AND DIARRHEA	NAUSEA VOMIT DIAR
NECK RIGID	NECK RIGID
NECK STIFF	NECK RIGID
NECROLYSIS EPIDERMAL	EPIDERM NECRO
NECROSIS	NECRO
NECROSIS ADRENAL	NECRO ADREN
NECROSIS ADRENAL CORTEX	NECRO ADREN
NECROSIS AORTAL (ARTERIAL)	NECRO
NECROSIS BONE	NECRO BONE
NECROSIS BOWEL	NECRO INTEST

NECROSIS CONJUNCTIVAL	ULCER CONJUNCT
NECROSIS CORNEAL	ULCER CORNEAL
NECROSIS HEPATOCELLULAR	NECRO LIVER
NECROSIS INJECTION SITE	NECRO INJECT SITE
NECROSIS INTESTINAL	NECRO INTEST
NECROSIS ISCHAEMIC	NECRO
NECROSIS ISCHEMIC	NECRO
NECROSIS KIDNEY CORTEX	NECRO KIDNEY CORTEX
NECROSIS KIDNEY PAPILLARY	NECRO KIDNEY PAPILL
NECROSIS KIDNEY TUBULAR	NECRO KIDNEY TUBUL
NECROSIS LIVER	NECRO LIVER
NECROSIS LIVER FOCAL	NECRO LIVER
NECROSIS MOUTH	ULCER MOUTH
NECROSIS MYOCARDIUM	NECRO
NECROSIS NASAL	NECRO
NECROSIS OVARY	NECRO
NECROSIS PAPILLARY KIDNEY	NECRO KIDNEY PAPILL
NECROSIS PITUITARY	NECRO
NECROSIS PLACENTA	NECRO
NECROSIS SKIN	NECRO SKIN
NECROSIS TUBULAR KIDNEY	NECRO KIDNEY TUBUL
NEONATAL DISORDER	PERINATAL DIS
NEONATAL FEEDING DISORDER	PERINATAL DIS
NEOPLASIA GI	NEOPL GI
NEOPLASIA RENAL	NEOPL
NEOPLASM (NOS)	NEOPL
NEOPLASM ADRENAL	NEOPL
NEOPLASM BILIARY TRACT	NEOPL BIL
NEOPLASM BLADDER	NEOPL BLADDER
NEOPLASM BONE	NEOPL BONE
NEOPLASM BREAST	NEOPL BREAST
NEOPLASM CERVIX	NEOPL CERVIX
NEOPLASM CNS	NEOPL CNS
NEOPLASM ENDOMETRIUM	NEOPL ENDOMETR
NEOPLASM LARYNX	NEOPL LARYNX
NEOPLASM LIVER	NEOPL LIVER
NEOPLASM MALIGNANT	CARCINOMA
NEOPLASM MOUTH	NEOPL MOUTH
NEOPLASM NOS	NEOPL
NEOPLASM PROSTATE	NEOPL PROSTATE
NEOPLASM SKIN	NEOPL SKIN
NEOPLASM THYROID	NEOPL THYR
NEOPLASM URINARY BLADDER	NEOPL BLADDER
NEOPLASM UROGENITAL	NEOPL UG
NEOPLASM UTERINE	NEOPL UTER
NEOPLASM UTERINE CERVIX	NEOPL CERVIX
NEPHRITIS	NEPHRITIS
NEPHRITIS HEMORRHAGIC	GLOMERULITIS
NEPHRITIS INTERSTITIAL	NEPHRITIS
NEPHRITIS INTERSTITIAL ACUTE	NEPHRITIS
NEPHRITIS INTERSTITIAL CHRONIC	FIBRO KIDNEY
NEPHRITIS RADIATION	NEPHRITIS
NEPHROCALCINOSIS	NEPHROCALCINOSIS
NEPHROLITHIASIS	KIDNEY CALCULUS
NEPHROPATHY HYPERCALCEMIC	NEPHROCALCINOSIS
NEPHROPATHY HYPERTENSIVE	NEPHROSCLEROSIS
NEPHROPATHY TOXIC	NEPHROPATHY TOXIC

NEPHROPATHY TUBULAR	KIDNEY TUBUL DIS
NEPHROSCLEROSIS	NEPHROSCLEROSIS
NEPHROSCLEROSIS ARTERIOLAR	NEPHROSCLEROSIS
NEPHROSIS	NEPHROSIS
NEPHROSIS LOWER NEPHRON	KIDNEY TUBUL DIS
NEPHROTIC SYNDROME	NEPHROSIS
NERVE COMPRESSION	NEURALGIA
NERVE DAMAGE	NEUROPATHY
NERVE PAIN	NEURALGIA
NERVE ROOT LESION	NEUROPATHY
NERVE ROOT LIAISON	NEUROPATHY
NERVOUS SYSTEM DISORDER	NEUROPATHY
NERVOUS SYSTEM DISORDER, CENTRAL	CNS DEPRESS
NERVOUS TENSION	NERVOUSNESS
NERVOUSNESS	NERVOUSNESS
NERVUS MELANOCYTIC	MELANOSIS
NERVUS PIGMENTED	MELANOSIS
NEURALGIA	NEURALGIA
NEURALGIA FACIAL	NEURALGIA
NEURALGIA TRIGEMINAL	NEURALGIA
NEURASTHENIA	NEUROSIS
NEURITIS	NEURITIS
NEURITIS B6 DEFICIENCY	NEURITIS
NEURITIS BL DEFICIENCY	NEURITIS
NEURITIS BULBAR	NEURITIS
NEURITIS CRANIAL	NEURITIS
NEURITIS MOTOR	NEURITIS
NEURITIS OPTIC	NEURITIS OPTIC
NEURITIS PERIPHERAL	NEURITIS PERIPH
NEURITIS RETROBULBAR	NEURITIS RETROBULBAR
NEURITIS SCIATIC	NEURITIS
NEURITIS SENSORY	NEURITIS
NEUROBLASTOMA	NEOPL
NEUROCIRCULATORY ASTHENIA	NEUROSIS
NEURODERMATITIS	ECZEMA
NEUROFIBROMATOSIS AGGRAVATED	NEUROPATHY
NEUROLEPTIC MALIGNANT SYNDROME	NEUROLEPTIC MAL SYND
NEUROLOGIC CHANGES	NEUROPATHY
NEUROLOGIC COMPLICATION	NEUROPATHY
NEUROLOGIC DISORDER NOS	NEUROPATHY
NEUROLOGIC FINDINGS ABNORMAL (NOS)	NEUROPATHY
NEUROLOGIC REACTION	NEUROPATHY
NEUROLOGIC SYMPTOMS	NEUROPATHY
NEUROMA	NEOPL CNS
NEUROMUSCULAR BLOCK	PARALYSIS FLACCID
NEURONITIS	NEURITIS
NEUROPATHY	NEUROPATHY
NEUROPATHY - (NOS)	NEUROPATHY
NEUROPATHY PERIPHERAL	NEURITIS PERIPH
NEUROSIS	NEUROSIS
NEUROSIS CARDIOVASCULAR	NEUROSIS
NEUROSIS CONVERSION	NEUROSIS
NEUROSIS GI	NEUROSIS
NEUROTIC REACTION	NEUROSIS
NEUROTIC TOXICITY	NEUROPATHY
NEUTROPENIA	LEUKOPENIA
NEUTROPENIA MALIGNANT	AGRANULOCYTOSIS

NEVUS	NEOPL SKIN
NEVUS MELANOTIC	MELANOSIS
NEVUS SPIDER ACQUIRED	VASC DIS
NEVUS SPIDER CONGENITAL	ANOMALY VASCUL
NEVUS VASCULAR	ANOMALY VASCUL
NIGHT SWEAT	SWEAT
NIGHT TERRORS	DREAM ABNORM
NIGHTMARES	DREAM ABNORM
NIPPLE ULCERATION	MASTITIS
NITROGEN NONPROTEIN BLOOD INCREASED	NPN INC
NITROGEN RETENTION	NPN INC
NITROGEN UREA BLOOD INCREASED	BUN INC
NO DRUG EFFECT	NO DRUG EFFECT
NOCTURIA	NOCTURIA
NODULE INJECTION SITE	MASS INJECT SITE
NODULE SKIN	NODULE SKIN
NODULE SUBCUTANEOUS	NODULE SUBCUTAN
NOMA	ULCER MOUTH
NONPROTEIN NITROGEN BLOOD ELEVATED	NPN INC
NONSPECIFIC REACTION	REACT UNEVAL
NOREPINEPHRINE ELEVATED SERUM	ALTERED NEUROTR LEVEL
NOSE CONGESTION	RHINITIS
NOSE DRYNESS	RHINITIS
NOSE EDEMA	RHINITIS
NOSEBLEED	EPISTAXIS
NPN INCREASED	NPN INC
NUMBNESS	PARESTHESIA
NUMBNESS CIRCUMORAL	PARESTH CIRCUMORAL
NUMBNESS IN BACK OF HEAD	HYPESTHESIA
NUMBNESS LOCALIZED	HYPESTHESIA
NUMBNESS PERIORAL	PARESTH CIRCUMORAL
NYCTALOPIA	BLIND NIGHT
NYSTAGMUS	NYSTAGMUS
NYSTAGMUS CONGENITAL	NYSTAGMUS
OBESITY	OBESITY
OBSESSIVE REACTION	NEUROSIS
OBSESSIVE-COMPULSIVE REACTION	NEUROSIS
OBSTRUCTION BOWEL	OBSTRUCT INTEST
OBSTRUCTION BRONCHIAL	LUNG DIS
OBSTRUCTION COLON	OBSTRUCT INTEST
OBSTRUCTION DUODENAL	OBSTRUCT INTEST
OBSTRUCTION ESOPHAGUS	STENO ESOPH
OBSTRUCTION GASTRIC	STENO PYLOR
OBSTRUCTION INTESTINAL	OBSTRUCT INTEST
OBSTRUCTION LUNG DISEASE	LUNG DIS
OBSTRUCTION PYLORIC	STENO PYLOR
OBSTRUCTION SMALL INTESTINE	OBSTRUCT INTEST
OBSTRUCTION URETER	HYDRONEPHROSIS
OBSTRUCTION URINARY BLADDER	STENO BLADDER
OBTUNDATION MENTAL	THINKING ABNORM
OCCLUSION CAROTID	OCCLUS CAROTID
OCCLUSION CORONARY ARTERY	OCCLUS CORONARY
OCCLUSION MESENTERIC	OCCLUS MESENTER
OCCLUSION MESENTERIC ARTERY	OCCLUS MESENTER ART
OCCLUSION MESENTERIC VEIN	OCCLUS MESENTER VEN
OCCLUSION RETINAL ARTERY	OCCLUS RETINAL ART
OCCLUSION RETINAL VEIN	THROM RETINAL VEIN

OCULAR HAEMORRHAGE	HEM EYE
OCULAR HEMORRHAGE	HEM EYE
OCULAR TENSION INCREASED	GLAUCOMA
OCULOGYRIC CRISIS	OCULOGYRIC CRISIS
OCULOMOTOR DYSKINESIA	OCULOGYRIC CRISIS
OCULOMOTOR NERVE PARALYSIS	PARALYSIS EXTRAOCUL
OCULOMOTOR PARALYSIS	PARALYSIS EXTRAOCUL
OCULOMOTOR PARESIS	PARALYSIS EXTRAOCUL
OCULOMOTOR SPASM	OCULOGYRIC CRISIS
ODONTOGENESIS IMPAIRED	ANOMALY TOOTH
ODOR BODY	BODY ODOR
ODOR BREATH	HALITOSIS
OEDEMA	EDEMA
OEDEMA CEREBRAL	EDEMA BRAIN
OEDEMA DEPENDENT	EDEMA PERIPH
OEDEMA GENERALISED	EDEMA GENERAL
OEDEMA GENITAL	EDEMA GENITAL
OEDEMA LEGS	EDEMA PERIPH
OEDEMA PERIORBITAL	EDEMA FACE
OEDEMA PERIPHERAL	EDEMA PERIPH
OEDEMA SCROTUM	EDEMA SCROTUM
OESOPHAGEAL ATRESIA	STENO ESOPH
OESOPHAGEAL CARCINOMA	CARCINOMA GI
OESOPHAGEAL PERFORATION	ULCER ESOPH
OESOPHAGEAL STRICTURE	STENO ESOPH
OESOPHAGEAL ULCERATION	ULCER ESOPH
OESOPHAGEAL ULCERATION HAEMORRHAG	ULCER ESOPH
OESOPHAGEAL VARICES	HEM ESOPH
OESOPHAGITIS	ESOPHAGITIS
OESOPHAGOSPASM	CARDIOSPASM
OLIGEMIA	HYPOVOLEM
OLIGOMENORRHEA	HYPOMENORRHEA
OLIGOPHRENIA	MENTAL RETARD
OLIGOSPERMIA	FERTIL DEC MALE
OLIGURIA	OLIGURIA
ONEIRISM	DREAM ABNORM
ONYCHIA	NAIL DIS
ONYCHOLYSIS	NAIL DIS
OOPHORITIS	OVAR DIS
OPACITY CORNEAL	CORNEAL OPACITY
OPACITY LENTICULAR	CATARACT
OPHTHALMIA NEONATORUM	OPHTHALMITIS
OPHTHALMITIS	OPHTHALMITIS
OPHTHALMOPLEGIA (NOS)	OPHTHALMOPLEGIA
OPHTHALMOPLEGIA EXTERNA	ACCOMMODATION ABNORM
OPHTHALMOPLEGIA INTERNA	PARALYSIS EXTRAOCUL
OPISTHOTONOS	OPISTHOTONOS
OPPRESSION	DEPRESSION
OPTIC ATROPHY	ATROPHY OPTIC
OPTIC DISC PALLOR EXCESSIVE	ATROPHY OPTIC
OPTIC DISCS BLURRED	PAPILLEDEMA
OPTIC NEURITIS	NEURITIS OPTIC
OPTIC PAPILLITIS	NEURITIS OPTIC
ORAL DRYNESS	DRY MOUTH
ORAL HAEMORRHAGE	HEM
ORAL HEMORRHAGE	HEM
ORAL MUCOSAL ERUPTION	STOMATITIS

ORAL NEOPLASM BENIGN	NEOPL MOUTH
ORAL ULCERATION	STOMATITIS ULCER
ORCHITIS	ORCHITIS
ORTHOPNEA	DYSPNEA
ORTHOSTATIC DIZZINESS	HYPOTENS POST
ORTHOSTATIC HYPOTENSION	HYPOTENS POST
OSTEOLYSIS	OSTEOMALACIA
OSTEOMALACIA	OSTEOMALACIA
OSTEOMYELITIS	OSTEOMYELITIS
OSTEONECROSIS	NECRO BONE
OSTEOPATHY	BONE DIS
OSTEOPOROSIS	OSTEOPOROSIS
OSTEOPOROSIS WITH FRACTURE	OSTEOPOROSIS FRACT
OSTEOSCLEROSIS	OSTEOSCLEROSIS
OSTEOSIS	BONE DIS
OTITIS EXTERNA	OTITIS EXT
OTITIS MEDIA	OTITIS MED
OTOSALPINGITIS	EAR DIS
OTOSCLEROSIS	EAR DIS
OTOTOXICITY	EAR DIS
OVALOCYTOSIS	RBC ABNORM
OVARIAN CANCER	CARCINOMA OVAR
OVARIAN CYST	CYST
OVARIAN CYST MALIGNANT	CARCINOMA
OVARIAN DISORDER	OVAR DIS
OVARIAN NEOPLASIA	CARCINOMA OVAR
OVARY ENLARGED	OVAR DIS
OVERDOSE	OVERDOSE
OVERDOSE ACCIDENTAL	OVERDOSE ACCID
OVERDOSE EFFECT	OVERDOSE
OVERDOSE INTENTIONAL	OVERDOSE INTENT
OVERGROWTH BACTERIAL	BACT RESIST
OVERHYDRATION	WATER INTOX
OVERSEDATION	SOMNOLENCE
OVERTRANQUILAZATION	SOMNOLENCE
OVULATION DELAYED	OVULAT FAIL
OVULATION FAILURE	OVULAT FAIL
OVULATION INHIBITED	OVULAT FAIL
OXYCORTICOSTEROIDS INCREASED	GLUCOCORT INC
OXYSTEROID ACTIVITY INCREASED	GLUCOCORT INC
OZENA	RHINITIS ATROPH
PAC	EXTRASYSTOLES SUPVENT
PAIN	PAIN
PAIN ABDOMINAL	PAIN ABDO
PAIN ANKLE	PAIN
PAIN BACK	PAIN BACK
PAIN BILIARY	PAIN BIL
PAIN BLADDER	PAIN
PAIN BONE	PAIN BONE
PAIN BREAST	PAIN BREAST
PAIN CHEST	PAIN CHEST
PAIN CHEST SUBSTERNAL	PAIN CHEST SUBSTERN
PAIN DORSAL	PAIN BACK
PAIN EAR	PAIN EAR
PAIN EPIGASTRIC	PAIN ABDO
PAIN ESOPHAGEAL	ESOPHAGITIS
PAIN EYE	PAIN EYE

