ICDB Interstitial Cystitis Data Base

INTERSTITIAL CYSTITIS DATA BASE STUDY

CLINICAL CENTER

MANUAL OF OPERATIONS

VERSION 4.1

June 14, 1995

ICDB Clinical Centers at: 1)University of California at San Diego, 2)Northwestern University/University of Wisconsin, 3)William Beaumont Hospital/Henry Ford Hospital, 4)University of Pennsylvania, and 5)University of Oklahoma
ICDB Data Coordinating Center at: M. S. Hershey Medical Center, Hershey, PA

Table of Contents

Interstitial cystitis (IC) is a chronic, inflammatory bladder condition of unknown etiology. The symptom complex, found in a significant percentage of the adult population, affects women predominantly. The symptoms are variable, but usually include some combination of pelvic and/or perineal pain and urinary frequency (as often as every 15 minutes in severe cases). Some patients are incapacitated by the pain or by the sleep deprivation resulting from nocturnal urinary frequency. In spite of this significant morbidity, there has been little research concerning IC until recently. However, the existing data contain many conflicting and incongruous findings, possibly because the condition "IC" includes more than one disease process. (For a review, see Hanno [1]).

Several factors have inhibited advances in the understanding of IC. These include the lack of specific diagnostic criteria, the lack of specific histopathologic changes, the unpredictable fluctuation in symptoms, and the extreme variability among patients in terms of symptoms, objective findings, and treatment responses.

In order to understand the treated history of IC, a database containing longitudinal data on patients with IC symptomatology needs to be established and maintained. Such a database affords the possibility of identifying patient subgroups with specific symptoms, physical findings, histopathologic findings, and common treatment responses. In this manner, etiologic factors may be identified and treatments may become more focused.

2. Specific Aims June 14, 1995

The overriding goal of the ICDB Study is to develop and maintain a centralized, standardized registry containing data on patients with symptomatology consistent with IC. Data collected on patients at baseline and longitudinally will include demographic and diagnostic information, dietary habits, patient and family medical history, symptoms, and treatments and their outcomes. In addition, bladder tissue specimens will be stored in a specimen bank for future use by qualified investigators.

The ICDB Study investigators plan to meet the following objectives once the data and specimen registry has been developed:

Primary Objectives
The primary study objectives are:

1. To determine the treated history of IC based on the longitudinal patient data.

2. To identify the age, sex, race, and other demographic characteristics of patients in the database with symptomatology consistent with IC.

3. To maintain a bladder biopsy specimen bank.

Secondary Objectives
The secondary study objectives are:

1. To develop a symptom index which discriminates among patients with varying kinds and levels of IC symptoms. The symptom index will be used to formulate distinct subgroups of patients with the IC symptom complex.

2. To provide other interested and qualified investigators with data and bladder specimen samples so that they may conduct their own epidemiological and clinical studies.

Operational Objectives
The ICDB Study has the following operational objectives:

1. To recruit, and retain throughout the follow-up period, at least 273 study patients in each of the five Clinical Centers.

2. To ensure the attainment of high quality data via adherence to and monitoring of standardized data collection procedures.

3. To ensure efficient and accurate transfer of data between each of the five Clinical Centers and the Data Coordinating Center.

The ICDB Study organization contains 5 Clinical Centers, a Data Coordinating Center, a Core Anatomic Pathology Laboratory, a Steering Committee, an External Advisory Committee, NIDDK Project Staff, and several working subcommittees. The responsibilities of each component are described below.

3.1. CLINICAL CENTERS

The responsibilities of each of the 5 Clinical Centers include:

1. Recruiting and following patients throughout the course of the four-year study.
2. Confirming eligibility of each patient based on the study criteria identified in the protocol.
3. Adhering to study protocol in the implementation of procedures and the acquisition of data.
4. Collecting data of high quality.
5. Collaborating with other study investigators in the development of the manual of operations, acquisition of high quality data, and the analysis and publication of study results.

3.2. DATA COORDINATING CENTER

The Data Coordinating Center is responsible for coordinating all activities pertaining to forms development, forms production, forms distribution, data collection, data entry, data management and data analysis. Additional responsibilities include:

1. Based on collaboration with the Steering Committee and NIDDK Project Officer, preparing the study protocol, manual of operations, and data forms.
2. Providing overall leadership in the epidemiological study design.
3. Collaborating with other study investigators in the development and testing of data forms and study procedures.
4. Developing data and specimen tracking procedures.
5. Training Clinical Center staff and monitoring clinic performance in overall study procedures.
6. Coordinating Steering Committee and External Advisory Committee meetings.
7. Coordinating the Core Anatomic Pathology Laboratory.
8. Providing detailed reports regarding patient recruitment and retention, data collection activities, and interim results to the External Advisory Committee.
9. Collaborating with other study investigators in the analysis and publication of study results.

3.3. NIDDK PROJECT OFFICER

The NIDDK Project Officer's primary responsibility is to provide scientific support in all aspects of the ICDB Study, including protocol development, quality control, interim data monitoring, final data analysis and interpretation, preparation of publications, and performance monitoring.

3.4. CORE ANATOMIC PATHOLOGY LABORATORY

The Core Anatomic Pathology Laboratory (APL) is primarily responsible for successfully receiving, evaluating and storing ICDB bladder biopsy specimens. To ensure the successful receipt of specimens, the APL is responsible for tracking specimens shipped from each of the 5 Clinical Centers. To evaluate bladder specimens, the Director of the APL will create a Pathology Reading Group (PRG) comprised of 3 genitourinary pathologists. Each of the 3 PRG members will evaluate each biopsy specimen individually, then the PRG will convene as necessary to arrive at a consensus on conflicting assessments. To ensure safe storage of all database specimens, the APL will store the adequately labelled specimens in a secure, locked cabinet.

3.5. STEERING COMMITTEE

The Steering Committee is the primary governing body of the study. Steering Committee members include the NIDDK Project Officer and the principal investigator from each of the Clinical Centers and the Data Coordinating Center. Although other study investigators will often attend meetings, all major scientific decisions will be made by the Steering Committee (one vote for each member). The primary responsibilities of the Steering Committee include:

1. Identifying the specific aims of the study.
2. Determining study eligibility criteria.
3. Developing the study plan.
4. Developing the study protocol and manual of operations, and participating in data forms development.
5. Overseeing standardized implementation of the study protocol.
6. Establishing subcommittees, as needed.
7. Reviewing and approving all publications based on any data collected for the ICDB Study.
8. Monitoring overall study quality control.
9. Approving outside study investigators for access to data and stored specimens for their own epidemiological and clinical studies.
10. Establishing the time line for the study.
11. Establishing the goals and the agenda for Steering Committee meetings.
12. Recommending the timing of the External Advisory Committee meetings, and providing input for the agenda of these meetings.