PAIN FLANK	PAIN FLANK
PAIN FOOT	PAIN
PAIN GAS	PAIN ABDO
PAIN GASTRIC	PAIN ABDO
PAIN GROIN	PAIN PELVIC
PAIN GUM	GINGIVITIS
PAIN HEAD	HEADACHE
PAIN HUNGER	PAIN ABDO
PAIN INJECTION SITE	PAIN INJECT SITE
PAIN JAW	PAIN
PAIN JOINT	ARTHRALGIA
PAIN KIDNEY	PAIN KIDNEY
PAIN KNEE	PAIN
PAIN LOIN	PAIN BACK
PAIN LUMBOSACRAL	PAIN BACK
PAIN MENSTRUAL	DYSMENORRHEA
PAIN MOUTH	STOMATITIS
PAIN MUSCLE	MYALGIA
PAIN NECK	PAIN NECK
PAIN NERVE	NEURALGIA
PAIN ON LOWER THIGH	PAIN
PAIN OVARIAN	PAIN
PAIN PELVIC	PAIN PELVIC
PAIN PEPTIC ULCER	PEPTIC ULCER SYND
PAIN PHARYNX	PHARYNGITIS
PAIN PLEURAL	PAIN
PAIN PRECORDIAL	PAIN CHEST SUBSTERN
PAIN PROSTATIC	PAIN
PAIN RECTAL	PAIN
PAIN RETROSTERNAL	PAIN CHEST SUBSTERN
PAIN RIGHT UPPER QUANDRANT	PAIN ABDO
PAIN SACROILIAC	PAIN BACK
PAIN STOMACH	PAIN ABDO
PAIN SUBSTERNAL	PAIN CHEST SUBSTERN
PAIN THROAT	PHARYNGITIS
PAIN THYROID	PAIN
PAIN TONGUE	GLOSSITIS
PAIN URETHRAL	PAIN URETHRA
PAIN-LEFT SIDE	PAIN
PAINFUL SENSITIVENESS TO SOUND	HYPERACUSIS
PAINFUL URINATION	DYSURIA
PALATE AND LIP CLEFT	CLEFT PALATE
PALATE CLEFT	CLEFT PALATE
PALLOR	PALLOR
PALPITATION	PALPITAT
PALSY	PARALYSIS
PALSY BELLS	PARALYSIS FACIAL
PALSY CEREBRAL	ANOMALY CONGEN CNS
PALSY EXTRAOCULAR	PARALYSIS EXTRAOCUL
PALSY PERONEAL	FOOT DROP
PALSY RADIAL	WRIST DROP
PALSY SHAKING	EXTRAPYR SYND
PANAGIITIS	VASCULITIS
PANARTERITIS	ARTERITIS
PANCARDITIS	PANCARDITIS
PANCREAS NEOPLASM MALIGNANT	CARCINOMA GI
PANCREATIC DISORDER	PANCREAS DIS

PANCREATIC INSUFFICIENCY	PANCREAS DIS
PANCREATITIS	PANCREATITIS
PANCREATITIS ACUTE	PANCREATITIS
PANCREATITIS CHRONIC	PANCREATITIS
PANCREATITIS HEMORRHAGIC	PANCREATITIS HEM
PANCREATITIS NECROTIZING	PANCREATITIS NECRO
PANCREATITIS RELAPSING	PANCREATITIS
PANCYTOPENIA	PANCYTOPENIA
PANHYPOPITUITARISM FOETAL	PIT ACTIV DEC
PANIC REACTION	AGITATION
PANMYELOPHTHISIS	PANCYTOPENIA
PANMYELOSIS	MARROW HYPERPLASIA
PANNICULITIS	CELLULITIS
PANOPHTHALMITIS	OPHTHALMITIS
PAPANICOLAU SMEAR POSITIVE	PAP SMEAR SUSP
PAPANICOLAU SMEAR SUSPICIOUS	PAP SMEAR SUSP
PAPILLARY NECROSIS RENAL	NECRO KIDNEY PAPILL
PAPILLEDEMA	PAPILLEDEMA
PAPILLITIS OPTIC	NEURITIS OPTIC
PAPILLITIS RENAL NECROTIZING	NECRO KIDNEY PAPILL
PAPILLOEDEMA	PAPILLEDEMA
PAPILLOMA SKIN	NEOPL SKIN
PAPULAR RASH	RASH MAC PAP
PAPULOSQUAMOUS RASH	RASH MAC PAP
PAPULOVESICULAR RASH	RASH VESIC BULL
PARADOXICAL PRESSOR RESPONSE	HYPERTENS
PARAESTHESIA	PARESTHESIA
PARAGEUSIA	TASTE PERVERS
PARALYSIS	PARALYSIS
PARALYSIS AGITANS	EXTRAPYR SYND
PARALYSIS BULBAR	PARALYSIS
PARALYSIS CILIARY MUSCLE	ACCOMMODATION ABNORM
PARALYSIS EXTRAOCULAR MUSCLE (S)	PARALYSIS EXTRAOCUL
PARALYSIS FACIAL	PARALYSIS FACIAL
PARALYSIS FLACCID	PARALYSIS FLACCID
PARALYSIS FLACCID CONGENITAL	ANOMALY CONGEN
PARALYSIS GASTRIC	STOMACH ATONY
PARALYSIS LOWER MOTOR NEURON TYPE	PARALYSIS FLACCID
PARALYSIS MUSCLE GENERAL SKELETAL	PARALYSIS
PARALYSIS MUSCLE LOCAL SKELETAL	PARALYSIS
PARALYSIS OCULOMOTOR	PARALYSIS EXTRAOCUL
PARALYSIS ONE SIDE OF BODY	HEMIPLEGIA
PARALYSIS PERONEAL	FOOT DROP
PARALYSIS RADIAL	WRIST DROP
PARALYSIS RECURRENT LARYNGEAL NERVE	PARALYSIS VOCAL CORD
PARALYSIS SKELETAL MUSCLE	PARALYSIS
PARALYSIS SPASTIC	PARALYSIS SPASTIC
PARALYSIS SPASTIC CONGENITAL	PARALYSIS SPASTIC
PARALYSIS URINARY BLADDER	URIN RETENT
PARALYSIS VOCAL CORD	PARALYSIS VOCAL CORD
PARAMETRITIS	SALPINGITIS
PARANOIA	PARANOID REACT
PARANOID PSYCHOSIS	PARANOID REACT
PARANOID REACTION	PARANOID REACT
PARAPLEGIA	PARAPLEGIA
PARASYMPATHOMIMETIC SYNDROME	CHOLINERG SYND
PARATHYOID DISORDER	PARATHYR DIS

PARATHYROID DYSFUNCTIUON	PARATHYR DIS
PARESIS	PARALYSIS
PARESTHESIA	PARESTHESIA
PARESTHESIA CIRCUMORAL	PARESTH CIRCUMORAL
PARESTHESIA DISTAL	PARESTHESIA
PARESTHESIA MOUTH	PARESTH CIRCUMORAL
PARESTHESIA MUCOSAL	PARESTHESIA
PARESTHESIA SKIN	PARESTHESIA
PARKINSON'S SYNDROME	EXTRAPYR SYND
PARKINSONISM	EXTRAPYR SYND
PARKINSONISM AGGRAVATED	EXTRAPYR SYND
PARLAYSIS ILEUM	ILEUS
PARONIRIA	DREAM ABNORM
PARONYCHIA	NAIL DIS
PAROSMIA	PAROSMIA
PAROTID ENLARGEMENT	PAROTID ENLARGE
PAROTID GLAND ENLARGEMENT OF	PAROTID ENLARGE
PAROTITIS	SIALADENITIS
PAROXYSMAL ATRIAL TACHYCARDIA	TACHYCARDIA SUPVENT
PAROXYSMAL TACHYCARDIA (NOS)	TACHYCARDIA
PAROXYSMAL VENTRICULAR TACHYCARDIA	TACHYCARDIA VENT
PARTIAL THROMBOPLASTIN TIME PROLONGED	THROMBOPLASTIN DEC
PASSED OUT	SYNCOPE
PAT	TACHYCARDIA SUPVENT
PATENT DUCTUS ARTERIOSUS	DUCT ART PAT
PBI DECREASED	PBI DEC
PBI INCREASED	PBI INC
PEDALING	HYPERKINESIA
PEELING	DERM EXFOL
PEELY SKIN	DERM EXFOL
PEFORATION BOWEL	INTEST PER
PELIOSIS HEPATITIS	HEPATITIS
PELVIC INFLAMMATION	SALPINGITIS
PELVIC INFLAMMATORY DISEASE	SALPINGITIS
PEMPHIGOID PEMPHIGUS	RASH VESIC BULL
PEMPHIGOID REACTION	RASH VESIC BULL
PENIS DISORDER	PENIS DIS
PENIS INFLAMMATION	BALANITIS
PEPTIC ULCER	ULCER PEPTIC
PEPTIC ULCER AGGRAVATED	ULCER PEPTIC
PEPTIC ULCER HAEMORRHAGIC	ULCER PEPTIC HEM
PEPTIC ULCER HAEMPER	ULCER PEPTIC PERHEM
PEPTIC ULCER HEMORRHAGIC	ULCER PEPTIC HEM
PEPTIC ULCER PAIN	PEPTIC ULCER SYND
PEPTIC ULCER PERFORATED	ULCER PEPTIC PER
PEPTIC ULCER PERFORATION AND HEMORRHAGE	ULCER PEPTIC PERHEM
PEPTIC ULCER REACTIVATED	ULCER PEPTIC REACT
PEPTIC ULCER SYNDROME	PEPTIC ULCER SYND
PERFORATION AND GASTRIC ULCER AND HEMORRHAGE	ULCER STOMACH PERHEM
PERFORATION COLON	INTEST LARGE PER
PERFORATION CORNEAL	PER CORNEAL
PERFORATION DUODENAL	ULCER DUODEN PER
PERFORATION ESOPHAGUS	ULCER ESOPH
PERFORATION GASTROINTESTINAL	GI PER
PERFORATION ILEAL	INTEST SMALL PER
PERFORATION INTESTINAL	INTEST PER
PERFORATION JEJUNAL	INTEST SMALL PER

PERFORATION LARGE INTESTINE	INTEST LARGE PER
PERFORATION NASAL SEPTUM	NASAL SEPTUM DIS
PERFORATION SMALL INTESTINE	INTEST SMALL PER
PERFORATION STOMACH	ULCER STOMACH PER
PERFORATION UTERINE	UTER RUPT
PERICARDIAL EFFUSION	EFFUS PERICARD
PERICARDITIS	PERICARDITIS
PERINATAL DISORDER	PERINATAL DIS
PERINEAL PAIN FEMALE	PAIN PELVIC
PERINEAL PAIN MALE	PAIN PELVIC
PERIODONTITIS	PYORRHEA
PERIORAL NUMBNESS	PARESTH CIRCUMORAL
PERIOSTEAL DISORDER	PERIOST DIS
PERIOSTEITIS	PERIOST DIS
PERIOSTITIS	PERIOST DIS
PERIOSTITIS HYPERTROPHIC	PERIOST DIS
PERIPHERAL COLDNESS	VASC DIS PERIPH
PERIPHERAL GANGRENE	GANGRENE PERIPH
PERIPHERAL ISCHAEMIA	VASC DIS PERIPH
PERIPHERAL ISCHEMIA	VASC DIS PERIPH
PERIPHERAL NEURITIS	NEURITIS PERIPH
PERIPHERAL VASCULAR DISEASE	VASC DIS PERIPH
PERIPHERAL VASCULAR DISORDER	VASC DIS PERIPH
PERIPHERAL VISION DEFECTIVE	VISUAL FIELD DEFECT
PERIPORTAL SINUS DILATATION	LIVER DAMAGE
PERITONEAL EFFUSION BLOODY	HEMOPERITON
PERITONEAL HEMORRHAGE	HEMOPERITON
PERITONITIS	PERITONITIS
PERITONITIS SCLEROSING	FIBRO RETROPERIT
PERMEABILITY CAPILLARY INCREASED	CAPILL FRAGIL INC
PERSONAL APPEARANCE NEGLECT OF	PERSON DIS
PERSONAL IRRESPONSIBILITY	PERSON DIS
PERSONALITY DISORDER	PERSON DIS
PERSONALITY UNSTABLE	EMOTION LABIL
PERSPIRATION EXCESSIVE	SWEAT
PERVERSION OLFACTORY	PAROSMIA
PETECHIA	PETECHIA
PETIT MAL	CONVULS
PETIT MAL CONVULSION	CONVULS
PEYRONIES DISEASE	PENIS DIS
PH REDUCED	ACIDOSIS
PHAEOCHROMOCYTOMA	NEOPL
PHANEROSIS FATTY LIVER	LIVER FATTY
PHANTOM PREGNANCY	ABDO ENLARGE
PHARYNGITIS	PHARYNGITIS
PHARYNX DRY	DRY MOUTH
PHARYNX NEOPLASM MALIGNANT	NEOPL
PHENYLKETONURIA	PHENYLKETONURIA
PHENYLKETOURIA	PHENYLKETONURIA
PHEOCHROMOCYTOMA	NEOPL
PHLEBITIS	PHLEB
PHLEBITIS ALONE	PHLEB
PHLEBITIS DEEP	PHLEB DEEP
PHLEBITIS INJECTION SITE	PHLEB
PHLEBITIS SUPERFICIAL	PHLEB
PHLEBOTHROMBOSIS	THROMBOPHLEB
PHOBIA	NEUROSIS

PHOCOMELIA	ECTROMELIA
PHOSPHATASE ACID INCREASED	PHOSPHATASE ACID INC
PHOSPHATASE ALKALINE INCREASED	PHOSPHATASE ALK INC
PHOSPHOKINASE CREATINE SERUM INCREASED	CREATINE PK INC
PHOTOONYCHOLYSIS	NAIL DIS
PHOTOPHOBIA	PHOTOPHOBIA
PHOTOPSIA	VISION ABNORM
PHOTOSENSITIVITY (NOS)	PHOTOSENSITIVITY
PHOTOSENSITIVITY ALLERGIC REACT	PHOTOSENSITIVITY
PHOTOSENSITIVITY REACTION	PHOTOSENSITIVITY
PHOTOSENSITIVITY REACTION (NOS)	PHOTOSENSITIVITY
PHOTOSENSITIVITY TOXIC REACTION	PHOTOSENSITIVITY
PICA	NEUROSIS
PIGMENTATION ABNORMAL	SKIN DISCOLOR
PIGMENTATION LENTICULAR	LENS PIGMENT
PIGMENTATION RETINAL	RETINAL PIGMENT
PIGMENTATION SKIN	SKIN DISCOLOR
PILL HANGOVER	HANGOVER
PILOERECTION	HAIR DIS
PILONIDAL CYST	ANOMALY CONGEN
PIMPLES	ACNE
PITHIATISM	PERSON DIS
PITUITARY ACTIVITY DECREASED	PIT ACTIV DEC
PITUITARY ACTIVITY INCREASED	PIT ACTIV INC
PITUITARY INSUFFICIENCY	PIT ACTIV DEC
PITUITARY NEOPLASM BENIGN	NEOPL
PITYRIASIS ROSEA	RASH MAC PAP
PLACENTAL DISORDER	PLACENTA DIS
PLANTAR RESPONSE EXTENSOR	BABINSKI SIGN POS
PLAQUE MOUTH	LEUKOPLAKIA ORAL
PLASMA OSMALARITY INCREASED	DEHYDRAT
PLASMA OSMOLALITY INCREASED	DEHYDRAT
PLASMACYTOSIS	PLASMACYTO
PLASMIN INCREASED	FIBRINOLYSIS INC
PLASMINOGEN ACTIVITY INCREASED	FIBRINOLYSIS INC
PLATELET ADHESIVENESS DECREASED	PLAT ADHESIVE DEC
PLATELET ADHESIVENESS INCREASED	PLAT ADHESIVE INC
PLATELET AGGREGATION INCREASED	PLAT ABNORM
PLATELET CHANGES	PLAT ABNORM
PLATELET DESTRUCTION INCREASED	THROMBOCYTOPENIA
PLATELET DISORDER	PLAT ABNORM
PLATELET PRODUCTION DECREASED	THROMBOCYTOPENIA
PLATELETS ABNORMAL	PLAT ABNORM
PLATELETS DECREASED	THROMBOCYTOPENIA
PLATELETS INCREASED	THROMBOCYTHEM
PLATHPNEA	DYSPNEA
PLEOCYTOSIS	PLEOCYTOSIS
PLEURAL EFFUSION	EFFUS PLEURAL
PLEURAL FIBROSIS	PLEURAL DIS
PLEURAL MESOTHELIOMA	ANOMALY CONGEN RESP
PLEURAL PAIN	PAIN
PLEURISY	PLEURAL DIS
PLEURODYNIA	PAIN
PLUEROTHOTONUS	ATAXIA CEREBELL
PNC	EXTRASYSTOLES SUPVENT
PNEUMOCONIOSIS	FIBRO LUNG
PNEUMONIA	PNEUMONIA

PNEUMONIA EOSINOPHILIC	PNEUMONIA EOSINOPHIL
PNEUMONIA LOBAR	PNEUMONIA
PNEUMONITIS	PNEUMONIA
PNEUMOTHORAX	PNEUMOTHORAX
PODAGRA	GOUT
POLAND'S SYNDROME	ANOMALY CONGEN MS
POLIO-LIKE PARALYSIS	PARALYSIS FLACCID
POLIOENCEPHALITIS	ENCEPHALITIS
POLIOMYELITIS	INFECT
POLYARTERITIS NODOSA	POLYARTERITIS NODOSA
POLYARTHRALGIA	ARTHRALGIA
POLYARTHRITIS	ARTHRITIS
POLYARTHRITIS GENERALIZED	ARTHRITIS
POLYCYSTIC DISEASE PANCREAS	PANCREAS DIS
POLYCYTHAEMIA	POLYCYTHEMIA
POLYDACTYLY	ANOMALY CONGEN MS
POLYDYPSIA	THIRST
POLYGLANDULAR DISORDER	ENDO DIS
POLYLOGIA	PERSON DIS
POLYMYALGIA RHEUMATICA	MYALGIA
POLYMYOSITIS	MYOSITIS
POLYNEURITIS	POLYNEURITIS
POLYNEUROPATHY	NEUROPATHY
POLYPHAGIA	APPETITE INC
POLYPS	NEOPL
POLYPS NASAL	NEOPL
POLYSEROSITIS	POLYSEROSITIS
POLYURIA	POLYURIA
PORENCEPHALY	PORENCEPHALY
PORPHYRIA	PORPHYRIA
PORPHYRINURIA	PORPHYRINURIA
PORT WINE STAIN	ANOMALY VASCUL
POSTHITIS	PENIS DIS
POSTMATURITY SYNDROME	BIRTH POSTMAT
POSTNASAL DRIP	RHINITIS
POSTURAL HYPOTENSION	HYPOTENS POST
POTASSIUM DEFICIENCY	HYPOKALEM
POTASSIUM RETENTION	HYPERKALEM
POTASSIUM SERUM DECREASED	HYPOKALEM
POTASSIUM SERUM INCREASED	HYPERKALEM
POVERTY EMOTIONAL	APATHY
PR INTERVAL PROLONGED	PR PROLONGED
PR INTERVAL SHORTENED	PR SHORTENED
PREGNANCY ECTOPIC	PREGN DIS
PREGNANCY FALSE	ABDO ENLARGE
PREGNANCY MULTIPLE	PREGN MULT
PREGNANCY PHANTOM	ABDO ENLARGE
PREGNANCY SPURIOUS	ABDO ENLARGE
PREGNANCY TEST FALSE POSITIVE	PREGN TEST FALSE POS
PREGNANCY UNINTENDED	PREGN UNINTEND
PREMATURE LABOR	LABOR ABNORM
PREMATURE VENTRICULAR CONTRACTIONS	EXTRASYSTOLES VENT
PREMATURITY	BIRTH PREMAT
PREMATURITY SYNDROME	BIRTH PREMAT
PREMENSTRUAL SYNDROME	MENS DIS
PRESBYOPIA	REFRACT DIS
PRESSOR RESPONSE PARADOXICAL	HYPERTENS

PRESSURE	PAIN
PRESSURE ARTERIAL DECREASED	HYPOTENS
PRESSURE BLOOD INCREASED	HYPERTENS
PRESSURE CENTRAL VENOUS INCREASED	VEN PRESS INC
PRESSURE CEREBROSPINAL FLUID INCREASED	INTRACRAN HYPERTENS
PRESSURE CHEST	PAIN CHEST
PRESSURE FEET	PAIN
PRESSURE INTRACRANIAL INCREASED	INTRACRAN HYPERTENS
PRESSURE INTRAOCULAR INCREASED	GLAUCOMA
PRESSURE VENOUS INCREASED	VEN PRESS INC
PRESYNCOPE	DIZZINESS
PRIAPISM	PRIAPISM
PROCTALGIA	RECTAL DIS
PROCTITIS	PROCTITIS
PROCTITIS MONILIAL	MONILIA GI
PROCTITIS ULCERATIVE	PROCTITIS ULCER
PROGERIA	GROWTH ACCELER
PROLACTIN INCREASED	PROLACTIN INC
PROPTOSIS	EXOPHTHALMOS
PROSTATIC DISORDER	PROSTAT DIS
PROSTATIC SPECIFIC ANTIGEN DECREASE	PSA DEC
PROSTATIC SPECIFIC ANTIGEN INCREASE	PSA INC
PROSTRATION	ASTHENIA
PROTEIN BOUND IODINE SERUM DECREASED	PBI DEC
PROTEIN BOUND IODINE SERUM INCREASED	PBI INC
PROTEINS BENCE JONES PRESENT	GLOBULIN INC BJ
PROTEINS SERUM PLASMA LOW	HYPOPROTEINEM
PROTEINURIA	ALBUMINURIA
PROTHROMBIN DECREASED	PROTHROMBIN DEC
PROTHROMBIN INCREASED	PROTHROMBIN INC
PROTHROMBIN TIME INC	PROTHROMBIN DEC
PROTRUSION TONGUE	BUCCOGLOSSAL SYND
PRURITIC RASH	RASH
PRURITUS	PRURITUS
PRURITUS ANI	RECTAL DIS
PRURITUS GENITAL	PRURITUS
PSEUDO LYMPHOMA	LYMPHOMA LIKE REACT
PSEUDO MONONUCLEOSIS	LYMPHOCYTOSIS
PSEUDOCYESIS	ABDO ENLARGE
PSEUDOHERMAPHRODITISM	VIRILISM
PSEUDOLYMPHOMA	LYMPHOMA LIKE REACT
PSEUDONEOPLASM ABDOMINAL	ABDO ENLARGE
PSEUDOPARKINSONISM	EXTRAPYR SYND
PSEUDOTUMOR CEREBRI	INTRACRAN HYPERTENS
PSORIASIS AGGRAVATED	PSORIASIS
PSP EXCRETION DECREASED	PSP DEC
PSYCHIC DISORDER	PERSON DIS
PSYCHIC DISTURBANCE	PERSON DIS
PSYCHOMOTOR DEVELOPMENT IMPAIRED	MENTAL RETARD
PSYCHOMOTOR EPILEPSY	CONVULS
PSYCHOMOTOR HYPERACTIVITY	HYPERKINESIA
PSYCHOMOTOR RESTLESSNESS	HYPERKINESIA
PSYCHONEUROSIS	NEUROSIS
PSYCHOPHYSIOLOGIC REACTION	NEUROSIS
PSYCHOSIS	PSYCHOSIS
PSYCHOSIS DEPRESSIVE	DEPRESSION PSYCHOTIC
PSYCHOSIS MANIC	MANIC REACT

PSYCHOSIS MANIC-DEPRESSIVE	MANIC DEPRESS REACT
PSYCHOSIS PARANOID	PARANOID REACT
PT PROLONGED	PROTHROMBIN DEC
PTOSIS	PTOSIS
PTT PROLONGED	THROMBOPLASTIN DEC
PTYALISM	SALIVA INC
PUBERTY PRECOCIOUS	SEX MAT ACCEL
PUFFINESS FACE	EDEMA FACE
PULMONARY ARREST	APNEA
PULMONARY CARCINOMA	CARCINOMA LUNG
PULMONARY COLLAPSE	ATELECTASIS
PULMONARY CONGESTION	LUNG DIS
PULMONARY DISORDER	LUNG DIS
PULMONARY EDEMA	EDEMA LUNG
PULMONARY EDEMA CARDIAC CAUSE	HEART FAIL LEFT
PULMONARY FIBROSIS	FIBRO LUNG
PULMONARY GRANULOMA	GRANULOMA
PULMONARY HAEMORRHAGE	HEM LUNG
PULMONARY HEMORRHAGE	HEM LUNG
PULMONARY INFARCTION	INFARCT PULM
PULMONARY INFILTRATION	RESPIRAT DIS
PULMONARY MALFORMATION	ANOMALY CONGEN RESP
PULMONARY MYCOSIS	PULM MYCOSIS
PULMONARY OEDEMA	EDEMA LUNG
PULMONARY SCLEROSIS	FIBRO LUNG
PULMONARY TUBERCULOSIS AGGRAVATED	PULM TUBERCUL AGGRAV
PULMONARY TUBERCULOSIS REACTIVATED	PULM TUBERCUL REACT
PULMONIC STENOSIS CONGENITAL	ANOMALY VASCUL
PULSE IRREGULARITY NOS	ARRHYTHMIA
PULSE RATE DECREASE	BRADYCARDIA
PULSE RATE INCREASED	TACHYCARDIA
PULSUS BIGEMINUS	EXTRASYSTOLES BIGEM
PUPILLARY REFLEX IMPAIRED	PUPIL DIS
PUPILS CONSTRICTED	MIOSIS
PUPILS DILATED	MYDRIASIS
PUPILS PINPOINT	MIOSIS
PURPURA	PURPURA
PURPURA ALLERGIC	PURPURA
PURPURA FULMINANS	PURPURA FULMINANS
PURPURA NEONATAL	PURPURA
PURPURA THROMBOCYTOPENIC	PURPURA THROMBOPEN
PURPURA THROMBOPENIC THROMBOTIC	PURPURA THROMBOPEN TH
PVC'S	EXTRASYSTOLES VENT
PYELONEPHRITIS	PYELONEPHRITIS
PYELONEPHRITIS ACUTE NECROTIZING	NECRO KIDNEY PAPILL
PYEMIA	SEPSIS
PYLORIC STENOSIS	STENO PYLOR
PYLOROSPASM	DYSPEPSIA
PYLORUS HYPERTROPHIC CONGENITAL	STENO PYLOR
PYODERMA (SKIN INFECTION)	INFECT
PYODERMA GANGRENOSUM	NECRO SKIN
PYODERMA GANGRENOUS	NECRO SKIN
PYORRHEA	PYORRHEA
PYRAMIDAL TRACT LESION	NEUROPATHY
PYREXIA	FEVER
PYROMANIA	INJURY INTENT
PYROSIS	DYSPEPSIA

PYURIA	PYURIA
QRS INCREASED IN TIME	BUNDLE BRANCH BLOCK
QRS TIME PROLONGED	BUNDLE BRANCH BLOCK
QRS WIDENED	BUNDLE BRANCH BLOCK
QT INCREASED	QT PROLONGED
QT INTERVAL SHORTENED	QT SHORTENED
QUADRIPLEGIA	QUADRIPLEGIA
QUEASY	NAUSEA
QUINCKE'S EDEMA	ANGIOEDEMA
QUININE INTOXICATION	CINCHONISM
RADIATION INJURY	RADIAT INJ
RAGE	HOSTILITY
RALES	LUNG DIS
RASH	RASH
RASH ACNEFORM	ACNE
RASH BULLOUS	RASH VESIC BULL
RASH DESQUAMATING	DERM EXFOL
RASH ECCHYMOTIC	RASH PURPUR
RASH ERYTHEMATOUS	RASH
RASH FOLLICULAR	ACNE
RASH HEMORRHAGIC	RASH PURPUR
RASH HERPETIFORM	RASH VESIC BULL
RASH IMPETIGINOUS	RASH PUST
RASH INJECTION SITE	HYSN INJECT SITE
RASH LUPUS-LIKE	RASH LE
RASH MACULAR	RASH MAC PAP
RASH MACULO-PAPULAR	RASH MAC PAP
RASH MORBILLIFORM	RASH MAC PAP
RASH NEONATAL	RASH
RASH PAPULAR	RASH MAC PAP
RASH PAPULOSQUAMOUS	RASH MAC PAP
RASH PAPULOVESICULAR	RASH VESIC BULL
RASH PEMPHIGOID	RASH VESIC BULL
RASH PETECHIAL	RASH PETECH
RASH PHOTOSENSITIVITY	PHOTOSENSITIVITY
RASH PSORIAFORM	PSORIASIS
RASH PURPITIC	RASH VESIC BULL
RASH PURPURIC	RASH PURPUR
RASH PUSTULAR	RASH PUST
RASH SCALY	RASH
RASH SCARLATINIFORM	RASH MAC PAP
RASH SEBORRHEIC	SEBORRHEA
RASH URTICARIAL	URTICARIA
RASH VARICELLIFORM	RASH VESIC BULL
RASH VESICULAR	RASH VESIC BULL
RASH VESICULOBULLOUS	RASH VESIC BULL
RASH VESICULOPUSTULAR	RASH VESIC BULL
RAYNAUD-LIKE DISORDER	VASC DIS PERIPH
RAYNAUD-LIKE PHENOMENA	VASC DIS PERIPH
RBC ABNORMAL (NOS)	RBC ABNORM
RBC DECREASED	ANEMIA
RBC SEDIMENTATION INCREASED	ESR INC
RBC URINE	HEMATURIA
REACTION AGGRAVATION	REACT AGGRAV
REACTION ALARM	ANXIETY
REACTION ALLERGIC (NOS)	ALLERG REACT
REACTION ANAPHYLACTIC ANAPHYLACTOID	ANAPHYL

REACTION ANTISOCIAL	ANTISOCIAL REACT
REACTION ANXIETY	ANXIETY
REACTION APPLICATION SITE	APPLICAT SITE REACT
REACTION ASOCIAL	ANTISOCIAL REACT
REACTION BELLIGERENT	HOSTILITY
REACTION CATABOLIC	WEIGHT DEC
REACTION CATATONIC	CATATON REACT
REACTION COMBATIVE	HOSTILITY
REACTION CONVERSION	HYSTERIA
REACTION DISSOCIATIVE	DEPERSONAL
REACTION ECZEMATOUS	ECZEMA
REACTION EMOTIONAL	EMOTION LABIL
REACTION FEBRILE	FEVER
REACTION GASTROINTESTINAL	GI DIS
REACTION HYPERSENSITIVITY (NOS)	ALLERG REACT
REACTION HYPOGLYCEMIC	HYPOGLYCEM REACT
REACTION INJECTION SITE (NOS)	INJECT SITE REACT
REACTION LEUKEMOID	LEUKEMOID REACT
REACTION LYMPHOMA-LIKE	LYMPHOMA LIKE REACT
REACTION MANIC	MANIC REACT
REACTION MANIC-DEPRESSIVE	MANIC DEPRESS REACT
REACTION MONONUCLEOID	LYMPHOCYTOSIS
REACTION MYASTHENIA GRAVIS-LIKE	MYASTHENIA
REACTION NEONATAL	NEUROSIS
REACTION NEUROTIC	NEUROSIS
REACTION NONSPECIFIC	REACT UNEVAL
REACTION NOT STATED	REACT UNEVAL
REACTION OBSESSIVE-COMPULSIVE	NEUROSIS
REACTION PANIC	AGITATION
REACTION PARANOID	PARANOID REACT
REACTION PERINATAL	PERINATAL DIS
REACTION PHOBIC	NEUROSIS
REACTION PHOTOSENSITIVITY (NOS)	PHOTOSENSITIVITY
REACTION PSYCHOPHYSIOLOGIC	NEUROSIS
REACTION SCHIZOID	SCHIZOPHRENIC REACT
REACTION SCLERODERMA-LIKE	SCLERODERMA
REACTION SERUM SICKNESS-LIKE	SERUM SICK
REACTION SKIN	RASH
REACTION TIME DECREASED	CNS DEPRESS
REACTION UNEVALUABLE	REACT UNEVAL
RECTAL BLEEDING	HEM RECTAL
RECTAL CARCINOMA	CARCINOMA GI
RECTAL DISORDER	RECTAL DIS
RECTAL PAIN	PAIN
RECTAL PRESSURE SEVERE	TENESMUS
REDUCING TEST URINE FALSE POSITIVE	URIN ABNORM
REFLEX CORNEAL DIMINISHED ABSENT	CORNEAL REFLEX DEC
REFLEXES TENDON DECREASED ABSENT	REFLEXES DEC
REFLEXES TENDON INCREASED	REFLEXES INC
REFRACTION DISORDER OF	REFRACT DIS
REGIONAL ILEITIS AGGRAVATED	ILEITIS
REITER'S SYNDROME	SKIN DIS
RELAXED	SOMNOLENCE
REM SLEEP ANBORMAL	SLEEP DIS
RENAL ABSCESS	ABSCESS KIDNEY
RENAL ACIDOSIS TUBULAR	KIDNEY TUBUL DIS
RENAL AGENESIS	ANOMALY CONGEN UG