3.6. WORKING SUBCOMMITTEES

The Steering Committee establishes working subcommittees as needed to carry out various tasks to achieve the specific aims. Subcommittees (refer to Appendix A: *ICDB Working Subcommittees)* have been established to carry out the following charges:

1. Committee on the Use of a Control Group
   This subcommittee is responsible for addressing the following questions pertaining to the use of a control group:
   - Is a control group necessary for the ICDB Study?
   - If so, how many control groups, and what type?
   - What is the anticipated additional cost of including control groups?
   - Is it feasible to include control groups in this project?

2. Committee on Data Coordination
   This subcommittee is responsible for recommending to the Steering Committee what data should be collected for the ICDB Study.

3. Patient Incentives Committee
   This subcommittee is responsible for recommending to the Steering Committee incentives to recruit and retain patients in the ICDB Study.

4. Committee on Psychological Considerations
   This subcommittee is responsible for recommending to the Steering Committee whether questions concerning a patient's sexual and psychological history should be included in the database.

5. Committee on Access to ICDB Study Data and Patient Specimens
   This subcommittee is responsible for handling all issues pertaining to the access of ICDB Study data and patient specimens, including:
   - Developing a policy of handling internal and external requests for patient data and specimens.
   - Implementing the policy of handling requests for access to patient data and specimens.

6. ICDB Promotional Flyer Committee
   This subcommittee is responsible for developing a flyer to promote the ICDB Study to potential participants.
7. Public Information Committee
   This subcommittee is responsible for handling all issues pertaining to the dissemination of general information on the ICDB Study to the general public.

8. Committee on Publications, Presentations, and Ancillary Studies
   This subcommittee is responsible for reviewing for approval all proposed ancillary studies and handling all issues pertaining to publications and presentations, including:
   - Recommending policy and procedures for review and approval of all communications regarding the ICDB Study to outside groups.
   - Identifying publications to be written during the course of the study, including target dates for each.
   - Proposing policy guidelines for authorship of ICDB publications.
   - Monitoring the writing of each paper to ensure publication in a timely fashion.
   - Selecting writing groups to prepare each proposed manuscript.
   - Establishing standards of excellence for ICDB publications.
   - Reviewing, editing, and approving all ICDB publications and presentations prior to submission, enlisting the assistance of ICDB study members whenever appropriate.
   - Reviewing, recommending necessary revisions, and approving any publications arising from approved ancillary studies prior to their submission for publication.
   - Suggesting appropriate journals for ICDB publications, and monitoring the process of publication.
   - Performing other writing, reviewing or editing tasks as assigned by the Steering Committee.

9. Patient Classification Working Group Committee
   This subcommittee is responsible for developong an objective classification system(s) derived from baseline screening variables that will permit patients with the IC symptom complex to be assigned to clinically meaningful subgroups. Ideally, the resulting symptom index(es) will discriminate among patients with varying kinds and levels of IC symptoms, and potentially different IC processes.

10. Patient Outcomes Working Group Committee
    This subcommittee is responsible for developing an objective scoring system(s) derived from contrasts between baseline screening and follow-up variables that will permit patient outcomes to be defined.
11. Medication/Treatment Working Group Committee
    This subcommittee is responsible for developing an aggregate classification system of medications and treatments, utilizing the 6-digit code recorded for each treatment and/or concomitant medication event in the ICDB. This will be based on data collected on treatments and concomittant medications at baseline (not historical information).

12. Patient/Study Closeout Committee
    This subcommittee is responsible for developing a policy for the timely and efficient closeout of patient data collection and study activities.

3.7. EXTERNAL ADVISORY COMMITTEE

The External Advisory Committee is an independent advisory group composed of experts in relevant medical, statistical, and bioethical fields. The primary responsibility of the Committee is to periodically review the progress of the ICDB Study, and to provide advice to the NIDDK Project Officer regarding the scientific merit of the study.

4.1. CHANGING THE PROTOCOL

The objectives of the ICDB Study are most likely to be achieved if the protocol does not require alteration during the study. Any changes in the protocol will result in some degree of heterogeneity of the data, which complicates the analyses and may compromise the scientific integrity of the study. However, occasions may arise in which protocol changes are necessary. Therefore, changes in the protocol will be considered only if they are required to ensure patient safety or will significantly enhance the scientific validity of the study.

Initiating a Protocol Change

Any member of the ICDB Study may request a change to any portion of the study protocol. The member wishing to change the protocol should present the proposed change(s) in writing to either the Chair of the Steering Committee or the Principal Investigator of the Data Coordinating Center (DCC), who will then contact the other. The DCC Principal Investigator and the Chair of the Steering Committee will then jointly decide on the appropriate mechanism (letter, conference call, meeting) to handle the proposal depending on the implications of the proposed change. Proposed changes with only a minor impact on the current course of the ICDB study can be properly handled through a letter to each member of the Steering Committee. Proposed changes with a greater impact on the course of the ICDB Study will be presented to the Steering Committee via conference call or formal meeting to allow all members to benefit from the scientific debate generated in these discussions. Proposed changes can be implemented only after: 1) the Steering Committee reaches a majority vote, 2) the NIDDK Project Officer approves of the proposed changes, and 3) the External Advisory Committee has been notified of the change(s). Once a proposed change has been approved, the DCC will coordinate all activities required to implement the change.

4.2. PUBLICATIONS AND PRESENTATIONS

4.2.1 Introduction

The policy of the ICDB Study concerning publications and presentations is designed to achieve five objectives:

i. To assure timely publication of the results of the ICDB Study to the appropriate professional audiences,

ii. To avoid premature publication of results that might compromise the performance of the study (such as by publication of trend results before such trends become statistically convincing) or that might compromise the ability to publish the results in high quality peer reviewed journals (as by premature release to the lay press),

iii. To maintain high standards of quality of all material published by the ICDB Study,

iv. To guard against duplicate publication of results by assuring absence of overlap of materials prepared by various writing committees, and

v. To assure equitable attribution of credit to all of the professionals participating in the ICDB Study.

To accomplish these ends, it is the policy of the ICDB Study that preparation of all publications or presentations, other than materials prepared for local publicity purposes, must be assigned by the Steering Committee to specifically appointed writing committees, and that all such materials must be reviewed and approved by the Publications, Presentations, & Ancillary Studies (PP&AS) Committee before publication. For more information, see Section 3.8: *Committee on Publications, Presentation, and Ancillary Studies* and Appendix A: *Committee Listings*.

4.2.2 Scope of Policy and Exception for Local Publicity Materials

All material to be presented orally or submitted for publication or dissemination by individuals associated with the ICDB Study and dealing with any aspect of the ICDB Study must receive prior review and approval by the PP&AS Committee with the following exception:

> Material prepared for publicity purposes either nationally or within the recruitment region of an ICDB Clinical Center, or presented orally or as handouts or posters to professional audiences solely for the purposes of informing the profession of the ICDB Study and its objectives, need not be reviewed by the PP&AS Committee. Such material must be limited to a background discussion of the disease Interstitial Cystitis and a description of the ICDB Study organization, objectives, and entrance criteria, and to results of the study that have previously been presented to a scientific body or published in a scientific journal. It must not influence discussion of any previously unpresented or unpublished ICDB Study outcomes or results, and must not itself result in publication of an abstract or other citable professional reference.

4.2.3 Source of Suggestions for Publications of the ICDB Study

All participants in the ICDB Study are invited to suggest topics appropriate for presentation as abstracts, peer reviewed papers, or chapters and reviews from the ICDB Study. Such suggestions should be made to the Chair of the PP&AS Committee, who shall review the request to be certain that there is no overlap with materials previously assigned to other writing committees. The Chair of the PP&AS Committee will forward copies to the Chair of the Steering Committee. Where such overlap exists, the Chair of the PP&AS Committee may make recommendations to the Steering Committee that the suggestion be referred to an existing writing committee, that additional

participants be added to existing writing committees, or make other suggestions to resolve the overlap. However, final decision in this matter rests with the PP&AS Committee Chair.

It is the policy of the ICDB Study to encourage non-physician professionals to prepare scientific presentations for their own professional meetings and to prepare scientific papers for their own professional journals in addition to participating in the preparation of papers for medical journals. Since the subject matter of these reports and papers may overlap with material being prepared by writing committees for medical journals, it is the policy of the ICDB Study that under these circumstances, rather than forming a new writing committee, such non-physician professionals should be added to the existing writing committee concerned with related matters, specifically for the purposes of preparing such reports. The authors of these presentations and reports will be the members of the writing committee, with first author being the individual added to the committee for this purpose, using the appropriate authorship style described in section 4.2.6.

In addition, the PP&AS Committee will formulate and maintain a list of suggested topics that should be prepared for publication, to assure that all completed aspects of the work of the ICDB Study are reported to the scientific community in a timely fashion.

4.2.4 **Assignment of Writing Committees**

The Chair of the PP&AS Committee, upon receipt of a recommendation for preparation of a topic for publication, and after confirming that the topic does not overlap with a previous assignment to another writing committee, will submit a proposal to the Steering Committee for approval of the publication effort and the approval of the chair of the writing committee. Appointments of writing committee chairmanships will be made in an equitable fashion to all professionals -- physicians, research coordinators, nurses, statisticians, and others -- in a fashion that recognizes the special contributions of each member of the ICDB Study to its performance.

Upon appointment of the Chair of a new writing committee, the Chair of the PP&AS Committee will notify each collaborating center, including clinical centers, the DCC, the APL, and the NIH, of the new writing committee, soliciting indications of interest to be on that writing committee. If more individuals express interest than is practical to assign to a committee, the PP&AS Committee Chair shall make the final assignments of the members of the committee.

In all cases, writing committees dealing with an issue that requires analysis of data by the DCC will have a member of the DCC assigned to it.

From time to time it may be expedient for the chairmanship of a writing committee to be reassigned to another member of that committee, or for members to be dropped from or added to a writing committee. The Chair of the PP&AS Committee is authorized to make such changes with the consensus of the members of the writing and PP&AS committees, or on his own authority where there is clear cause.

4.2.5 Classes of Reports of the ICDB Study

There are four classes of reports of the ICDB Study:

A. Reports of the major outcomes of the Study. It is assumed that there will generally be only one or two such overall reports derived from each phase of the Study. Generally these reports will be prepared by the Steering Committee serving as the writing committee, with the Chair of the Steering Committee as the Chair of this committee.

B. Reports addressing in detail one aspect of the ICDB Study, but in which the data are derived from the entire study.

C. Reports of data derived from a subset of centers by members of the ICDB Study, (e.g., substudies or ancillary studies), or originally conceived analyses of data from the entire ICDB Study (original analyses).

D. Reports of investigations initiated outside of the ICDB Study, but using data or samples collected by the ICDB Study. The investigators may be ICDB or other investigators, but the source of the ideas and the funding for the study will have been derived outside of the ICDB Study itself.

4.2.6 Authorship Policy

The authorship policy of the ICDB Study must achieve two somewhat conflicting goals. First, it is recognized that the findings of the study, especially the findings reported in Type A and B reports, are derived from the efforts of the entire ICDB professional staff. Thus, all reports, of whatever type, must give recognition to all the participants of the ICDB Study, and reports of Types A and B must give primary recognition to the entire study professional staff. On the other hand, it is recognized that the preparation of a manuscript places special demands on the assigned writing committee, and especially on the Chair of the writing committee. Further, recognition of special effort and achievement is important in the professional careers of the study staff, and specific listing as an author is a significant motivating factor that will help assure prompt completion of writing assignments and timely publication of the results of the ICDB Study. The ICDB authorship policy attempts to recognize each of these goals. The authors of ICDB publications will be listed as detailed below for each type of publication. The order of authorship shall be determined by the Steering Committee after receiving recommendations from the PP&AS.

All publications and presentations:

Abstracts: by members of the writing committee, listed according to the Steering Committee's recommendations "and the ICDB Study"[1], presented by XXXX. (This will usually be the Chair of the writing committee).

Papers: by members of the writing committee, listed according to the Steering Committee's recommendations "and the ICDB Study"[1]

[1]
- The ICDB participant box, Table 4.1, must be included in Type A papers.
- The ICDB participant box will be included in all papers if this can be arranged with the publisher. Otherwise it will be referenced in one of the Type A papers. It will not be practical to publish the entire list of participants in abstracts.
- The participant box will be included in all Type C papers if this can be arranged with the publisher. Otherwise it will be referenced in one of the Type A paper
- The ICDB participant box In type D papers, the list of participants will be referenced in all cases. It will not be practical to publish the entire list of participants in abstracts.

4.2.7 Listing of Professional Participants in the ICDB Participant Box

The ICDB Study participant box will list all professionals that have participated in the ICDB Study for a minimum of one year. The participants for each participating center will be listed together, with the center Principal Investigator listed first, and identified as "P.I." followed by the other center staff listed alphabetically. Each participant will be listed only by his/her professional and academic degrees, not by the specific position which he/she held in the study.
The centers will be listed in the following order:

Chair of the Steering Committee
Clinical Centers
DCC
APL
NIH

Prior to the publication of any papers from the ICDB Study, each center will be asked to confirm and approve the listing of the personnel from that center in the ICDB Participant Box.