RENAL CALCULUS	KIDNEY CALCULUS
RENAL CARCINOMA	CARCINOMA
RENAL CLEARANCES LOW	KIDNEY FUNC ABNORM
RENAL COLIC	PAIN KIDNEY
RENAL CONCENTRATING POWER DECR	KIDNEY FUNC ABNORM
RENAL CORTICAL NECROSIS	NECRO KIDNEY CORTEX
RENAL CYST	KIDNEY POLYCYSTIC
RENAL DISORDER	URIN TRACT DIS
RENAL DYSGENESIS	ANOMALY CONGEN UG
RENAL FAILURE	KIDNEY FAIL
RENAL FAILURE ACUTE	KIDNEY FAIL ACUTE
RENAL FAILURE ACUTE HYPOTENSIVE	KIDNEY FAIL ACUTE
RENAL FAILURE ACUTE ISCHEMIC	KIDNEY FAIL ACUTE
RENAL FAILURE CHRONIC	UREMIA
RENAL FUNCTION ABNORMAL	KIDNEY FUNC ABNORM
RENAL FUNCTION ABNORMAL GLOMER	KIDNEY FUNC ABNORM
RENAL FUNCTION TESTS NOS ABNORMAL	KIDNEY FUNC ABNORM
RENAL INSUFFICIENCY	KIDNEY FUNC ABNORM
RENAL INTERSTITIAL FIBROSIS	FIBRO KIDNEY
RENAL NEOPLASIA	NEOPL
RENAL PAIN	PAIN KIDNEY
RENAL PAPILLARY NECROSIS	NECRO KIDNEY PAPILL
RENAL PAPILLITIS NECROTIZING	NECRO KIDNEY PAPILL
RENAL SHUTDOWN ACUTE	KIDNEY FAIL ACUTE
RENAL STONE	KIDNEY CALCULUS
RENAL TUBULAR DISORDER	KIDNEY TUBUL DIS
RENAL TUBULAR NECROSIS	NECRO KIDNEY TUBUL
RENAL VESSEL DISORDER	VASCULITIS KIDNEY
REPETITIVE SPEECH	SPEECH DIS
RES STIMULATED	RE HYPERPLASIA
RESISTANCE BACTERIAL	BACT RESIST
RESISTANCE CAPILLARY DECREASED	CAPILL FRAGIL INC
RESORPTION BONE INCREASED	OSTEOMALACIA
RESP DISTRESS SYNDROME NEONATAL	PERINATAL DIS
RESP GAS EXCHANGE DISORDER NOS	RESPIRAT DIS
RESP TRACT HAEMORRHAGE NEONATAL	HEM LUNG
RESP TRACT HEMORRHAGE NEONATAL	HEM LUNG
RESPIRATION BIOT-TYPE	HYPOVENTIL
RESPIRATION CHEYNE-STOKES-TYPE	HYPOVENTIL
RESPIRATION DEPRESSED	HYPOVENTIL
RESPIRATION FAILURE	APNEA
RESPIRATION LABORED	DYSPNEA
RESPIRATION RATE DECREASED	HYPOVENTIL
RESPIRATION RATE INCREASED	HYPERVENTIL
RESPIRATORY ARREST	APNEA
RESPIRATORY DEPRESSION	HYPOVENTIL
RESPIRATORY DEPRESSION NEONATAL	HYPOVENTIL
RESPIRATORY DISORDER	RESPIRAT DIS
RESPIRATORY DISORDER (NOS)	RESPIRAT DIS
RESPIRATORY DISTRESS	DYSPNEA
RESPIRATORY DISTRESS SYNDROME ADULT	RESPIRAT DISTRES SYND
RESPIRATORY DISTRESS SYNDROME NEWBORN	PERINATAL DIS
RESPIRATORY DYSFUNCTION NOS	RESPIRAT DIS
RESPIRATORY FAILURE	APNEA
RESPIRATORY INSUFFICIENCY	RESPIRAT DIS
RESPIRATORY LESION	RESPIRAT DIS
RESPIRATORY RATE DECREASED	HYPOVENTIL

RESPIRATORY SYSTEM DISORDER OF	RESPIRAT DIS
RESPIRATORY TRACT HAEMORRHAGE	HEM LUNG
RESPIRATORY TRACT HEMORRHAGE	HEM LUNG
RESPIRATORY TRACT MALFORMATION	ANOMALY CONGEN RESP
RESPONSES VOLUNTARY REDUCED	HYPOKINESIA
RESTLESS LEGS	HYPERKINESIA
RESTLESSNESS	NERVOUSNESS
RESTLESSNESS (PHENOTHIAZINE)	AKATHISIA
RESTLESSNESS MARKED	AKATHISIA
RETARDATION MENTAL	MENTAL RETARD
RETCHING	VOMIT
RETENION GASTRIC	PARALYSIS
RETENTION CARBON DIOXIDE	ACIDOSIS RESP
RETENTION ELECTROLYTE BLOOD	EDEMA GENERAL
RETENTION SULFOBROMOPHTHALEIN	BSP ABNORM
RETENTION URINARY	URIN RETENT
RETENTION WATER	EDEMA GENERAL
RETICULOCYTOSIS	RE HYPERPLASIA
RETICULOENDOTHELIAL BLOCKADE	RE BLOCK
RETICULOENDOTHELIAL HYPERPLASIA	RE HYPERPLASIA
RETICULOENDOTHELIOSIS	RE HYPERPLASIA
RETINAL ARTERY OCCLUSION	OCCLUS RETINAL ART
RETINAL DEGENERATION	RETINAL DEGENERAT
RETINAL DEPIGMENTATION	RETINAL DEPIGMENT
RETINAL DEPOSITS	RETINAL DIS
RETINAL DETACHMENT	RETINAL DETACH
RETINAL DISORDER	RETINAL DIS
RETINAL HAEMORRHAGE	HEM RETINAL
RETINAL HEMORRHAGE	HEM RETINAL
RETINAL VASCULAR DISORDER	RETINAL VASC DIS
RETINAL VASCULITIS	RETINAL VASC DIS
RETINAL VEIN OCCLUSION	THROM RETINAL VEIN
RETINAL VEIN THROMBOSIS	THROM RETINAL VEIN
RETINITIS	RETINITIS
RETINITIS PIGMENTOSA	RETINAL PIGMENT
RETINOPATHY	RETINAL DIS
RETRACTION CLOT ACCELERATED	CLOT RETRACT ACCEL
RETRACTION CLOT RETARD	CLOT RETRACT RETARD
RETROBULBAR NEURITIS	NEURITIS RETROBULBAR
RETROPERITONEAL FIBROSIS	FIBRO RETROPERIT
RETROSTERNAL PAIN	PAIN CHEST SUBSTERN
REYE'S SYNDROME	BRAIN SYND ACUTE
REYES SYNDROME	BRAIN SYND ACUTE
RHABDOMYOLYSIS	RHABDO
RHAGADES	CHEILITIS
RHEUMATISM (JOINTS ONLY)	ARTHRITIS RHEUMAT
RHEUMATOID ARTHRITIS	ARTHRITIS RHEUMAT
RHEUMATOID FACTOR	LAB TEST ABNORM
RHINITIS	RHINITIS
RHINITIS ALLERGIC	RHINITIS
RHINITIS ATROPHIC	RHINITIS ATROPH
RHINITIS MEDICAMENTOUS	RHINITIS
RHINITIS ULCERATIVE	RHINITIS
RHINORRHEA	RHINITIS
RHYTHM IDIOVENTRICULAR	AV BLOCK COMP
RHYTHM NODAL	ARRHYTHMIA
RICKETS	BONE DIS

RIGHT UPPER QUADRANT PAIN	PAIN ABDO
RIGIDITY COGWHEEL	COGWHEEL RIGID
RIGIDITY MUSCLE	HYPERTONIA
RIGIDITY NECK	NECK RIGID
RIGOR	CHILLS
RIGORS	CHILLS
RINGING IN EARS	TINNITUS
RISUS SARDONICUS	TRISMUS
ROSACEA	ACNE
ROULEAUX FORMATION	RBC ABNORM
RUNTING	DWARFISM
RUPTURE ACHILES TENDON	TENDON RUPT
RUPTURE SPLEEN	SPLEEN RUPT
RUPTURE TENDON	TENDON RUPT
RUPTURE UTERUS	UTER RUPT
SACRAL EDEMA	EDEMA
SACRO-ILIAC PAIN	PAIN BACK
SALICYLISM	SALICYLISM
SALIVA ALTERED	SALIVA INC
SALIVA DECREASED	DRY MOUTH
SALIVA INCREASED	SALIVA INC
SALIVA VISCID	SALIVA INC
SALIVARY DUCT OBSTRUCTION	SALIV GLAND ENLARGE
SALIVARY GLAND ENLARGEMENT	SALIV GLAND ENLARGE
SALIVARY GLAND PAIN	PAIN
SALPINGITIS	SALPINGITIS
SALT DEFICIENCY	HYPONATREM
SALT DEPLETION	HYPONATREM
SALT INTOXICATION	HYPERNATREM
SALT RETENTION	HYPERNATREM
SARCOIDOSIS	SARCOIDOSIS
SARCOMA	SARCOMA
SARCOMA BONE	SARCOMA BONE
SARCOMA OSTEOGENIC	SARCOMA BONE
SCALP NUMBNESS	HYPESTHESIA
SCAR CORNEAL	CORNEAL OPACITY
SCHIZOPHRENIA	SCHIZOPHRENIC REACT
SCHIZOPHRENIC REACTION	SCHIZOPHRENIC REACT
SCLERITIS	SCLERITIS
SCLERODERMA	SCLERODERMA
SCLERODERMA-LIKE REACTION	SCLERODERMA
SCLEROSIS MULTIPLE	SCLEROSIS MULT
SCOTOMA	VISUAL FIELD DEFECT
SCOTOMA CENTRAL	VISUAL FIELD DEFECT
SCOTOMA PERIPHERAL	VISUAL FIELD DEFECT
SCOTOMA SCINTILLATING	VISION ABNORM
SCRATCH EYE	CORNEAL LESION
SCREAMING SYNDROME	SCREAMING SYND
SCROTAL PAIN	PAIN
SEBACEOUS CYST	CYST
SEBACEOUS GLANDS OVERACTIVITY	SEBORRHEA
SEBORRHEA	SEBORRHEA
SEBORRHOEA	SEBORRHEA
SECRETION GASTRIC ABSENT	ACHLORHYDRIA
SEDATION EXCESSIVE	SOMNOLENCE
SEDIMENDATION RATE ERYTHROCYTES DECREASED	ESR DEC
SEDIMENDATION RATE ERYTHROCYTES INCREASED	ESR INC

SEIZURE	CONVULS
SEIZURE CEREBRAL	CONVULS
SEIZURE GRAND MAL	CONVULS GRAND MAL
SEMEN ABNORMAL	FERTIL DEC MALE
SEMI-COMA	STUPOR
SEMINOMA	CARCINOMA
SENSORIUM DECREASED	STUPOR
SENSORY ABERRATIONS	PARESTHESIA
SENSORY DISTURBANCE	PARESTHESIA
SENSORY HALLUCINATIONS	HALLUCIN
SEPSIS	SEPSIS
SEPSIS NEONATAL	SEPSIS
SEPSIS POSTPARTUM	SEPSIS
SEPSIS SECONDARY	SEPSIS
SEPTAL DEFECT INTERATRIAL	ATR SEPT DEF
SEPTICEMIA	SEPSIS
SEPTUM ATRIAL PATENT	ATR SEPT DEF
SEPTUM INTERVENTRICULAR PATENT	VENT SEPT DEF
SERUM FOLATE TEST ABNORMAL	LAB TEST ABNORM
SERUM GLUTAMIC-OXALOACETIC TA INC	SGOT INC
SERUM GLUTAMIC-PYRUVIC TA INCR	SGPT INC
SERUM IRON DECREASED	ANEMIA HYPOCHROM
SERUM IRON INCREASED	SERUM IRON INC
SERUM PROTEIN DECREASED	HYPOPROTEINEM
SERUM SICKNESS	SERUM SICK
SERUM SICKNESS-LIKE REACTION	SERUM SICK
SETTING FIRES	INJURY INTENT
SEX CHROMOSOME DISORDER	CHROMOSOME ABNORM
SEX INHIBITION	LIBIDO DEC
SEX MATURATION FEMALE ACCELERATED	SEX MAT ACCEL
SEX MATURATION MALE ACCELERATED	SEX MAT ACCEL
SEXUAL DYSFUNCTION	SEX FUNC ABNORM
SGOT INCREASED	SGOT INC
SGPT INCREASED	SGPT INC
SHAKINESS	NERVOUSNESS
SHAKING	TREMOR
SHIVERING	CHILLS
SHOCK	SHOCK
SHOCK ANAPHYLACTIC ANAPHYLACTOID	ANAPHYL
SHOCK CARDIOGENIC	SHOCK
SHOCK CIRCULATORY	SHOCK
SHOCK HYPOGLYCEMIC	HYPOGLYCEM REACT
SHOCK INSULIN	HYPOGLYCEM REACT
SHOCK VASCULAR	SHOCK
SHORT SIGHTEDNESS	REFRACT DIS
SHORT STATURE	GROWTH RETARD
SHORTNESS OF BREATH	DYSPNEA
SHOULDER BLADE PAIN	PAIN BONE
SHOULDER PAIN	PAIN
SHUTDOWN RENAL	ANURIA
SIADH	ADH INAPPROP
SIALADENITIS	SIALADENITIS
SIALOADENITIS	SIALADENITIS
SICCA SYNDROME	SALIV GLAND ENLARGE
SIGN BABINSKI PRESENT	BABINSKI SIGN POS
SIN PIGMENTATION	SKIN DISCOLOR
SINGULTUS	HICCUP

SINKING FEELING	ANXIETY
SINUS ARREST	HEART ARREST
SINUS BRADYCARDIA	BRADYCARDIA SINUS
SINUS CONGESTION	RHINITIS
SINUS HEADACHE	HEADACHE
SINUS TACHYCARDIA	TACHYCARDIA
SINUSITIS	SINUSITIS
SITUS INVERSUS THORIACIC ORGAN	ANOMALY CONGEN
SJOGREN'S SYNDROME	SALIV GLAND ENLARGE
SKELETAL MALFORMATION	ANOMALY CONGEN MS
SKELETAL MUSCLE PARALYSIS	PARALYSIS
SKELETAL PAIN	PAIN
SKIN ATROPHY	ATROPHY SKIN
SKIN CARCINOMA	CARCINOMA SKIN
SKIN COLD CLAMMY	SWEAT
SKIN DEPIGMENTATION	LEUKODERMA
SKIN DISCOLORATION	SKIN DISCOLOR
SKIN DISCOLOURATION	SKIN DISCOLOR
SKIN DISORDER	SKIN DIS
SKIN DISORDER (NOS)	SKIN DIS
SKIN DRY	SKIN DRY
SKIN EXFOLIATION	DERM EXFOL
SKIN FLUSHED	VASODILAT
SKIN GRANULOMA	GRANULOMA SKIN
SKIN GREASY	SEBORRHEA
SKIN HYPEREMIA	VASODILAT
SKIN HYPERPIGMENTATION	SKIN DISCOLOR
SKIN HYPERTROPHY	HYPERTROPHY SKIN
SKIN HYPOPLASIA	SKIN DIS
SKIN IRRITATION	RASH
SKIN NECROSIS	NECRO SKIN
SKIN NEOPLASM MALIGNANT	NEOPL SKIN
SKIN NODULE	NODULE SKIN
SKIN ODOR ABNORMAL	BODY ODOR
SKIN PEELING	DERM EXFOL
SKIN REACTION	RASH
SKIN RED	RASH
SKIN SCALY	SKIN DRY
SKIN SEBORRHEIC	SEBORRHEA
SKIN STRIAE	SKIN STRIAE
SKIN TEST ABNORMAL	SKIN DIS
SKIN TEST REACTION	SKIN DIS
SKIN TUMOR-LIKE CONDITION (NOS)	HYPERTROPHY SKIN
SKIN ULCERATION	ULCER SKIN
SKIN VASODILATING	VASODILAT
SKIN WARM	VASODILAT
SLEEP APNEA	RESPIRAT DIS
SLEEP DECREASED	INSOMNIA
SLEEP DIFFICULT	INSOMNIA
SLEEP DISORDER	SLEEP DIS
SLEEP DISORDER (NOS)	SLEEP DIS
SLEEP DISTURBED	INSOMNIA
SLEEP REM ABNORMAL	SLEEP DIS
SLEEP RESTLESS	INSOMNIA
SLEEP RHYTHM REVERSAL	SLEEP DIS
SLEEP WALKING	SLEEP DIS
SLEEPINESS	SOMNOLENCE

SLEEPLESSNESS	INSOMNIA
SLOUGH INJECTION SITE	NECRO INJECT SITE
SLOUGHING	DERM EXFOL
SLUGGISHNESS	SOMNOLENCE
SLURRED SPEECH	SPEECH DIS
SMALL FOR GESTATIONAL AGE	BIRTH WEIGHT SUBNORM
SMALL INTESTINE GANGRENE	GANGRENE
SMALL INTESTINE OBSTRUCTION	OBSTRUCT INTEST
SMALL INTESTINE ULCER	ULCER INTEST SMALL
SMARTING	PAIN
SMELL ALTERATION	PAROSMIA
SMELL CHANGE	PAROSMIA
SMELL LOSS	PAROSMIA
SMELL PERVERSION	PAROSMIA
SMELLY BODY	BODY ODOR
SMELLY BREATH	HALITOSIS
SNEEZING	RHINITIS
SNEEZING EXCESSIVE	RHINITIS
SOB (SHORTNESS OF BREATH)	DYSPNEA
SOCIAL DEGENERATION	PERSON DIS
SOCIAL IRRESPONSIBILITY	PERSON DIS
SOCIOPATHY	ANTISOCIAL REACT
SODIUM BLOOD DECREASED	HYPONATREM
SODIUM BLOOD INCREASED	HYPERNATREM
SODIUM DEPLETION	HYPONATREM
SODIUM INCREASED	HYPERNATREM
SODIUM REPLETION SERUM	HYPERNATREM
SODIUM RETENTION	HYPERNATREM
SOMNAMBULISM	SLEEP DIS
SOMNOLENCE	SOMNOLENCE
SOMNOLENCE NEONATAL	SOMNOLENCE
SORE ROOF OF MOUTH	STOMATITIS
SORE THROAT	PHARYNGITIS
SORENESS BREAST	PAIN BREAST
SORENESS GUM	GINGIVITIS
SPASM ARTERIAL ARTERIOLAR	ARTERIOSPASM
SPASM BILIARY	PAIN BIL
SPASM BRONCHIAL	ASTHMA
SPASM CARPOPEDAL	TETANY
SPASM CEREBROVASCULAR	ISCHEMIA CEREBR
SPASM CILIARY MUSCLE	ACCOMMODATION ABNORM
SPASM CORONARY ARTERY	ANGINA PECTORIS
SPASM ESOPHAGEAL	CARDIOSPASM
SPASM EYELID	TWITCH
SPASM GENERALIZED	SPASM GENERAL
SPASM GLOTTIS	LARYNGISMUS
SPASM LARYNX	LARYNGISMUS
SPASM MUSCLE	HYPERTONIA
SPASM OCULOMOTOR	OCULOGYRIC CRISIS
SPASM OROPHARYNGEAL	BUCCOGLOSSAL SYND
SPASM PYLORIC	DYSPEPSIA
SPASM TEMPOROMANDIBULAR	TRISMUS
SPASM TONGUE	BUCCOGLOSSAL SYND
SPASM UTERINE	UTER SPASM
SPASM VASCULAR RETINAL	RETINAL VASC DIS
SPASMS	SPASM GENERAL
SPASTICITY CONGENITAL	PARALYSIS SPASTIC

SPASTICITY MUSCLE	HYPERTONIA
SPECIFIC GRAVITY FIXED	KIDNEY FUNC ABNORM
SPEECH DISORDER	SPEECH DIS
SPEECH LOSS	SPEECH DIS
SPERM DISORDER OF	TESTIS DIS
SPERMATOGENESIS ARRESTED	SPERM ARREST
SPERMATORRHOEA	EJACULAT ABNORM
SPHEROCYTOSIS	SPHEROCYTOSIS
SPIDER ANGIOMA	ANGIOMA SPIDER
SPIDER NEVI	VASC DIS
SPINA BIFIDA	SPINA BIFIDA
SPINA BIFIDA OCCULTA	SPINA BIFIDA
SPINAL FLUID ABNORM	CSF ABNORM
SPINE MALFORMATION	ANOMALY CONGEN MS
SPINE RIGIDLY EXTENDED	OPISTHOTONOS
SPINNING SENSATION	VERTIGO
SPLEEN DISORDER	SPLEEN DIS
SPLEEN ENLARGED	SPLENOMEGALY
SPLEEN RUPTURE OF	SPLEEN RUPT
SPLENOMEGALY	SPLENOMEGALY
SPOTS BEFORE EYES	VISION ABNORM
SPOTTING BETWEEN MENSES	METRORRHAGIA
SPOTTING MENSTRUAL	METRORRHAGIA
SPRUE	MALABSORP SYND
SPUTUM BLOODY	HEMOPTYSIS
SPUTUM INCREASED	SPUTUM INC
SQUINT	STRABISMUS
ST DEPRESSED	ST DEPRESSED
ST ELEVATED	ST ELEVATED
ST SEGMENT DEPRESSED	ST DEPRESSED
ST SEGMENT ELEVATED	ST ELEVATED
STAGGERING	GAIT ABNORM
STAIN TOOTH	DISCOLOR TOOTH
STAMMERING	SPEECH DIS
STANDSTILL CARDIAC	HEART ARREST
STATION ABNORMAL	COORDINAT ABNORM
STATUS ASTHMATICUS	ASTHMA
STATUS EPILEPTICUS	CONVULS GRAND MAL
STEATORRHEA	MALABSORP SYND
STEATORRHOEA	MALABSORP SYND
STEATOSIS HEPATIC	LIVER FATTY
STENOSIS AORTIC VALVE	STENO AORTIC
STENOSIS BLADDER	STENO BLADDER
STENOSIS BRONCHIAL	BRONCHOSTENO
STENOSIS COLON	STENO INTEST COLON
STENOSIS ESOPHAGEAL	STENO ESOPH
STENOSIS ILEUM	STENO INTEST ILE
STENOSIS INTESTINAL	STENO INTEST
STENOSIS JEJUNUM	STENO INTEST JEJ
STENOSIS PULMONIC VALVE	STENO PULM
STENOSIS PYLORIC	STENO PYLOR
STENOSIS PYLORIC HYPERTROPHIC CONGENITAL	STENO PYLOR
STENOSIS SMALL INTESTINE	STENO INTEST SMALL
STENOSIS TRIGONE URINARY BLADDER	STENO BLADDER
STENOSIS URETERAL	HYDROURETER
STENOSIS URINARY BLADDER	STENO BLADDER
STERILITY	FERTIL DEC FEM

STERILITY FEMALE	FERTIL DEC FEM
STEROID WITHDRAWAL SYNDROME	ADDISON CRISIS
STEVENS JOHNSON SYNDROME	STEVENS JOHNSON SYND
STIFFNESS JOINTS	JOINT DIS
STIFFNESS MUSCLE	HYPERTONIA
STILLBIRTH	STILLBIRTH
STIMULATION CNS	CNS STIMULAT
STINGING	PARESTHESIA
STIPPLING BASOPHILIC	BASOPHILIA
STOKES-ADAMS SYNDROME	ADAMS STOKES SYND
STOMACH ACHE	PAIN ABDO
STOMACH ATONY	STOMACH ATONY
STOMACH CARCINOMA	CARCINOMA GI
STOMACH DILATATION	STOMACH DILAT
STOMACH HEMORRHAGE	HEM GI
STOMACH INFLAMMATION	GASTRITIS
STOMACH PAIN	PAIN ABDO
STOMACH PERFORATION	ULCER STOMACH PER
STOMACH ULCER	ULCER STOMACH
STOMACH UPSET	DYSPEPSIA
STOMATITIS	STOMATITIS
STOMATITIS APHHNOUS	STOMATITIS APHTH
STOMATITIS APHTHOUS	STOMATITIS APHTH
STOMATITIS HEMORRHAGIC	STOMATITIS
STOMATITIS MONILIAL	MONILIA ORAL
STOMATITIS NECROTIZING	STOMATITIS ULCER
STOMATITIS RADIATION	STOMATITIS
STOMATITIS ULCERATIVE	STOMATITIS ULCER
STONES COMMON DUCT	CHOLELITH
STOOL BLACK	MELENA
STOOL BLOODY	HEM GI
STOOL LIGHT COLORED	STOOL ABNORM
STOOL TABLET IN	NO DRUG EFFECT
STOOL TARRY	MELENA
STOOLS HARD	CONSTIP
STOOLS LOOSE	DIARRHEA
STOOLS WATERY	DIARRHEA
STRABISMUS	STRABISMUS
STRANGURY	DYSURIA
STRAWBERRY MARK	ANOMALY VASCUL
STRENGTH LOSS OF	ASTHENIA
STRIAE	SKIN STRIAE
STRIAE ATROPHIC	SKIN STRIAE
STRIAE PURPLE	SKIN STRIAE
STRIAE SKIN	SKIN STRIAE
STRICTURE ESOPHAGUS	STENO ESOPH
STRICTURE INTESTINAL	STENO INTEST
STRIDOR	STRIDOR
STRIDOR INSPIRATORY	STRIDOR
STROKE	CEREBROVASC ACCID
STUMBLING	GAIT ABNORM
STUPOR	STUPOR
STUTTERING	SPEECH DIS
SUBARACHNOID HAEMORRHAGE	HEM SUBARACHNOID
SUBARACHNOID HEMORRHAGE	HEM SUBARACHNOID
SUBARACHNOID PRESSURE INCREASED	INTRACRAN HYPERTENS
SUBDURAL HEMATONIA	HEMATOMA SUBDURAL

SUBGLOTTIC EDEMA	EDEMA LARYNX
SUBINVOLUTION UTERINE	UTER SUBINVOLUT
SUBMAXILLARY GLAND ENLARGED	SALIV GLAND ENLARGE
SUBSTERNAL PAIN	PAIN CHEST SUBSTERN
SUDDEN DEATH	SUDDEN DEATH
SUDDEN INFANT DEATH	SIDS
SUDDEN INFANT DEATH SYNDROME	SIDS
SUFFOCATION FEELING	DYSPNEA
SUGAR BLOOD DECREASED	HYPOGLYCEM
SUGAR BLOOD INDREASED	HYPERGLYCEM
SUGAR FASTING BLOODLEVEL INC	HYPERGLYCEM
SUGAR URINARY PRESENT	GLYCOSURIA
SUICIDAL DEPRESSION	DEPRESSION PSYCHOTIC
SUICIDAL TENDENCY	DEPRESSION
SUICIDE	SUICIDE ATTEMPT
SUICIDE ATTEMPT	SUICIDE ATTEMPT
SUICIDE GESTURE	SUICIDE ATTEMPT
SULFHAEMOGLOBINAEMIA	SULFHEMOGLOBIN
SULFHEMOGLOBINEMIA	SULFHEMOGLOBIN
SULFOBROMOPHTHALEIN RETENTION	BSP ABNORM
SUNBURN	PHOTOSENSITIVITY
SUPERINFECTION	INFECT SUPER
SUPPURATION GUM	GINGIVITIS
SUPRAVENTRICULAR TACHYCARDIA	TACHYCARDIA SUPVENT
SUPRESSION ADRENAL	ADREN INSUFFIC
SURFACTANT DEFICIENCY SYNDROME ADULT	RESPIRAT DISTRES SYND
SURFACTANT DEFICIENCY SYNDROME NEONATAL	PERINATAL DIS
SUSPICIOUSNESS	PARANOID REACT
SWALLOWING DIFFICULT	DYSPHAGIA
SWALLOWING DISORDER	DYSPHAGIA
SWALLOWING IMPAIRED	DYSPHAGIA
SWALLOWING PAINFUL	DYSPHAGIA
SWALLOWING SPASM	DYSPHAGIA
SWEAT DISCOLOURATION	SWEAT
SWEAT GLAND DISORDER	SWEAT
SWEATING	SWEAT
SWEATING DECREASED	SWEAT DEC
SWEATING INCREASED	SWEAT
SWEATY PLAMS	SWEAT
SWELLING	EDEMA
SWELLING ABDOMEN	ABDO ENLARGE
SWELLING LIPS	EDEMA FACE
SWELLING NON-INFLAMMATORY	EDEMA
SWOLLEN ABDOMEN	ABDO ENLARGE
SWOLLEN JOINTS	ARTHROSIS
SWOONING	SYNCOPE
SYMPHYSEOLYSIS	BONE DIS
SYNCOPE	SYNCOPE
SYNCOPE EXERTIONAL	SYNCOPE
SYNCOPE POSTURAL	SYNCOPE
SYNCOPE VASOVAGAL	SYNCOPE
SYNDACTYLY	SYNDACTYLY
SYNDROME ABDOMINAL ACUTE	ABDO SYND ACUTE
SYNDROME ADAMS-STOKES	ADAMS STOKES SYND
SYNDROME ADULT RESPIRATORY	RESPIRAT DISTRES SYND
SYNDROME ADULT RESPIRATORY DISTRESS	RESPIRAT DISTRES SYND
SYNDROME ANTICHOLINERGIC	ANTICHOLINERG SYND

SYNDROME ATROPINE-LIKE	ANTICHOLINERG SYND
SYNDROME BRAIN ACUTE	BRAIN SYND ACUTE
SYNDROME BRAIN CHRONIC	BRAIN SYND CHRON
SYNDROME BUCCOGLOSSAL	BUCCOGLOSSAL SYND
SYNDROME BUDD-CHIARI	THROM
SYNDROME CARPEL TUNNEL	TENOSYNOVITIS
SYNDROME CEREBELLAR	CEREBELL SYND
SYNDROME CHOLINERGIC	CHOLINERG SYND
SYNDROME CORTICOSTEROID WITHDRAWAL	ADDISON CRISIS
SYNDROME CUSHING'S	CUSHINGS SYND
SYNDROME DIGUGLIELMO'S	MARROW HYPERPLASIA
SYNDROME DISSEMINATED LUPUS ERYTHEMATOSIS	LE SYND
SYNDROME DOWN'S	MENTAL RETARD
SYNDROME DYSKINETIC	DYSKINESIA
SYNDROME EFFORT	NEUROSIS
SYNDROME EXTRAPYRAMIDAL	EXTRAPYR SYND
SYNDROME FANCONI-LIKE	FANCONI SYND
SYNDROME FETAL DISTRESS	PERINATAL DIS
SYNDROME FLU	FLU SYND
SYNDROME GILLES DE LA TOURETTE	TWITCH
SYNDROME GOOD PASTURE	GLOMERULITIS
SYNDROME GOOD POSTURES	GLOMERULITIS
SYNDROME GUILLAIN-BARRE	GUILLAIN BARRE SYND
SYNDROME HEAD-FACE-NECK	DYSKINESIA
SYNDROME HEMOLYTIC UREMIC	UREMIA
SYNDROME HEPATORENAL	HEPATORENAL SYND
SYNDROME HYPERKINETIC	HYPERKINESIA
SYNDROME HYPOKALEMIC	HYPOKALEM
SYNDROME INAPPROPRIATE ADH	ADH INAPPROP
SYNDROME LOW SALT	HYPONATREM
SYNDROME LUPUS	LE SYND
SYNDROME LYELL'S	EPIDERM NECRO
SYNDROME MALABSORPTION	MALABSORP SYND
SYNDROME MENIERE'S	VESTIBUL DIS
SYNDROME MENOPAUSAL	MENOPAUSE
SYNDROME MS-LIKE	SCLEROSIS MULT
SYNDROME NEPHROTIC	NEPHROSIS
SYNDROME PARASYMPATHOLYTIC	ANTICHOLINERG SYND
SYNDROME PARASYMPATHOMIMETIC	CHOLINERG SYND
SYNDROME PARKINSON'S	EXTRAPYR SYND
SYNDROME PARKINSONISM	EXTRAPYR SYND
SYNDROME PEPTIC ULCER	PEPTIC ULCER SYND
SYNDROME POLANDS	ANOMALY CONGEN MS
SYNDROME POSTMATURITY	BIRTH POSTMAT
SYNDROME PREMATURITY	BIRTH PREMAT
SYNDROME PREMENSTRUAL	MENS DIS
SYNDROME RESPIRATORY DISTRESS ADULT	RESPIRAT DISTRES SYND
SYNDROME RESPIRATORY DISTRESS NEWBORN	PERINATAL DIS
SYNDROME RESTLESS LEGS	HYPERKINESIA
SYNDROME REYES	BRAIN SYND ACUTE
SYNDROME SCREAMING	SCREAMING SYND
SYNDROME SICCA	SALIV GLAND ENLARGE
SYNDROME SICK SINUS	BRADYCARDIA SINUS
SYNDROME SJOGREN'S	SALIV GLAND ENLARGE
SYNDROME SPRUE-LIKE	MALABSORP SYND
SYNDROME STEVENS-JOHNSON	STEVENS JOHNSON SYND
SYNDROME STOKES-ADAMS	ADAMS STOKES SYND

SYNDROME TOURETTE	TWITCH
SYNDROME TOXIC SHOCK	INFECT
SYNDROME UREMIC	UREMIA
SYNDROME WITHDRAWAL	WITHDRAW SYND
SYNDROME ZOLLINGER ELLISON	ULCER PEPTIC
SYNOSTOSIS	BONE DIS
SYNOVITIS	SYNOVITIS
SYPHILIS TEST FALSE POSITIVE	SYPH TEST FALSE POS
T WAVE INVERTED	T INVERTED
TABLET IN STOOL	NO DRUG EFFECT
TACHYCARDIA	TACHYCARDIA
TACHYCARDIA ATRIAL	TACHYCARDIA SUPVENT
TACHYCARDIA IRREGULAR	TACHYCARDIA
TACHYCARDIA NODAL	TACHYCARDIA NODAL
TACHYCARDIA PAROXYSMAL	TACHYCARDIA
TACHYCARDIA PAROXYSMAL ATRIAL	TACHYCARDIA SUPVENT
TACHYCARDIA PAROXYSMAL VENTRICULAR	TACHYCARDIA VENT
TACHYCARDIA SINUS	TACHYCARDIA
TACHYCARDIA SUPRAVENTRICULAR	TACHYCARDIA SUPVENT
TACHYCARDIA VENTRICULAR	TACHYCARDIA VENT
TACHYPHYLAXIS	TOLER INC
TACHYPNEA	HYPERVENTIL
TALIPES	CLUBFOOT
TALIPES EQUINES	CLUBFOOT
TAMPERING WITH MEDICATION	MED ERROR
TAMPONADE CARDIAC	EFFUS PERICARD
TANNING	SKIN DISCOLOR
TARDIVE DYSKINESIA	DYSKINESIA TARDIVE
TASTE ABSENT	TASTE LOSS
TASTE ALTERATION	TASTE PERVERS
TASTE BITTER	TASTE PERVERS
TASTE GARLIC	TASTE PERVERS
TASTE LOSS	TASTE LOSS
TASTE METALLIC	TASTE PERVERS
TASTE PECULIAR	TASTE PERVERS
TASTE PERVERSION	TASTE PERVERS
TASTE PERVERSION OF	TASTE PERVERS
TEAR DISORDER	LACRIMATION DIS
TEARING DECREASED	EYE DIS
TEARING EYES	LACRIMATION DIS
TEETH GRATING	TOOTH DIS
TEETH GRINDING	TOOTH DIS
TEETH MOTTLED	DISCOLOR TOOTH
TEETH STAINED	DISCOLOR TOOTH
TEETH YELLOW	DISCOLOR TOOTH
TEETH-GRINDING	NEUROSIS
TELANGIECTASES ACQUIRED	VASC DIS
TELANGIECTASES CONGENITAL	ANOMALY VASCUL
TELANGIECTASIS	VASC DIS
TEMPERATURE BODY DECREASE	HYPOTHERMIA
TEMPERATURE ELEVATION	FEVER
TEMPORAL HEADACHE	HEADACHE
TENDEN DISORDER	TENDON DIS
TENDERNESS (NOS)	PAIN
TENDERNESS BREAST	PAIN BREAST
TENDERNESS EYE	PAIN EYE
TENDERNESS LIVER	LIVER TENDER