ICDB Study Group

University of Pennsylvania
- Alan J. Wein, MD (PI)
- Marilou Foy, RN
- Philip M. Hanno, MD
- Frederick Monson, PhD
- Denise Nigro, MD
- Kristene E. Whitmore, MD

University of California at San Diego
- C. Lowell Parsons, MD (PI)
- Paul Stein, PhD
- Mary Williams

University of Oklahoma
- Daniel J. Culkin, MD (PI, 1996+)
- Johnny B. Roy, MD (PI, 1993-1996))
- Robert E. Hurst, PhD
- Lori Mulrooney, RN (1995+)
- Linda Walker, RN (1993-1995)

Northwestern University
- Anthony Schaeffer, MD (PI)
- Mary Neiweglowski, RN, BS (1993-1996)
- Gwen Maurer, RN (1996+)

University of Wisconsin at Madison
- David T. Uehling, MD (Co-PI, 1995+)
- Edward M. Messing, MD (Co-PI, 1993-95)
- Diane Pauk, BS

William Beaumont Hospital
- Ananias C. Diokno, MD (Co-PI)
- Alexandre Afanasyev, MD (1993-1996)
- Eleanor Anton, RN (1996+)
- Bruce W. Steinert, PhD

Henry Ford Hospital
- Aaron Kirkemo, MD (PI)
- David Burks, MD
- Michelle Peabody RN, BSN

The Pennsylvania State University College of Medicine (DCC)
- J. Richard Landis, PhD (PI)
- Laura J. Simon, MA
- Yvonne L. Matthews Cook, MA
- Deborah Erickson, MD
- Douglas W. Gray, MS, MPA
- Allen R. Kunselman, MA
- Brenda Phillips BA
- Susan J. Boehmer, MA
- Amy Paynter, BS
- Suzanne Trosko Abele, BS
- Elizabeth Phillips, BS
- Patricia Rawa, BS
- Brenda Beers
- Randy Hilderbrand, BS
- Steve Durborow, BS

University of Pennsylvania (Anatomic Pathology Laboratory)
- John E. Tomaszewski, MD (Director)
- Li-Ping Wang, MD
- Pathology Reading Group
  - Thomas Williams, MD, University of New Mexico
  - Valentina Russack, MD, Scripps Clinic & Research Foundation

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
- Leroy M. Nyberg, PhD, MD (Project Officer)
- John W. Kusek, PhD
- Camille Jones, MD, MPH

ICDB Study Consultants
- Edward M. Messing, MD (1995+), University of Rochester
- Michael O'Leary, MD, Brigham and Women's Hospital

4.1 ICDB Study Participant Box

4.2.8 Acknowledgement of Support and Reprint Addresses

Acknowledgement of grant support is to be used in all papers reporting results of the ICDB Study. In the case of ancillary studies, additional sources of support should be cited as appropriate.

The ICDB Study is supported by the Division of Kidney, Urologic and Hematologic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases, NIH, through cooperative agreements.

The following information regarding reprint requests should be included in all papers prepared for the ICDB Study. The DCC will maintain an inventory of all ICDB Studies and will address all requests for reprints.

Requests for reprints should be addressed to:

The ICDB Data Coordinating Center
Center for Biostatistics & Epidemiology
Penn State College of Medicine
M. S. Hershey Medical Center
P.O. Box 850
500 University Drive
Hershey PA 17033

4.2.9 Schedule for Completion of Writing Assignments and Resolution of Overlaps Between Writing Committees

At the time that a writing committee is constituted by the Chair of the Steering Committee, the PP&AS Committee will establish a timetable for the completion of the writing assignment that takes into account deadlines for the publication, the amount of time that will be required for data analysis, the other commitments of the DCC, and the priority of the publication. The Chair of the writing committee must provide the Chair of the PP&AS Committee a general outline of the proposed publication within 30 days of receiving its assignment, to permit the PP&AS Committee to identify any overlap with the assignments of other writing committees, and to permit establishment of an appropriate timetable. Where overlaps of materials to be covered by different writing committees are detected, the Chair of the PP&AS Committee will attempt to resolve these informally with the chairs of the involved writing committees. In the event that this effort at mediation fails, the issue will be resolved by the Chair of the Steering Committee. The Chair of the PP&AS Committee will report at each meeting of the External Advisory Committee and the Steering Committee on the progress of the various writing committees.

4.2.10 Review of Abstracts and Presentations by the PP&AS Committee

To expedite review of abstracts, oral presentations, and any other material for which there is an

explicit deadline for submission, the following procedure will be used:

i. The writing committee wanting to submit an abstract, give a talk, or submit other material for which there is an explicit submission deadline must contact the Chair of the PP&AS Committee 14 days prior to the submission deadline. In the event that the Chair is unavailable, Co-Chair may be contacted. The Chair (or Co-Chair) will name a subcommittee of three (3) members of the PP&AS Committee to review the submitted materials and will inform the writing committee and the PP&AS subcommittee of their appointment. The submitted material must be mailed by the submitter directly to the PP&AS members so as to reach them no fewer than seven (7) days prior to the deadline for submission.

ii. The members of the PP&AS subcommittee will review the submitted material and notify the Chair of the PP&AS Committee solely, in writing, of their approval or disapproval. If there is unanimous approval, the PP&AS Committee Chair (or Co-Chair) shall inform the submitter that he/she has ICDB Study approval for the submission. In the event of a split vote for approval, the issue will be submitted to the Steering Committee for resolution.

iii. All materials submitted for approval in this fashion will be distributed by overnight mail, together with notice of the disposition, to all members of the PP&AS Committee. All approved materials will also be forwarded to the NIH Project Officer, and for record-keeping purposes to the DCC, and will be distributed to the entire membership of the Steering Committee at the next meeting of that Committee as an appendix to the report of the PP&AS Committee.

iv. In the case of abstracts or other similar written material, the entire material to be submitted must be sent by the submitter for review by the entire Steering Committee.

v. In the case of an oral presentation, an outline of the talk and a copy of any slides to be presented must be submitted for review to the PP&AS Committee.

vi. Approval for submission of an abstract does not automatically grant approval of the material ultimately to be presented. This material must also be submitted for review and approval in accordance with the above rules at least seven (7) days prior to the scheduled oral or poster presentation.

4.2.11 **Review of Papers by the PP&AS Committee**

All materials for which there is no explicit deadline, and all full papers that may result in a citable scientific reference, whether or not there is a deadline for submission, must be submitted to the Chair of the PP&AS Committee for formal review by the entire Steering Committee. If there is a deadline

for submission of a formal paper, it is the responsibility of the submitter to be certain that it is submitted to the PP&AS Committee Chair, at least 30 days prior to the deadline, to permit such review. This review will be conducted as follows:

i. The PP&AS Committee Chair shall appoint a panel of three primary reviewers, two of whom must be PP&AS Committee members and one of whom may be any professional member of the ICDB Study Group with appropriate expertise. The Chair shall distribute the material to all members of the PP&AS Committee and to the Principal Investigator of each center participating in the ICDB Study. The three members of the review panel shall each prepare and send to the Chair a written critique of the submitted material for distribution to the entire PP&AS Committee. The P.I.s of the various clinical centers will be given a deadline by which any comments or critiques from their center must be received by the PP&AS Committee Chair. This mechanism will assure that each professional participating in the ICDB Study will have an opportunity to review all materials that will be submitted for publication bearing his/her name as a participant and co-author.

ii. The PP&AS Committee Chair shall schedule a meeting of the Committee (generally by conference call) to discuss review of papers and other non-time critical materials such as agenda items. The reviews of the panel members and any comments received from the clinical center P.I.s will be distributed to the committee with the agenda.

iii. While discussion of the submitted papers and other materials will be led by the three appointed reviewers, all members of the Steering Committee will be invited to participate and all shall vote on final disposition.

iv. In keeping with medical editorial traditions, there are three possible dispositions: approval of the material as submitted (possibly with some recommendations for revision that do not require re-review), non-acceptance of the material as submitted but with recommendations to the authors for revisions and resubmission, and disapproval of the material.

v. The PP&AS Committee Chair shall be responsible for communicating the decision of the Committee to the authors, together with a summary of suggestions for revision, if any. If the Committee has recommended non-acceptance of the material as submitted but with suggestions for revision and resubmission, he and the writing committee may agree not to proceed with a report to the External Advisory or Steering Committees at that time, pending revision and resubmission.

vi. If there is a recommendation for approval or final disapproval of submitted material, or if there is a recommendation for revision which is contested by the author(s), the PP&AS Committee Chair shall report this outcome in writing to the Steering Committee for final action. In the case of a dispute between the PP&AS Committee and the author(s), the

PP&AS Committee Chair shall provide a copy of the submitted material and a summary critique to the Steering Committee, and the chair of the writing committee shall be given an opportunity to submit a rebuttal.

vii. The authority to grant final approval for a formal scientific paper of the ICDB Study rests with the Steering Committee. In the event that a delay until the next Steering Committee meeting would be disadvantageous, the Steering Committee shall meet via a phone conference and vote for approval.

viii. All materials submitted for approval in this fashion will be forwarded, together with notice of disposition, to the Chair of the Steering Committee. All materials receiving final approval by the Steering Committee will also be forwarded to the NIH Project Officer, and for record-keeping purposes to the Principal Investigator of the DCC.

ix. In the event that editors of a scientific journal to which an approved ICDB scientific manuscript is submitted suggest or require revisions of the manuscript, the revised manuscript must be reviewed again by the PP&AS Committee prior to resubmission in the same manner as described above. The PP&AS Chair should attempt to appoint the same reviewers that first read the paper to review the revision, and every effort will be made to expedite such repeat reviews. The authors should include the journal reviewers comments and suggested revisions with their resubmission to the PP&AS Committee.

4.2.12 Criteria for Review of Materials by the PP&AS Committee

All materials submitted to the PP&AS Committee will be reviewed for acceptability on two grounds:

i. Materials will be evaluated for scientific accuracy, quality, importance, and style. The intent is to assure that all approved ICDB materials reflect well on the ICDB Study.

ii. Materials will be reviewed to assure appropriateness of the content. The material will be reviewed to assure that it conforms to the assignment of the writing committee, addressing satisfactorily the assigned topics and not encroaching on material assigned to other writing groups. In addition, the material will be reviewed to assure that it does not divulge prematurely additional outcomes or findings of the ICDB Study or compromise the eventual publication of ICDB findings in high quality peer reviewed journals. In this latter regard, it must be remembered that publication of reports of more than 400 words are generally taken to constitute prior publication of a body of material and will generally preclude subsequent publication of the material in a peer reviewed journal.

4.2.13 Maintenance of Records of Publications and Presentations

The DCC will maintain a record of all official publications and presentations of the ICDB, separated

into the following categories:

i. Peer reviewed papers accepted and published in professional journals
ii. Invited editorials, reviews, chapters, and books
iii. Abstracts published in citable journals
iv. Other presentations at regional or national meetings which do not result in a citable abstract

This listing will be updated at least every six months and will be distributed to the P.I. of each center participating in the ICDB Study, together with reprints or copies of any papers, chapters, or abstracts accepted for publication since the last update. This is intended to facilitate the updating of curricula vitae and the timely submission of reports to any research offices within the participating centers.

4.2.14 Acknowledgement and Acceptance of ICDB Policies on Publications and Presentations by the Professional Participants in the ICDB Study

To assure that all professionals involved with the ICDB Study know and understand the policies of the ICDB Study, and to preclude the possibilities of misunderstandings after initiation of the Study, each professional member will be given a copy of this Chapter and will be asked to sign a Statement of Understanding Form (Appendix B) listing the major provisions of the Chapter and attesting to his/her acceptance of these policies. The original of the signed Statement of Understanding Form should be returned to the DCC for record-keeping purposes. The copies of the Chapter and the signed Statement of Understanding Form should be kept by the ICDB professional participant for reference.

4.3. ANCILLARY STUDIES

Any ancillary study must be undertaken with careful consideration of its impact on the objectives of the ICDB. Ancillary studies which complement the objectives may enhance the value of the ICDB and may promote the continued interest of the investigators. However, to protect the integrity of the major study, a proposal to conduct an ancillary study must be reviewed by the PP&AS Committee before its initiation. All ancillary studies also will be reviewed for potential impact on the overall ICDB Study.

4.3.1 Definition of an Ancillary Study

An ancillary study is defined as research or data collection involving ICDB Study patients using any technique, medication, procedure, questionnaire or observation other than those set forth in the ICDB Protocol.

The investigator responsible for the conduct of an ancillary study must be a member of the ICDB Study Group.

4.3.2 **Reason for Requirement of Approval**

Investigators and patients are entitled to prior assurance that all ancillary studies are of high scientific merit and that no ancillary study will:

- cause a deviation from the Protocol;
- complicate interpretation of the study results;
- adversely affect patient cooperation;
- jeopardize the public image of the study;
- create a significant diversion of the study resources locally or at the Data Coordinating Center or any other ICDB unit;
- in any way negatively influence the cooperative spirit of the collaborating investigators;
- otherwise compromise the scientific integrity of the study.

4.3.3 **Outline for Submission of Ancillary Studies Proposals**

The proposal should include a brief description of the objectives, methods, significance of the study, plans for analysis and publications, and information regarding funding level and source. If a proposal is being submitted elsewhere for funding (e.g., a grant application), the source of funding should be identified and the application may be used as the basis for the request. Full details should be given concerning any procedures or tests to be carried out on an ICDB Study patient, including any observations to be made or procedures to be conducted on patients outside of the clinic; any extra clinic visits required of the patient or any prolongation of the patient's usual clinic visits; any additional specimens (blood, urine, etc.) to be obtained or additional procedures to be done on specimens collected according to the ICDB Protocol. The proposal should discuss the measures to be taken to ensure patient safety and confidentiality and an assessment by the investigator(s) of the potential impact of the ancillary study on the ICDB Study. Prior approval by the appropriate Human Subjects Review Committee(s) must be demonstrated.