TENDERNESS MUSCLE	MYALGIA
TENDINITIS	TENDON DIS
TENDON ACHILLES RUPTURE OF	TENDON RUPT
TENDON DISORDER	TENDON DIS
TENDON RUPTURE	TENDON RUPT
TENDONITIS	TENDON DIS
TENESMUS	TENESMUS
TENOSYNOVITIS	TENOSYNOVITIS
TENSENESS	NERVOUSNESS
TENSION NERVOUS	NERVOUSNESS
TENSION OCULAR INCREASED	GLAUCOMA
TERATOGENICITY	ANOMALY CONGEN
TERATOMA	NEOPL
TEST THYMOL TURBIDITY	THYMOL TURBID ABNORM
TESTICULAR DISORDER	TESTIS DIS
TESTICULAR HYPOPLASIA	HYPOGONAD MALE
TESTIS DISORDER	TESTIS DIS
TESTIS NEOPLASM MALIGNANT	CARCINOMA
TESTOSTERONE DEC	ALTERED HORMONE LEVEL
TETANUS LIKE	TETANY
TETANY	TETANY
TETANY HYPOCALCEMIC	TETANY HYPOCALCEM
TETRALOGY OF FALLOT	TETRAL FALLOT
THERAPEUTIC EFFECT UNEXPECTED	UNEXPECTED BENEFIT
THERAPEUTIC RESPONSE DECREASED	TOLER INC
THERAPEUTIC RESPONSE INCREASED	TOLER DEC
THINKING ABNORMAL	THINKING ABNORM
THINKING IRRATIONAL	THINKING ABNORM
THINKING SLOW	THINKING ABNORM
THINKING SLUGGISH	THINKING ABNORM
THIRST	THIRST
THIRST EXCESSIVE	THIRST
THOUGHT BLOCK	THINKING ABNORM
THRESHOLD CONVULSION LOWERED	CONVULS
THROAT DRY	DRY MOUTH
THROAT SORE	PHARYNGITIS
THROAT TIGHTNESS	LARYNGISMUS
THROMBASTHENIA	PLAT ABNORM
THROMBIN DECREASED	THROMBIN DEC
THROMBIN INCREASED	THROMBIN INC
THROMBOCYTES ABNORMAL (NOS)	PLAT ABNORM
THROMBOCYTHAEMIA	THROMBOCYTHEM
THROMBOCYTHEMIA	THROMBOCYTHEM
THROMBOCYTOPATHY	PLAT ABNORM
THROMBOCYTOPENIA	THROMBOCYTOPENIA
THROMBOCYTOPENIA NEONATAL	THROMBOCYTOPENIA
THROMBOCYTOPENIA PURPURA	PURPURA THROMBOPEN
THROMBOCYTOSIS	THROMBOCYTHEM
THROMBOEMBOLISM	EMB
THROMBOPENIA	THROMBOCYTOPENIA
THROMBOPHLEBITIS	THROMBOPHLEB
THROMBOPHLEBITIS ARM	THROMBOPHLEB
THROMBOPHLEBITIS ARM DEEP	THROMBOPHLEB DEEP
THROMBOPHLEBITIS ARM SUPERFICIAL	THROMBOPHLEB
THROMBOPHLEBITIS CEREBRAL VEIN	THROM CEREBR VEN
THROMBOPHLEBITIS DEEP	THROMBOPHLEB DEEP
THROMBOPHLEBITIS INJECTION SITE	THROMBOPHLEB

THROMBOPHLEBITIS LEG	THROMBOPHLEB
THROMBOPHLEBITIS LEG DEEP	THROMBOPHLEB DEEP
THROMBOPHLEBITIS LEG SUPERFICIAL	THROMBOPHLEB
THROMBOPHLEBITIS MESENTERIC VEIN	THROMBOPHLEB
THROMBOPHLEBITIS MULTIPLE	THROMBOPHLEB
THROMBOPHLEBITIS MULTIPLE DEEP	THROMBOPHLEB DEEP
THROMBOPHLEBITIS MULTIPLE SUPERFI	THROMBOPHLEB
THROMBOPHLEBITIS NEONATAL	THROMBOPHLEB
THROMBOPHLEBITIS PELVIC VEIN	THROMBOPHLEB
THROMBOPHLEBITIS RETINAL VEIN	THROMBOPHLEB
THROMBOPHLEBITIS SUPERFICIAL	THROMBOPHLEB
THROMBOPHLEBITIS VENA CAVA	THROMBOPHLEB
THROMBOPLASTIN DECREASED	THROMBOPLASTIN DEC
THROMBOPLASTIN INCREASED	THROMBOPLASTIN INC
THROMBOSIS	THROM
THROMBOSIS ARTERIAL	THROM ART
THROMBOSIS ARTERIAL ARM	THROM ART
THROMBOSIS ARTERIAL LEG	THROM ART
THROMBOSIS CAROTID	THROM CAROTID
THROMBOSIS CAROTID ARTERY	THROM CAROTID
THROMBOSIS CEREBRAL	THROM CEREBR
THROMBOSIS CEREBRAL ARTERIAL	THROM CEREBR ART
THROMBOSIS CEREBRAL VEIN	THROM CEREBR VEN
THROMBOSIS CORONARY	THROM CORONARY
THROMBOSIS MESENTERIC ARTERY	OCCLUS MESENTER ART
THROMBOSIS MESENTERIC VEIN	OCCLUS MESENTER VEN
THROMBOSIS MESENTERIC VESSEL	OCCLUS MESENTER
THROMBOSIS PULMONARY	THROM PULM
THROMBOSIS PULMONARY ARTERY	THROM PULM ART
THROMBOSIS RETINAL ARTERY	OCCLUS RETINAL ART
THROMBOSIS RETINAL VEIN	THROM RETINAL VEIN
THROMBOSIS VENOUS	THROMBOPHLEB
THROMBOSIS VENOUS ARM	THROMBOPHLEB
THROMBOSIS VENOUS DEEP	THROMBOPHLEB DEEP
THROMBOSIS VENOUS SUPERFICIAL	THROMBOPHLEB
THRUSH	MONILIA ORAL
THYMOL TURBIDITY ABNORMAL	THYMOL TURBID ABNORM
THYMOL TURBIDITY TEST ABNORMAL	THYMOL TURBID ABNORM
THYMUS HYPERTROPHY	ENDO DIS
THYROID ACTIVITY DECREASED	HYPOTHYR
THYROID ADENOMA	ADENOMA THYR
THYROID CARCINOMA	CARCINOMA THYR
THYROID CRISIS	HYPERTHYR
THYROID CYST	THYR DIS
THYROID DISORDER	THYR DIS
THYROID ENLARGED	GOITER
THYROID NEOPLASM MALIGNANT	CARCINOMA THYR
THYROID NODULAR	THYR DIS
THYROID STORM	HYPERTHYR
THYROIDITIS	THYROIDITIS
THYROTOXICOSIS	HYPERTHYR
THYROTOXICOSIS AGGRAVATED	HYPERTHYR
THYROXINE DECREASED	HYPOTHYR
THYROXINE INCREASED	HYPERTHYR
TIA	ISCHEMIA CEREBR
TIBC ABNORMAL	LAB TEST ABNORM
TIBIAL ARTERY THROMBOSIS	THROM ART

TICS	TWITCH
TIGHTNESS IN CHEST	PAIN CHEST
TIME COAGULATION PROLONGED	COAGUL TIME INC
TIME COAGULATION SHORTENED	COAGUL TIME DEC
TINGLING	PARESTHESIA
TINGLING FEET/HANDS	PARESTHESIA
TINGLING MUCOSAL	PARESTHESIA
TINGLING SKIN	PARESTHESIA
TINNITUS	TINNITUS
TIRED AND HEAVY	ASTHENIA
TIREDNESS	ASTHENIA
TISSUE FLUID INCREASED	EDEMA GENERAL
TISSUE PUFFING	EDEMA
TOLERANCE	TOLER INC
TOLERANCE DECREASED	TOLER DEC
TOLERANCE DECREASED (NOS)	TOLER DEC
TOLERANCE GLUCOSE DECREASED	GLUCOSE TOLER DEC
TOLERANCE INCREASED	TOLER INC
TONGUE BLACK	DISCOLOR TONGUE
TONGUE BROWN	DISCOLOR TONGUE
TONGUE DESQUAMATION	TONGUE DIS
TONGUE DISCOLORATION	DISCOLOR TONGUE
TONGUE DISCOLOURATION	DISCOLOR TONGUE
TONGUE DISORDER	TONGUE DIS
TONGUE EDEMA	EDEMA TONGUE
TONGUE GEOGRAPHIC	GLOSSITIS
TONGUE HAIRY	TONGUE DIS
TONGUE INFLAMMATION	GLOSSITIS
TONGUE OEDEMA	EDEMA TONGUE
TONGUE PAIN	GLOSSITIS
TONGUE PARALYSIS	TONGUE DIS
TONGUE PROTRUSION SPASTIC INVOLUNTARY	TONGUE DIS
TONGUE RED SWOLLEN PAIN	GLOSSITIS
TONGUE SLUGGISH	PARALYSIS
TONGUE SORE	GLOSSITIS
TONGUE THICK	EDEMA TONGUE
TONGUE TIE	SPEECH DIS
TONGUE ULCERATION	GLOSSITIS
TONGUE WEAK	TONGUE DIS
TONGUE WHITE	DISCOLOR TONGUE
TONSILLITIS	PHARYNGITIS
TOOTH CARIES	TOOTH CARIES
TOOTH CARIES AGGRAVATED	TOOTH CARIES
TOOTH DECALCIFICATION	TOOTH DIS
TOOTH DISCOLORATION	DISCOLOR TOOTH
TOOTH DISCOLOURATION	DISCOLOR TOOTH
TOOTH DISORDER	TOOTH DIS
TOOTH FORMATION RETARDED	ANOMALY TOOTH
TOOTH HYPOPLASIA	ANOMALY TOOTH
TOOTH MALFORMATION	ANOMALY TOOTH
TOOTHACHE	PAIN
TORPOR	STUPOR
TORPOR MENTAL	THINKING ABNORM
TORSADES DE POINTES	TORSADES DE POINTES
TORTICOLLIS	TORTICOLLIS
TORULOSIS	CRYPTOCOCCOSIS
TOUCH SENSITIVITY INCREASED	HYPERESTHESIA

TOURETTE SYNDROME	TWITCH
TOXEMIA BACTERIAL	SEPSIS
TOXEMIA OF PREGNANCY	PREGN TOXEMIA
TOXIC EPIDEONEAL NECROLYSIS	EPIDERM NECRO
TOXIC REACTION (NOS)	OVERDOSE
TOXIC SHOCK SYNDROME	INFECT
TOXICITY RENAL	NEPHROPATHY TOXIC
TOXOPLASMOSIS	INFECT
TRACHED-BRONCHIAL SECRETION EXCES	SALIVA INC
TRACHED-ESOPHAGEAL FISTULA	ANOMALY CONGEN
TRACHEITIS	BRONCHITIS
TRACHEO-OESOPHAGEAL FISTULA	ANOMALY CONGEN
TRACHEOBRONCHITIS	BRONCHITIS
TRANQUILLIZATION EXCESSIVE	SOMNOLENCE
TRANSAMINASE CELL CARCINOMA	CARCINOMA
TRANSAMINASE GLUTAMIC-OXALACETIC INCREASED	SGOT INC
TRANSAMINASE GLUTAMIC-PYRUVIC INCREASED	SGPT INC
TRANSIENT ISCHEMIC ATTACKS	ISCHEMIA CEREBR
TRANSPOSITION AORTA-PULMONARY ARTERY	TRANSPOS GREAT VESS
TRANSPOSITION OF GREAT VESSELS	TRANSPOS GREAT VESS
TRAUMA	INJURY ACCID
TRAUMA BIRTH	PERINATAL DIS
TRAUMATIC INJURY	INJURY ACCID
TREMBLING	TREMOR
TREMBLING INSIDE	NERVOUSNESS
TREMOR	TREMOR
TREMOR COARSE	TREMOR
TREMOR FINE	TREMOR
TREMOR INTENTION	TREMOR
TREMOR LIMB	TREMOR
TREMOR MUSCLE	TREMOR
TREMOR NEONATAL	TREMOR
TREMOR NERVE	TREMOR
TREMOR PERIORAL	TREMOR
TREMOR SEMIRRHYTHMIC	TREMOR
TREMULOUSNESS	TREMOR
TREMULOUSNESS NERVOUS	NERVOUSNESS
TREPOPNEA	DYSPNEA
TRIGEMINAL NEURALGIA	NEURALGIA
TRIGEMINY	EXTRASYSTOLES
TRIGLYCERIDES ELEVATED SERUM	HYPERLIPEM
TRISMUS	TRISMUS
TRUNK BOWED BACK	OPISTHOTONOS
TSALICYLATE INTOXICATION	SALICYLISM
TSH DECREASE	ALTERED HORMONE LEVEL
TSH INCREASE	ALTERED HORMONE LEVEL
TUBERCULOSIS AGGRAVATED	TUBERCUL AGGRAV
TUBERCULOSIS OF BONES AND JOINTS	INFECT
TUBERCULOSIS REACTIVATED	TUBERCUL REACT
TUBULAR VISION	VISUAL FIELD DEFECT
TUMOR LIVER	NEOPL LIVER
TUMOR LYSIS SYNDROME	TUMOR LYSIS SYND
TUMOR-LIKE SKIN CONDITION (NOS)	HYPERTROPHY SKIN
TUNNEL VISION	VISUAL FIELD DEFECT
TWITCH SKELETAL MUSCLE	TWITCH
TWITCHING	TWITCH
TYMPANIC MEMBRANE PERFORATION	EAR DIS

TYMPANITES	FLATUL
ULCER APHTHOUS ORAL	STOMATITIS APHTH
ULCER BLEEDING DUODENAL	ULCER DUODEN HEM
ULCER BLEEDING GASTRIC	ULCER STOMACH HEM
ULCER BLEEDING PEPTIC	ULCER PEPTIC HEM
ULCER BUCCAL	STOMATITIS ULCER
ULCER COLON	ULCER INTEST
ULCER CONJUNCTIVAL	ULCER CONJUNCT
ULCER CORNEAL	ULCER CORNEAL
ULCER CORNEAL PERFORATED	ULCER CORNEAL PER
ULCER DUODENAL	ULCER DUODEN
ULCER DUODENAL HEMORRHAGE	ULCER DUODEN HEM
ULCER DUODENAL REACTIVATED	ULCER DUODEN REACT
ULCER DUODENAL WITH PERF AND HEM	ULCER DUODEN PERHEM
ULCER DUODENAL WITH PERFORATION	ULCER DUODEN PER
ULCER ESOPHAGEAL	ULCER ESOPH
ULCER GASTRIC	ULCER STOMACH
ULCER GASTRODUODENAL	ULCER PEPTIC
ULCER GASTROINTESTINAL	ULCER PEPTIC
ULCER GASTROJENUNAL	ULCER PEPTIC
ULCER ILEUM	ULCER INTEST ILE
ULCER ILEUM PERFORATED	ULCER INTEST PER ILE
ULCER INTESTINAL	ULCER INTEST
ULCER INTESTINAL PERFORATED	ULCER INTEST PER
ULCER JEJUNUM	ULCER INTEST JEJ
ULCER JEJUNUM PERFORATED	ULCER INTEST PER JEJ
ULCER LARGE INTESTINE	ULCER INTEST
ULCER LIP	ULCER MOUTH
ULCER MOUTH	ULCER MOUTH
ULCER PEPTIC	ULCER PEPTIC
ULCER PEPTIC REACTIVATED	ULCER PEPTIC REACT
ULCER PEPTIC WITH HEMORRHAGE	ULCER PEPTIC HEM
ULCER PEPTIC WITH PERF AND HEM	ULCER PEPTIC PERHEM
ULCER PEPTIC WITH PERFORATION	ULCER PEPTIC PER
ULCER RECTAL	RECTAL DIS
ULCER SKIN	ULCER SKIN
ULCER SMALL INTESTINE	ULCER INTEST SMALL
ULCER STOMACH	ULCER STOMACH
ULCER STOMACH REACTIVATED	ULCER STOMACH REACT
ULCER STOMACH WITH HEMORRHAGE	ULCER STOMACH HEM
ULCER STOMACH WITH PERF AND HEM	ULCER STOMACH PERHEM
ULCER STOMACH WITH PERFORATION	ULCER STOMACH PER
ULCER STRESS	ULCER PEPTIC
ULCER SYNDROME PEPTIC	PEPTIC ULCER SYND
ULCERATION GUM	GINGIVITIS
ULCERATION MOUTH	ULCER MOUTH
ULCERATION TONGUE	GLOSSITIS
ULCERATIVE CALCITIS	COLITIS ULCER
ULCUS VENTRICULI	ULCER STOMACH
UNCINATE FITS	CONVULS
UNCONSCIOUS PARTIAL	STUPOR
UNCONSCIOUSNESS	COMA
UNEVALUABLE REACTION	REACT UNEVAL
UNEXPECTED THERAPEUTIC EFFECT	UNEXPECTED BENEFIT
UNRESPONSIVE	STUPOR
UNSTEADINESS	DIZZINESS
UPPER MOTOR NEURONE LESION	NEUROPATHY