To assure that proposals for ancillary studies to be undertaken in conjunction with the main ICDB Study protocol have adequate information to permit their evaluation, proposers must submit such proposals to the PP&AS Committee in the following format.

I. What is the hypothesis to be tested?
   What are the specific outcome variables that will be assessed?

II. What is the significance of the proposed ancillary study?
   Why it is necessary to perform this ancillary study within the context of the main study?

III. How will the performance of this ancillary study affect the main ICDB Study? Specifically:
   a. Will there be any additions to the main ICDB Study protocol? If so, what are they?
   b. How much additional patient, staff, DCC, and/or APL time will be required to complete this ancillary study?

IV. What will be the cost of the ancillary study? This estimate should include costs of needed equipment, supplies, forms, statistical analysis, personnel time, and funding source.

V. What training of personnel will be required?

VI. Data analysis and quality control.
   a. What information will be required from the main IC data base?
   b. What are the specific additional measurements that will be made? How frequently? On what group of patients?
   c. How will the investigators assure the accuracy and precision of the data that is obtained?
   d. What sample size will be required to get meaningful answers, and what assumptions have been made in the calculation of this estimate?
   e. What statistical methods will be used to analyze the resulting data?

VII. What will be the precise protocol? Specify in detail.

4.3.5 **Procedures for Obtaining Ancillary Study Approval**

The investigator should send his/her ancillary study proposal to the Chair of the PP&AS Committee, who will distribute it to all members of the PP&AS Committee. The proposal should be written in sufficient detail so that the PP&AS Committee can assess the study's scientific merit and potential impact on the ICDB Study. To ensure thorough scientific review, the Chair of the PP&AS Committee may elect to seek outside expert opinion in advance of the Committee meeting. Within 30 days of receiving the proposal, the Chair of the PP&AS Committee will summarize the questions and objections (if any) raised by members of the Committee and refer this summary to the applicant so that he/she may amplify, clarify, and/or withdraw his/her request. If not withdrawn, the members of the PP&AS Committee may re-review the request in light of the applicant's response(s) to the PP&AS original summary. The Chair will then prepare a statement of the Committee consensus, including any remaining reservations or objections. If the ancillary study requires access to the ICDB Study patient specimens, the approval statement and all correspondence with the applicant will be forwarded to the Chair of the Committee on Access of ICDB Study Data and Patient Specimens. Only if the Committee on Access of ICDB Study Data and Specimens approves the release of the specimens will the proposal be forwarded to the Steering Committee for review. If access to study specimens is not requested, the approval statement of the PP&AS Committee and

applicant correspondence will be forwarded directly to the Steering Committee. Each member should respond to the Chair of the PP&AS Committee within 30 days. No response will be considered approval. Approval or disapproval is based on majority opinion. Upon approval by the Steering Committee, ancillary studies will be forwarded to the NIDDK Project Officer for final authorization. The investigator may only proceed with the ancillary study once it has been authorized by the NIDDK.

In the event that the PP&AS Committee or the Committee on Access to Study Data and Patient Specimens, disapproves of a proposed ancillary project, the investigator can apply directly to the Steering Committee, whose decision may override that of the PP&AS Committee or Committee on Access to Study Data and Patients Specimens. If the Steering Committee also disapproves of the ancillary study, the proposed study can not be undertaken.

4.3.6 **Funding of Ancillary Studies**

No funds are available in the ICDB Study for the conduct of ancillary studies. This includes funding for extra activities which may be required by the central units, particularly the DCC. An ancillary study proposal submitted for review must not only identify the amount of money needed to conduct the study, but also the sources where funds may be obtained. For example, an investigator may wish to submit a new research grant application, request support from foundations or drug companies, or seek other sources of support.

4.3.7 **Publication of Ancillary Study Results**

All reports, manuscripts or presentations using data derived from the ancillary study must be approved by the PP&AS Committee prior to publication or presentation according to the procedures set forth in section 4.2.

4.4. ACCESS TO ICDB STUDY DATA AND PATIENT SPECIMENS

The primary goal of the ICDB Study is to develop and maintain a centralized, standardized registry containing data on patients with symptomatology consistent with IC. In order to fully develop the longitudinal data and to provide sufficient time to pursue the research interests of the ICDB Study investigators, study data and patient specimens will not be made available to external investigators until the current grant ends. At that time, all investigators, whether internal or external to the Study, must submit a proposal for approval to access ICDB Study data and/or patient specimens. Applications for access to ICDB Study data and/or patient specimens will be accepted for review on an annual basis.

4.4.1 Patient Data

Investigators may request and receive access to an extensive registry of patient data including

questionnaire and diagnostic information relevant to patient and family history, medication and treatment history, patient symptoms, voiding logs, dietary history, clinical examinations, and laboratory and diagnostic results.

4.4.2 Biopsy specimens

Biopsies are obtained and shipped to the Anatomic Pathology Laboratory (APL) following the protocol outlined in Section 10.3: *Biopsy Sampling and Handling Protocol.* The specimens are processed and serially sectioned at the APL, potentially yielding approximately 100 slides per biopsy for ICDB Study evaluation and distribution. The number of available slides per biopsy will vary according to the size of the biopsy. Only 20 percent of the biopsy resources will be made available for approved ancillary study during any one year period.

4.4.3 Requesting Access to Study Data and Specimens

Investigators will be invited to apply for access to the ICDB Study data and/or specimens on an annual basis. The Committee on Access to Study Data and Patient Specimens (see Appendix A for a list of Committee members) will work with the NIH to establish submission deadlines consistent with NIH RFA deadlines. Requests should be submitted to the PP&AS Chair as a proposal for an ancillary study following the guidelines described in Section 4.3.4: *Outline for Submission of Ancillary Studies Proposals.* The PP&AS Chair will evaluate the proposal and forward the request to the appropriate committee for review.

4.4.3.1 Requests for ICDB Study Data

The PP&AS Chair will forward requests received for access to ICDB Study data to the PP&AS Committee on an annual basis. The PP&AS Committee will consider the proposal as a request for Ancillary Study approval and will review the proposals for scientific merit and feasibility as outlined in Section 4.3: *Ancillary Studies.* If the PP&AS Committee grants approval to a proposal, the PP&AS Chair will forward the approved proposal, along with any comments from the PP&AS Committee to the Committee on Access to ICDB Study Data and Patient Specimens for approval of the release of the ICDB Study Data. The Committee on Access to ICDB Study Data and Patient Specimens will have 30 days to review the proposals and submit their decision to the Chair of the Committee on Access to ICDB Study Data and Specimens. The proposal and any comments from the reviewing committees will be presented at the next ICDB Steering Committee meeting for general ICDB Study approval. Upon Steering Committee approval, the proposal and all correspondence is forwarded for final review and approval by the NIH. In the event that the Steering Committee is no longer convening on a regular basis, the request will be forwarded directly to the NIH Project Officer after review by the Committee on Access to ICDB Study Data and Patient Specimens. The investigator may only proceed with the ancillary study once it has been authorized by the NIDDK. The Chair of the PP&AS Committee will notify all applicants in writing of final approval or disapproval.