UPPER RESP TRACT INFECTION	PHARYNGITIS
UPSET GASTROINTESTINAL	DYSPEPSIA
URAEMIA	UREMIA
URATES BLOOD INCREASED	HYPERURICEM
UREA BLOOD ELEVATED	BUN INC
UREA CLEARANCE DECREASED	UREA CLEAR DEC
UREA NITROGEN BLOOD INCREASED	BUN INC
UREMIA	UREMIA
UREMIA OF RENAL ORIGIN	UREMIA
UREMIC SYNDROME	UREMIA
URETER OBSTRUCTION	HYDRONEPHROSIS
URETERAL CALCULUS	KIDNEY CALCULUS
URETERAL PAIN	PAIN KIDNEY
URETERAL SLUDGE	URIN TRACT DIS
URETHRAL BURNING ON MICTURITION	DYSURIA
URETHRAL CALCULUS	BLADDER CALCULUS
URETHRAL DISORDER	URIN TRACT DIS
URETHRAL PAIN	PAIN URETHRA
URETHRAL SPASM	PAIN URETHRA
URETHRITIS	URETHRITIS
URGENCY URINATION	URIN URGENCY
URIC ACID BLOOD INCREASED	HYPERURICEM
URIC ACID NEPHROPATHY	KIDNEY TUBUL DIS
URIC ACID RETENTION	HYPERURICEM
URICACIDURIA	URICACIDUR
URINARY BLADDER CARCINOMA	CARCINOMA BLADDER
URINARY BLADDER OBSTRUCTION	STENO BLADDER
URINARY CASTS	URIN CASTS
URINARY HESITANCY	URIN IMPAIRED
URINARY INCONTINENCE	INCONTIN URIN
URINARY OUTPUT ARREST OF	ANURIA
URINARY RETENTION	URIN RETENT
URINARY TRACT BLEED MICROSCOPIC	HEMATURIA
URINARY TRACT BLEEDING	HEMATURIA
URINARY TRACT DISORDER OF	URIN TRACT DIS
URINARY TRACT INFECTION	INFECT URIN TRACT
URINARY TRACT INFECTION NEONATAL	INFECT URIN TRACT
URINARY TRACT MALFORMATION	ANOMALY CONGEN UG
URINARY TRACT STONE	UROLITH
URINARY URGENCY	URIN URGENCY
URINARY URGENCY/FREQUENCY	URIN FREQUENCY
URINATION DIFFICULTY	DYSURIA
URINATION FREQUENCY OF	URIN FREQUENCY
URINATION IMPAIRED	URIN IMPAIRED
URINATION INVOLUNTARY	INCONTIN URIN
URINATION PAIN	DYSURIA
URINATION URGENCY OF	URIN URGENCY
URINE ABNORMAL	URIN ABNORM
URINE ABNORMALITY	URIN ABNORM
URINE CONSTITUENTS ABNORMAL	URIN ABNORM
URINE DISCOLORATION	URIN ABNORM
URINE ELECTROLYTES ABNORM	URIN ABNORM
URINE FORMATION FAILURE OF	ANURIA
URINE FORMED ELEMENTS ABNORMAL (NOS)	URIN ABNORM
URINE INCONTINENCE	INCONTIN URIN
URINE PRODUCTION SCANTY	OLIGURIA
URINE RBC	HEMATURIA

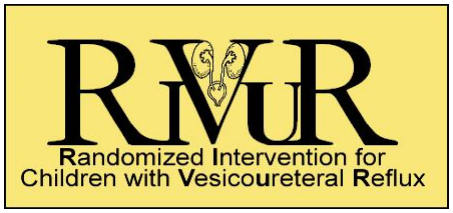
URINE SPECIFIC GRAVITY FIXED	KIDNEY FUNC ABNORM
URINE VOLUME DEFICIENT	OLIGURIA
UROGENITAL DISORDER	UG DIS
UROGENITAL MALFORMATION	ANOMALY CONGEN UG
UROGENITAL MALFORMATION ANOMALY	ANOMALY CONGEN UG
UROLITHIASIS	UROLITH
UROPATHY	URIN TRACT DIS
UROPATHY OBSTRUCTIVE	URIN TRACT DIS
URTICARIA	URTICARIA
URTICARIA ACUTE	URTICARIA
URTICARIA GIANT	ANGIOEDEMA
URTICARIA INJECTION SITE	HYSN INJECT SITE
URTICARIA VESICULOSA	URTICARIA
UTERINE ATONY	UTER ATONY
UTERINE CARCINOMA	CARCINOMA ENDOMETR
UTERINE CONCENTRATIONS	LABOR ABNORM
UTERINE CONTRACTIONS	LABOR ABNORM
UTERINE CONTRACTIONS WEAK	UTER ATONY
UTERINE DISORDER (NOS)	UTER DIS
UTERINE DISORDER CERVIX	CERVIX DIS
UTERINE DISORDER NOS	UTER DIS
UTERINE FIBROID	UTER FIBROID ENLARGE
UTERINE FIBROIDS DEGENERATED	UTER FIBROID DEGEN
UTERINE FIBROIDS ENLARGED	UTER FIBROID ENLARGE
UTERINE FIBROMYOMA	UTER FIBROID ENLARGE
UTERINE HAEMORRHAGE	HEM UTER
UTERINE HEMORRHAGE	HEM UTER
UTERINE INFLAMMATION	ENDOMETR DIS
UTERINE NEOPLASM	NEOPL UTER
UTERINE PERFORATION	UTER RUPT
UTERINE RELAXATION	UTER ATONY
UTERINE SPASM	UTER SPASM
UTERINE SUBINVOLUTION	UTER SUBINVOLUT
UTERUS ATONY OF	UTER ATONY
UTERUS ENLARGED	UTER ENLARGE
UTERUS RELAXED	UTER ATONY
UTERUS RUPTURED	UTER RUPT
UVEITIS	UVEITIS
VACCINATION COMPLICATION	POST VAC SYND
VACCINIA AGGRAVATED	POST VAC SYND
VACUOLIZATION ERYTHROCYTE	ERYTHRO VACUOL
VACUOLIZATION LEUKOCYTE	LEUKOCYTE VACUOL
VAGAL REACTION	SYNCOPE
VAGINAL DISCHARGE	LEUKORRHEA
VAGINAL HAEMORRHAGE	HEM VAGINAL
VAGINAL HEMORRHAGE	HEM VAGINAL
VAGINAL INFECTION	VAGINITIS
VAGINAL NEOPLASM BENIGN	NEOPL
VAGINAL NEOPLASM MALIGNANT	CARCINOMA
VAGINAL PAIN OR BURNING	VAGINITIS
VAGINITIS	VAGINITIS
VAGINITIS ATROPHIC	VAGINITIS
VAGINITIS ATROPIC	VAGINITIS
VAGINITIS TRICHOMONAL	VAGINITIS
VAGINITIS ULCERATIVE	VAGINITIS
VARICES ESOPHAGEAL	VEIN VARICOSE
VARICOSITY	VEIN VARICOSE

VASCULAR COLLAPSE	SHOCK
VASCULAR DISORDER	VASC DIS
VASCULAR DISORDER PERIPHERAL	VASC DIS PERIPH
VASCULAR DISORDER RETINAL	RETINAL VASC DIS
VASCULAR MALFORMATION PERIPHERAL	ANOMALY VASCUL
VASCULAR PURPURA	PURPURA VASC
VASCULITIS	VASCULITIS
VASCULITIS ALLERGIC	VASCULITIS
VASCULITIS DIFFUSE	VASCULITIS
VASCULITIS KIDNEY	VASCULITIS KIDNEY
VASCULITIS NECROTIZING	VASCULITIS
VASCULITIS NODULAR	VASCULITIS
VASCULITIS RETINAL	RETINAL VASC DIS
VASOCONSTRICTION	VASOSPASM
VASOCONSTRICTION PERIPHERAL	VASC DIS PERIPH
VASODILATATION	VASODILAT
VASODILATION	VASODILAT
VASOMOTOR COLLAPSE	SYNCOPE
VASOSPASM	VASOSPASM
VASOSPASM CEREBRAL	ISCHEMIA CEREBR
VASOVAGAL REACTION	SYNCOPE
VDRL FALSE POSITIVE	SYPH TEST FALSE POS
VEIN DISORDER	VASC DIS
VEIN DISTENDED	VASC DIS
VEIN PAIN	PAIN
VEIN THROMBOSIS MESENTERIC	OCCLUS MESENTER VEN
VEIN VARICOSE	VEIN VARICOSE
VENO-OCCLUSIVE LIVER DAMAGE	VENOOCCLUS LIVER SYND
VENOOCCLUSIVE LIVER DISEASE	VENOOCCLUS LIVER SYND
VENOSPASM	VENOSPASM
VENOUS PRESSURE INCREASED	VEN PRESS INC
VENOUS THROMBOSIS	THROMBOPHLEB
VENTRICULAR ASYSTOLIA	HEART ARREST
VENTRICULAR CONTRACTIONS PREMATURE	EXTRASYSTOLES VENT
VENTRICULAR FIBRILLATION	FIBRILLAT VENT
VENTRICULAR FIBRILLATION PAROXYSM	FIBRILLAT VENT
VENTRICULAR SEPTAL DEFECT	VENT SEPT DEF
VENTRICULAR TACHYCARDIA	TACHYCARDIA VENT
VENTRICULITIS	EPENDYMITIS
VERBOSITY	PERSON DIS
VERMICULATION	PARESTHESIA
VERRUCA	NEOPL SKIN
VERTIGO	VERTIGO
VERTIGO CNS ORIGIN	VERTIGO
VERTIGO LABYRINTHINE	VERTIGO
VERTIGO OBJECTIVE	VERTIGO
VERTIGO SUBJECTIVE	VERTIGO
VESICLES	RASH VESIC BULL
VESICULAR RASH	RASH VESIC BULL
VESICULOBULLOUS RASH	RASH VESIC BULL
VESICULOPUSTULAR RASH	RASH VESIC BULL
VESTIBULAR ABNORMALITIES	VESTIBUL DIS
VESTIBULAR DISORDER	VESTIBUL DIS
VESTIBULAR NERVE DAMAGE	VESTIBUL DIS
VIOLENT	HOSTILITY
VIRAL INFECTION	INFECT VIRAL
VIRILISM	VIRILISM

VIRILISM FOETAL	VIRILISM
VIRILIZATION	VIRILISM
VIRUS HEPATITIS	HEPATITIS
VISION ABNORMAL	VISION ABNORM
VISION ABNORMAL NEONATAL	VISION ABNORM
VISION BLURRED	AMBLYOPIA
VISION CENTRAL DEFECTIVE	VISUAL FIELD DEFECT
VISION COLOR TINGED	CHROMATOPSIA
VISION DECREASED	VISION ABNORM
VISION DIM	AMBLYOPIA
VISION DOUBLE	DIPLOPIA
VISION HALO	VISION ABNORM
VISION LOSS	BLIND
VISION LOSS NIGHT	BLIND NIGHT
VISION PERIPHERAL DECREASED	VISUAL FIELD DEFECT
VISION PERIPHERAL DEFECTIVE	VISUAL FIELD DEFECT
VISION TUBULAR	VISUAL FIELD DEFECT
VISION YELLOW	CHROMATOPSIA
VISUAL ACTIVITY DECREASED	VISION ABNORM
VISUAL DISTURBANCE	VISION ABNORM
VISUAL FIELD CONSTRICTION	VISUAL FIELD DEFECT
VISUAL FIELD DEFECT	VISUAL FIELD DEFECT
VISUAL IMPAIRMENT	VISION ABNORM
VITAMIN D DEFICIENCY	AVITAMINOSIS
VITAMIN DEFICIENCY	AVITAMINOSIS
VITAMIN EXCESS SPECIFIED	VITAMIN TOX
VITAMIN EXCESS UNSPECIFIED	VITAMIN TOX
VITAMIN TOXICITY SPECIFIED	VITAMIN TOX
VITAMIN TOXICITY UNSPECIFIED	VITAMIN TOX
VITILIGO	LEUKODERMA
VITREOUS DETACHMENT	VITREOUS DIS
VITREOUS DISORDER	VITREOUS DIS
VITREOUS FLOATER	VITREOUS DIS
VITREOUS OPACITY	VITREOUS DIS
VIVID DREAMS	DREAM ABNORM
VOCAL CORD EDEMA	EDEMA LARYNX
VOCAL CORD PARALYSIS	PARALYSIS VOCAL CORD
VOCAL CORD THICKENING	LARYNGITIS
VOICE ALTERATION	VOICE ALTERAT
VOLUME BLOOD DECREASED	HYPOVOLEM
VOLUME BLOOD INCREASED	HYPERVOLEM
VOLUME PLASMA DECREASED	HYPOVOLEM
VOLUME PLASMA INCREASED	HYPERVOLEM
VOLUME URINE DECREASED	OLIGURIA
VOMITING	VOMIT
VOMITING BLOOD	HEMATEMESIS
VOMITING NEONATAL	VOMIT
VOMITING PROJECTILE	VOMIT
VPC'S	EXTRASYSTOLES VENT
VULVA DISORDER	VULVOVAGINAL DIS
VULVOVAGINAL DISORDER	VULVOVAGINAL DIS
VULVOVAGINITIS	VULVOVAGINITIS
WAKEFULNESS	INSOMNIA
WALKING DIFFICULTY	GAIT ABNORM
WARMTH	VASODILAT
WART	NEOPL SKIN
WASTING	CACHEXIA

WASTING GENERALIZED	CACHEXIA
WATER EXCESSIVE LOSS OF	DEHYDRAT
WATER INTOXICATION	WATER INTOX
WATER RETENTION IN TISSUES	EDEMA GENERAL
WATER RETENTION OF	EDEMA GENERAL
WAVE AMPLITUDE DECREASED	T AMPLITUDE DEC
WBC ABNORMAL (NOS)	WBC ABNORM
WBC ABNORMAL NOS	WBC ABNORM
WBC DEC	LEUKOPENIA
WBC INC	LEUKOCYTOSIS
WEAKNESS DETRUSOR MUSCLE	INCONTIN URIN
WEAKNESS GENERALIZED	ASTHENIA
WEAKNESS LEFT OR RIGHT SIDE	MYASTHENIA
WEAKNESS MUSCLE	MYASTHENIA
WEAKNESS POSTURAL	ASTHENIA
WEAKNESS VOLUNTARY MUSCLE	HYPOTONIA
WEARINESS	ASTHENIA
WEB BAD FINGERS	SYNDACTYLY
WEEPING	EMOTION LABIL
WEGENER'S GRANULOMATOSIS	GRANULOMA
WEIGHT BIRTH EXCESSIVE	BIRTH POSTMAT
WEIGHT BIRTH SUBNORMAL	BIRTH WEIGHT SUBNORM
WEIGHT DECREASE	WEIGHT DEC
WEIGHT DECREASE NEONATAL	WEIGHT DEC
WEIGHT INCREASE	WEIGHT INC
WEIGHT LOSS	WEIGHT DEC
WELTS	URTICARIA
WENCKEBACH PHENOMENON	AV BLOCK SD
WHEALS	URTICARIA
WHEEZING	ASTHMA
WHEEZING EXPIRATORY	ASTHMA
WHEEZING INSPIRATORY	STRIDOR
WILMS TUMOR	CARCINOMA
WITHDRAWAL ARRHYTHMIA	ARRHYTHMIA
WITHDRAWAL BLEEDING	WITHDRAW BLEED
WITHDRAWAL CONVULSIONS	CONVULS
WITHDRAWAL EMOTIONAL	APATHY
WITHDRAWAL FROM SOCIAL CONTACTS	APATHY
WITHDRAWAL HEADACHE	HEADACHE
WITHDRAWAL SYNDROME	WITHDRAW SYND
WITHDRAWAL SYNDROME CORTICOSTEROID	ADDISON CRISIS
WITHDRAWAL SYNDROME NEONATAL	WITHDRAW SYND
WOOZINESS	DIZZINESS
WRITING IMPAIRED	COORDINAT ABNORM
WRONG DOSE ADMINISTERED	MED ERROR
WRONG DRUG ADMINISTERED	MED ERROR
WRONG PATIENT RECEIVED MEDICATION	MED ERROR
WRONG ROUTE OF ADMINISTRATION	MED ERROR
WRYNECK	TORTICOLLIS
XANTHOCHROMIA	CSF ABNORM
XANTHOMATOSIS	XANTHOMA
XANTHOPSIA	CHROMATOPSIA
XERODERMA	ICHTHYOSIS
XEROPHTHALMIA	DRY EYE
XEROSIS	DRY MOUTH
XEROSTOMIA	DRY MOUTH
YAWNING	YAWN