4.4.3.2 Requests for ICDB Patient Specimens

Requests for ICDB Patient Specimens will also be reviewed on an annual basis. Proposals including requests for access to ICDB Patient Specimens will be forwarded to the APL Director to determine if it technically possible to satisfy the request for biopsy specimens given the number of slides available for distribution. If the APL Director approves the technical feasibility of the study, then the proposal will be forwarded to the PP&AS Committee. The PP&AS Committee will consider the proposal as a request for Ancillary Study approval and will review the proposals for scientific merit and feasibility as outlined in Section 4.3: *Ancillary Studies*. If the PP&AS Committee grants approval to a proposal, the PP&AS Chair will forward the approved proposal, along with any comments from the PP&AS Committee to the Committee on Access to ICDB Study Data and Patient Specimens for approval for the release of the Study Data. The Committee on Access to ICDB Study Data and Patient Specimens will have 30 days to review the proposals and submit their decision to the Chair of the Committee on Access to ICDB Study Data and Specimens. The proposal and any comments from the reviewing committees will be presented at the next ICDB Steering Committee meeting for general ICDB Study approval. Upon Steering Committee approval, the proposal and all correspondence is forwarded for final review and approval by the NIH. In the event that the Steering Committee is no longer convening on a regular basis, the request will be forwarded to the NIH Project Officer after review by the Committee on Access to ICDB Study Data and Patient Specimens. The investigator may only proceed with the ancillary study once it has been authorized by the NIDDK. The Chair of the PP&AS Committee will notify all applicants in writing of final approval or disapproval.

4.5. HUMAN SUBJECT'S CONSIDERATIONS

4.5.1. **Informed Consent**

Each Clinical Center is responsible for ensuring that informed consent is obtained from each patient according to the guidelines of their local Institutional Review Board. The informed consent form, which must be written in clear, simple language, should describe, in detail, the screening process, the data collection and procedures schedule, and the *anticipated* length of follow-up. (Because the length of the study could be extended, it is advised to avoid exact time specifications regarding the anticipated length of follow-up). The informed consent form should also address the potential risks, benefits and costs due to the subject's participation in the study. Specifically, the following must be accomplished during the informed consent process:

- The patient must be informed that participation in the study is voluntary and refusal to participate will involve no penalty or loss of benefits.
- The patient must be informed of any alternative procedures.

- The patient must be made aware of her/his responsibilities throughout the screening phase and the entire follow-up period. The importance of continued follow-up should be stressed.

- An outline of safeguards to protect patient confidentiality must be included, as well as an indication of the patient's right to withdraw without penalty. This should be balanced with a discussion of the effect withdrawals have on the study, and the responsibility a patient has, within limits, to continue in the study if she/he decides to enroll.

- The consent form must include a statement of the policy of the local institution on compensation for study-related injuries, and information on any additional costs to the subject that may result from participation in the research.

- The patient must be informed of her/his right to have questions answered at any time, and whom to contact for answers or in the event of research-related injury.

- The patient must be informed that she/he will be notified of any changes in the protocol.

For more information on the informed consent process, see Meinert [2] or Pocock [3].

4.5.2. **Patient Confidentiality**

Extensive efforts will be made to ensure that the patient's confidentiality is maintained. Each patient will be assigned a unique patient identification number. A log of the patient names and patient ID numbers will be maintained in a locked file cabinet at each Clinical Center. The staff at the Data Coordinating Center will not have access to this log. Only the patient ID number will be given to the Data Coordinating Center staff and entered into the IC Data Base. Any communication between the Data Coordinating Center staff and the Clinical Center staff regarding patient data will occur via this patient ID number.

4.6. PERSONNEL ID NUMBERS

Each member of the Clinical Center staff involved in data collection for the ICDB Study will be assigned a unique identification number. This number is used to identify the individual responsible for completing or reviewing a form. The identifier will contain 4 digits corresponding to the last four digits of the person's social security number.

Statement of Understanding

Publications and Presentations Policy

To assure that all professionals involved with the ICDB study know and understand the policies regarding publications and presentations, and to preclude the possibilities of misunderstandings after initiation of the Study, each professional member will be given a copy of the chapter of the Manual of Operations detailing these policies and will be asked to sign this form attesting to his/her acceptance of these policies, which are summarized here.

I. Material covered by these policies

All material to be presented orally or submitted for publication or dissemination by individuals associated with the ICDB Study and dealing with any aspect of the ICDB Study must receive prior review and approval by the Publications, Presentations and Ancillary Studies (PP&AS) Committee and the Steering Committee with the following exception:

> Material prepared for publicity purposes either nationally or within the recruitment region of an ICDB Clinical Center, or presented orally or as handouts or posters to professional audiences solely for the purposes of informing the profession of the ICDB Study and its objectives, need not be reviewed by the PP&AS Committee. Such material must be limited to a background discussion of the disease interstitial cystitis and a description of the ICDB Study organization, objectives, and entrance criteria, and to results of the study that have previously been presented to a scientific body or published in a scientific journal. It must <u>not</u> include discussion of any previously unpresented and unpublished ICDB Study outcomes or results, and must <u>not</u> itself result in publication of an abstract or other citable professional reference.

II. Assignment of writing committees for publications

The ICDB Steering Committee will appoint writing committee Chairs to prepare <u>all</u> abstracts and papers for the ICDB Study, and will specify the subject material to be dealt with by each writing committee. All interested individuals will be given a chance to request appointment to the various writing committees, but the final appointments will be by the PP&AS Committee Chairs.

III. Authorship

The ICDB Study policies specify the authorship for each of the four different classes of publication or abstract (See Manual of Operations, Chapter 4.2.6). These policies are binding and must be followed in all publications derived from the ICDB Study.

IV. Review of Abstracts

All abstracts must be reviewed and approved by members of the PP&AS Committee before being submitted. These abstracts must be delivered to the reviewers at least seven (7) days before the submission deadline to permit time for this review. Abstracts not approved in this fashion will be withdrawn by the ICDB Study.

V. Review of Materials for Presentations

Approval for submission of an abstract does **not** automatically grant approval of the material ultimately to be presented. This material must also be submitted for review and approval by members of the PP&AS Committee at least seven (7) days prior to the scheduled oral or poster presentation.

VI. Review of Papers

All materials for which there is no explicit deadline, and all full papers that may result in a citable scientific reference, whether or not there is a deadline for submission, must be submitted to the Chair of the PP&AS Committee for formal review by the entire Committee. If there is a deadline for submission of a formal paper, it is the responsibility of the submitter to be certain that it is submitted to the PP&AS Committee Chair, at least 30 days prior to the deadline, to permit such review.