YELLOW SKIN	JAUNDICE
ZINC DEFICIENCY	ELECTROLYTE DEPLET
ZOLLINGER-ELLISON SYNDROME	ULCER PEPTIC



FORMS

Form	Name	Version	Current Version Date	QxQ Version Date
ADJ	Endpoints Adjudication Form	A	1/02/08	10/23/07
AEF	Adverse Events Form	B	10/12/09	1/29/10
BDF	Baseline Demographic Form	A	01/26/07	05/21/07
BMH	Baseline Medical History Form	A	01/25/07	05/21/07
BSR	Blood Specimen Results Form	A	06/28/07	07/17/07
CLR	Central Lab Blood Results Form	B	04/14/10	6/6/07
CMF	Concomitant Medication Form	B	07/18/08	08/07/08
CSL	Central Lab Specimen Shipping Log	B	04/19/10	04/19/10
DDF	Drug Discontinuation Form	A	04/19/07	05/30/07
DMF	DMSA Results Form	B	05/04/07	5/04/07
DSF	DMSA Sedation Form	A	02/07/07	05/21/07
DSS	DMSA Scan Shipping Form	A	02/20/07	06/11/07
DTF	DES Treatment Form	A	08/07/08	09/19/08
DVQ	DV Questionnaire	A	09/19/06	12/12/08
ERF	Eligibility and Randomization Form	D	05/27/09	05/27/09
ESD	Endpoint Source Documentation Cover Sheet	A	04/10/07	06/11/07
EXF	Exit Form	B	3/22/10	3/22/10
FDA 3500A	Medwatch FDA 3500 A	--	Exp. 10/31/08	Exp. 10/31/08
FSS	FDA Signature Sheet	A	1/31/08	1/31/08
FUP	Protocol Scheduled Follow-up Contact Form	C	07/18/08	08/07/08
ICT	Informed Consent Tracking Form	B	03/18/10	03/18/10
ITL	Initials and Training Log	A	1/31/08	1/31/08
LIQ	Life Impact Assessment (LIA) Questionnaire	A	08/31/06	8/31/06
MCA	Medical Care Abstraction Form	C	1/21/10	1/29/10
MCN	Medical Care Notification Form	D	02/23/10	02/23/10
MDD	Medication Dispensing and Dosing Form	A	06/29/07	7/16/07
MDL, MDL-P	Medication Distribution Log	A	07/02/07	7/02/07

Form	Name	Version	Current Version Date	QxQ Version Date
MRF	Medication Return Form	A	01/08/07	10/12/07
NIDDK- BSL	NIDDK Blood Shipping Log	--	Revised August 2006	--
NIDDK-USL	NIDDK Urine Shipping Log	--	4/16/08	--
PCF	Participant Contact Form	A	07/20/06	06/11/07
PEF	Physical Exam Form	A	03/30/07	06/07/07
PSL	Participant Screening Log	B	06/20/08	02/08/08
RCF	Record of Contacts Log	A	4/22/09	06/18/07
RSL	Rectal Swab Shipping Log	A	03/26/07	06/14/07
RSR	Rectal Swab Results Form	C	2/19/08	11/27/07
SCF	Specimen Collection Form	B	01/31/09	04/11/07
TRN	Transfer of Participant Form	A	06/16/08	11/18/08
URF	Ultrasound Results Form	C	05/08/07	6/18/07
USR	Urine Specimen Results Form	B	08/15/07	5/27/09
VRF	VCUG Results Form	C	05/08/07	6/18/07
VSF	VCUG Sedation Form	A	02/07/07	05/23/07
VUS	VCUG / US Scans Shipping Form	A	02/07/07	05/23/07

BASELINE Specimen Collection Scheme

RMUR Randomized Intervention for Children with Vesicoureteral Reflux

Urine Collection - Collect at Randomization

A. Dipstick

If leukocyte esterase Negative (-)
(Proceed with normal randomization)

B. Order local **microalbumin** & **creatinine** on collected urine using the volume required by local lab

C. 1-10 ml in orange-top cup, unfrozen
⇨ Ship to **Biosample Repository**

If leukocyte esterase Positive (trace to +++)*
Collect catheterized or clean-catch specimen & dip again for leukocyte esterase (LE)

If LE negative (-)
Proceed with normal randomization steps B & C to the left.

If LE positive (trace to +++)*
B. Order culture to determine if recurrent UTI
C. Tentatively reschedule randomization

*** WBC count obtained on dipped urine trumps dipstick results (i.e. if LE positive on dip, but WBC is negative, then child is eligible)**

Peri-rectal Swab - Collect at Randomization

⇨ Ship to **Central Lab in Pittsburgh, PA** (R label)
(If shipping delayed for more than 20 minutes, then refrigerate prior to shipping)

Blood Collection - Collect within 14 days of Randomization

1) 

0.5ml in purple EDTA tube for **CBC** ⇨ Send to **Local Lab** (no label)

2) 

1.5ml in yellow SS tube, aliquot serum

Priority 1: 0.5ml for **Cystatin C** and **Creatinine**
⇨ Batched & FROZEN at -70 , ship every 3 months to **Central Lab in Rochester, NY** (C label)

Priority 2 (collect if enough in *this* SS tube): 0.1ml serum for **Electrolytes**
⇨ Send to **Local Lab** (no label)

3) 

For kids ≤ 20lb: collect ONE 3.0 ml ACD tube
For kids > 20lb: collect TWO 3.0 ml ACD tubes, $^{2}/_{3}$ full
⇨ Ship room temperature to **Genetics Repository** (B label)
If ACD tube(s) not collected at Baseline, then collect at a later clinic visit.

4) 

*Collect **ONLY** from kids >20lb*
4.0ml in yellow SS tube ⇨ ***Spin*** and Ship unfrozen (with frozen gel pack) to **Biosample Repository** (S label)

Central Lab in Pittsburgh: Karen.Barbadora@chp.edu
Central Lab in Rochester: gfr@urmc.rochester.edu
Genetics Repository: Dana Witt witt@biology.rutgers.edu
Biosample Repository: BIO-NIDDKRepository@thermofisher.com

RIVUR
Randomized Intervention for Children with Vesicoureteral Reflux

Baseline Visit Checklist

Preparations		Associated Forms
Participant Contact Information (preliminary)		PCF
Urine culture and urinalysis results from index UTI		
Baseline Ultrasound report (performed within 16 weeks after diagnosis of index UTI)		
Baseline VCUG scan report (performed within 16 weeks after diagnosis of index UTI)		VSF
Medical records and reports from index UTI		
Task / Procedure		**Associated Forms**
Begin with…	Informed Consent	ICT
Items that must be performed in the specified order	1. Physical Exam	PEF
	2. Study Eligibility and Randomization	ERF
	3. Study Medication Assignment	MDD, MDL
Data to be collected at any time during the visit	Participant Contact Form	PCF (paper only)
	Baseline Demographic Form	BDF
	Baseline Medical History	BMH
	LIA Questionnaire	LIQ
	DV Questionnaire (if toilet-trained)	DVQ
	Concomitant Medications	CMF
Materials to be distributed to parent / participant	Medication, dosing cup and syringe	
	Participant Handbook/Diary	
	Copy of signed consent form	
Specimen Collection (see reverse)	Urine Collection (collected at randomization)	SCF, USR, BSR, RSL, NIDDK-USL, NIDDK-BSL
	Peri-rectal Swab Collection (collected at randomization)	
	Blood Collection (collected within 14 days of randomization)	
Baseline Imaging	Baseline DMSA scan (performed within 16 weeks after diagnosis of index UTI and within 2 weeks after date of randomization)	DSF, DSS
	Baseline VCUG and Ultrasound scans shipping	VUS

RIVUR

Randomized Intervention for Children with Vesicoureteral Reflux

Baseline Demographic Form

BDF Response Card #1

RIVUR

Randomized Intervention for Children with Vesicoureteral Reflux

Baseline Demographic Form

BDF Response Card #1

BDF RC #1
Annual Household Income

Under $13,500.....A

$13,500 – 23,499 .....B

$23,500 – 33,499 C

$33,500 – 57,999 .....D

$58,000 – 99,999 .....E

$100,000 – 149,999 ...F

$150,000 and above...G

BDF RC #1
Annual Household Income

Under $13,500.....A

$13,500 – 23,499.....B

$23,500 – 33,499.....C

$33,500 – 57,999.....D

$58,000 – 99,999.....E

$100,000 – 149,999 ...F

$150,000 and above...G

RIVUR

Randomized Intervention for Children with Vesicoureteral Reflux

Emergency Unblinding

Contact Information

RIVUR

Randomized Intervention for Children with Vesicoureteral Reflux

Emergency Unblinding

Contact Information

Emergency Unblinding

1. If suspected symptoms of an adverse event are related to study medication, the PI of the participant's clinical center should be notified.

2. If unblinding is necessary during normal DCC hours (Monday-Friday 8:30 am - 5:00 pm EST), contact the DCC using the RIVUR hotline: **1-866-257-7242**

3. If unblinding is necessary after normal DCC hours, contact Myra Carpenter:
   919-942-9408 (home) OR 919-720-0420 (cell)

4. If Myra Carpenter is unavailable, contact
   Lisa Gravens-Mueller:
   919-647-4776 (home) OR 919-793-3641(cell)

Emergency Unblinding

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2. If unblinding is necessary during normal DCC hours (Monday-Friday 8:30 am - 5:00 pm EST), contact the DCC using the RIVUR hotline: **1-866-257-7242**

3. If unblinding is necessary after normal DCC hours, contact Myra Carpenter:
   919-942-9408 (home) OR 919-720-0420 (cell)

4. If Myra Carpenter is unavailable, contact
   Lisa Gravens-Mueller:
   919-647-4776 (home) OR 919-793-3641(cell)

RMUR
Randomized Intervention for Children with Vesicoureteral Reflux

END OF STUDY Specimen Collection Scheme

Urine Collection - Collect at END OF STUDY visit

A. Dipstick to screen for leukocyte esterase
If trace or positive, send urine for culture.

B. Order local **microalbumin** & **creatinine** on collected urine using the volume required by local lab

C. Send collected urine (1-10 ml) in orange-top cup, unfrozen
⇨ Ship to **Biosample Repository** (U label)

Peri-rectal Swab* - Collect at END OF STUDY visit

⇨ Ship to **Central Lab in Pittsburgh, PA** (R label)
(If shipping delayed for more than 20 minutes, then refrigerate prior to shipping)

*** If off study medication for > 6 months, then swab is not required, however it is required for Treatment Failures**

Blood Collection - Collect at END OF STUDY visit

1) 

0.5ml in purple EDTA tube for **CBC**† ⇨ Send to **Local Lab** (no pre-printed label)

† **If Treatment Failure or off study medication for > 6 months, then CBC is not required**

2) 

1.5ml in yellow SS tube, aliquot serum

Priority 1: 0.5ml for **Cystatin C, Creatinine and C Reactive Protein**
⇨ Batched & FROZEN at -70° C, ship every 3 months to
Central Blood Lab in Rochester, NY (C label)

Priority 2 (collect if enough in *this* SS tube): 0.1ml serum for **Electrolytes**
⇨ Send to **Local Lab** (no pre-printed label)

3) 

*Collect **ONLY** from kids >20lb*
4.0ml in yellow SS tube ⇨ ***Spin*** and Ship unfrozen (with frozen gel pack) to
Biosample Repository (S label)

NOTE: If ACD tube(s) for Genetics Repository not previously collected, then collect at exit visit.

Central Swab Lab in Pittsburgh: Karen.Barbadora@chp.edu
Genetics Repository: Dana Witt witt@biology.rutgers.edu
Central Blood Lab in Rochester: paula_maier@urmc.rochester.edu
Biosample Repository: BIO-NIDDKRepository@thermofisher.com

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Randomized Intervention for Children with Vesicoureteral Reflux

Exit Visit Forms Checklist

Task / Procedure		Associated Forms
Data to be collected at any time during the visit	Participant Contact Form	PCF (paper only)
	Protocol Scheduled Follow-Up Form	FUP
	Physical Exam Form	PEF
	LIA Questionnaire	LIQ
	DV Questionnaire (if toilet-trained)	DVQ/DTF
	Concomitant Medications	CMF
	Exit Form	EXF
Study Medication	Collect used and unused study medication bottles	MRF
Specimen Collection (see reverse)	Urine Collection	SCF, USR, BSR, RSL, CSL, NIDDK-USL, NIDDK-BSL
	Peri-rectal Swab Collection	
	Blood Collection (exit blood collection may be collected at the exit DMSA)	
Exit Imaging	Exit DMSA scan (performed within 4 weeks of exit visit if permitted; treatment failures may already have had exit DMSA)	DSF, DSS
	Exit VCUG scan shipping	VUS, VSF

RMVUR
Randomized Intervention for Children with Vesicoureteral Reflux

Inclusion – child must meet all

- ☑ Age: 2 months to less than 6 years (72 months) at randomization
- ☑ **First or second** UTI with ≥ 38°C fever **OR** symptoms related to urinary tract documented within ± 24 hours of UTI work-up (symptoms include dysuria, urgency, frequency, abdominal pain, foul-smelling urine, and in infants, dehydration, hypothermia, and failure to thrive)
- ☑ Index UTI diagnosis occurred within 112 days of randomization
- ☑ Pyuria on UA shown in 1 of 3 ways:
  - ≥ 10 WBC/mm^3 **OR**
  - ≥ 5 WBC/HPF **OR**
  - Leukocyte esterase ≥ trace on dipstick
- ☑ Culture proven infection with single primary organism:
  - ≥ 50,000 CFU/mL (cath or aspirated) **OR**
  - ≥ 100,000 CFU/mL (clean void)
- ☑ Index UTI treated for 7+ days with effective drug OR test of cure (neg urine culture) post treatment
- ☑ VUR grade I-IV in at least one ureter

SEE OTHER SIDE FOR EXCLUSION

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RIVUR
Randomized Intervention for Children with Vesicoureteral Reflux

Exclusion – child meets one or more

- ☒ If child < 6 mos old, gestational age <34 wks
- ☒ VUR diagnosed or treated between 1st and 2nd UTI
- ☒ Greater than two organisms present on index UTI urine culture
- ☒ Second organism present at >10,000 CFU/mL
- ☒ Consent not obtained OR inability to complete protocol
- ☒ Allergy to TMP/SMZ
- ☒ Grade V VUR in either ureter
- ☒ Co-morbid urologic anomalies: hydronephrosis, ureterocele, urethral valve, solitary or profoundly small kidney, multicystic dysplastic kidney, neurogenic bladder pelvic kidney or fused kidney.
- ☒ History of other renal injury/disease
- ☒ Any bladder or renal surgeries
- ☒ Congenital or acquired immunodeficiency
- ☒ Underlying anomalies or chronic diseases that could potentially interfere with response to therapy such as gastrointestinal conditions (malabsorption, inflammatory bowel disease), liver/kidney failure or malignancy
- ☒ Complex cardiac disease
- ☒ Family hx of anaphylactic reaction to sulfa

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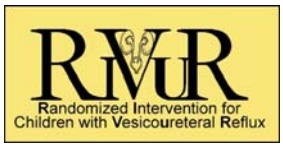
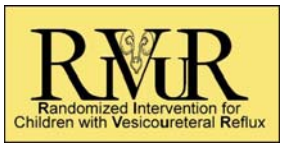


RIVUR HOTLINE:
1-866-257-7242

Topic	Primary Contact	
Emergency Un-blinding or Phone Randomization	During business hours call the hotline.	After hours: Lisa Gravens-Mueller 919-647-4776 (h), 919-564-5459 (c) Myra Carpenter 919-942-9408 (h), 919-720-0420 (c)
Website, Labels, Exit gifts, IRB	Rachel Goolsby: 919-843-0685; email: rwgoolsby@unc.edu	
Study Drug Issues & Monitoring Visits	Ashley Bizzell: 919-962-3231; email: AshleyBizzell@unc.edu	
Blind Replicate Matching & Data Mgmt Report	Gang Cui: 919-962-3259; email: gcui@unc.edu	
PACS & Data Checks	Ashley Britt: 919-962-3223; email: adbritt@unc.edu	
Endpoints & DMSA Reimbursements	Barbara Brown: 919 962-3092; email: barbw_brown@unc.edu	



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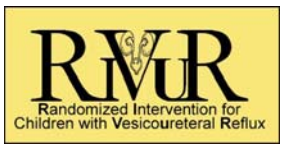

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