VII. Certification by ICDB Study Investigator

This is to certify that I have read the above statement of policies of the ICDB Study with regard to publications and presentations, understand it, and agree to abide by it in matters of all publications and presentations derived from the ICDB Study.

_____

(Name, *Please print*)

_____ _____

(Signature) (Date)

5.1. PATIENT RECRUITMENT

One of the most important factors contributing to the future success of the ICDB Study is the successful recruitment (and retention) of patients with the interstitial cystitis symptom complex. In order to achieve the goals of the ICDB Study, each Clinical Center is responsible for recruiting 74, 70, 67 and 62 patients in years 01, 02, 03 and 04, respectively. However, an individual center may enroll as many patients as they can in a given year up to the four year target. If it appears that any center is going to exceed its four year target, then the Steering Committee will discuss whether it is desirable from the standpoint of the study and desired by NIH for that center to exceed its quota. Because the best methods to achieve the recruitment goals depend largely on the organizational structures of the individual clinics, each Clinical Center is responsible for determining how best to recruit patients from their local population. This chapter is intended to provide information in order to assist Clinical Centers in selecting appropriate methods of recruitment. For additional information, see Meinert [2] or Friedman, Furburg, and DeMets [4].

5.1.1. **Methods of Recruitment**

There are a few different ways in which patients can be identified as potential ICDB study participants. Some methods rely on direct patient contact, namely through the urology clinic, mailings or telephone calls, and others rely on indirect patient contact via referring physicians, retrospective record reviews, radio/television advertisements, or the news media. All of these methods may need to be relied on at some time during the study by some or all of the clinical centers to achieve the desired recruitment levels. Each of the methods, and their potential success, is discussed below.

Via urology clinic:
Many potential study patients can and will be identified simply by considering the current and future patient populations in each of the urology clinics. The success of this method depends largely on the number of patients in the population who are eligible for and interested in the study. When considering this as the sole source of potential study patients, investigators should not only evaluate how many patients will meet the study criteria, but also what percentage will be willing to participate in and comply with the study protocol.

The chances of success with this method can be increased by ensuring that colleagues within the urology clinic are made fully aware of and are willing to support the study protocol. Clinic colleagues indirectly involved with the ICDB Study should be apprised of any changes made to the study protocol.

Via mailings or telephone calls:
Recruiting patients via mailings or telephone calls will likely only be useful in contacting former patients. Mailings or telephone calls to the general population will likely not prove beneficial. This

method should be used with caution. Direct appeals to patients can be viewed by others in the local medical community as an effort to "steal" patients, and can lead to the recruitment of patients only minimally interested in the study. Although this method may not prove useful for the general population, it can be used with caution in conjunction with retrospective record reviews to contact former patients of the clinic who may be interested in the study.

Via referring physicians:
If the current clinic patient populations do not provide large enough pools from which patients may be recruited, each Clinical Center will need to rely on physicians in their local community for referrals. In order to succeed, this method of recruitment requires the support of colleagues more than any other method. If potential referring physicians are not advocates of the study, or fear losing their patients to the study, the number of referrals will be minimal, and the method not reliable for recruiting patients.

The primary investigator at each of the Clinical Centers, with the support of the Steering Committee, can increase the chances of success of this recruitment method by publicizing the study. Letters can be sent to potential referring physicians and to editors of medical journals. Details of the study can be presented to colleagues in journal articles and to the lay press in newspaper articles. Presentations at medical conferences can also acquaint potential referring physicians with the study.

Via retrospective record reviews:
Reviewing clinic medical records can provide an additional pool of patients from which to recruit. This method, used in conjunction with direct mailings or telephone calls to potential study patients, should be used with caution. Additional care should be taken to ensure that solicited patients are motivated enough to comply with the study protocol.

Via radio/television advertisements and the news media:
Publicizing the study by way of television, radio, and/or newspaper advertisements can prove to be an effective way of informing the general public of the need for study patients. This method can work well when used with other methods of direct patient contact because the media coverage tends to have a "legitimizing" effect on the study.

Via requests for information from interested public:
Occasionally potential patients hear about the ICDB study from another patient or from reading an article in some form of media. These individuals may be good recruits as they have already demonstrated a willingness to become involved. Mailing an ICDB informational letter and a brochure to the potential recruit with a follow-up phone call may result in a successful recruit for the ICDB study.

5.1.2. **Patient Incentives**

Depending on the potential patient and the severity of their disease, the ICDB Study may involve several unpleasant, invasive procedures, the thought of which could keep a potential patient, especially those with mild disease, from joining the ICDB Study. Therefore, when introducing a potential patient to the ICDB Study, it will be important to emphasize the advantages and benefits that joining such a study provides. These benefits include, but are not limited to, the following.

- Patients will be further educated about the disease.
- Patients will have a dedicated research coordinator nurse available to answer questions and provide both medical and emotional support.
- Patients will develop close, long-term contacts with staff devoted to the care of IC patients.
- Patients will be offered a free membership in the Interstitial Cystitis Association for the duration of enrollment in the ICDB Study.
- Patients will likely be among the first patients contacted for future treatment studies.
- Patients will experience personal satisfaction in becoming actively involved in the solution of this serious disorder.

Free patient care will not be provided to patients enrolled in the ICDB Study. However, patient billing will be left to each institution's discretion since each is different with respect to its billing requirements. Patients will be billed in accordance with the institution's usual policies. At most, ICDB Study care will not cost any more than the usual IC evaluation and follow up, since most of these patients are seen in the office more frequently in a clinical practice.

5.1.3. **Monitoring Recruitment**

Study-wide and clinic-specific patient recruitment levels will be monitored by comparing the rates of enrollment (defined as completion of the screening phase) with those required to achieve the Clinical Center recruitment goals. Specific monitoring techniques will include the DCC generation of Accrual Reports and Recruitment Status Plots for each of the Clinical Centers.

The Accrual Report is a report in tabular form of each Clinical Center's recruitment level status. The report contains the number of subjects recruited in the reporting period as the cumulative recruitment to date.

The Recruitment Status Plot is a plot that allows actual Clinical Center recruitment to be compared with projected Clinical Center goals. The number of subjects recruited (i.e. enrolled) to date is plotted against time. Figure 5.1 is an example of a Recruitment Status Plot, in which a Clinical Center is regularly meeting its recruitment goal. The solid line, which indicates the expected number of subjects recruited to date, is generated by plotting the cumulative annual Clinical Center recruitment requirements and connecting the points (thus assuming constant recruitment throughout

each year). The dashed line, which indicates the number of subjects currently recruited (enrolled) to date, is generated by plotting the current cumulative recruitment monthly and connecting the points. Figure 5.2 is an example of a Recruitment Status Plot in which recruitment started out slowly and subsequently increased, while Figure 5.3 is an example of a Recruitment Status Plot in which desired recruitment levels were never attained. The plots may change from month-to-month in either direction due to both adding newly recruited (enrolled) patients and withdrawing patients previously recruited (enrolled) in the study.

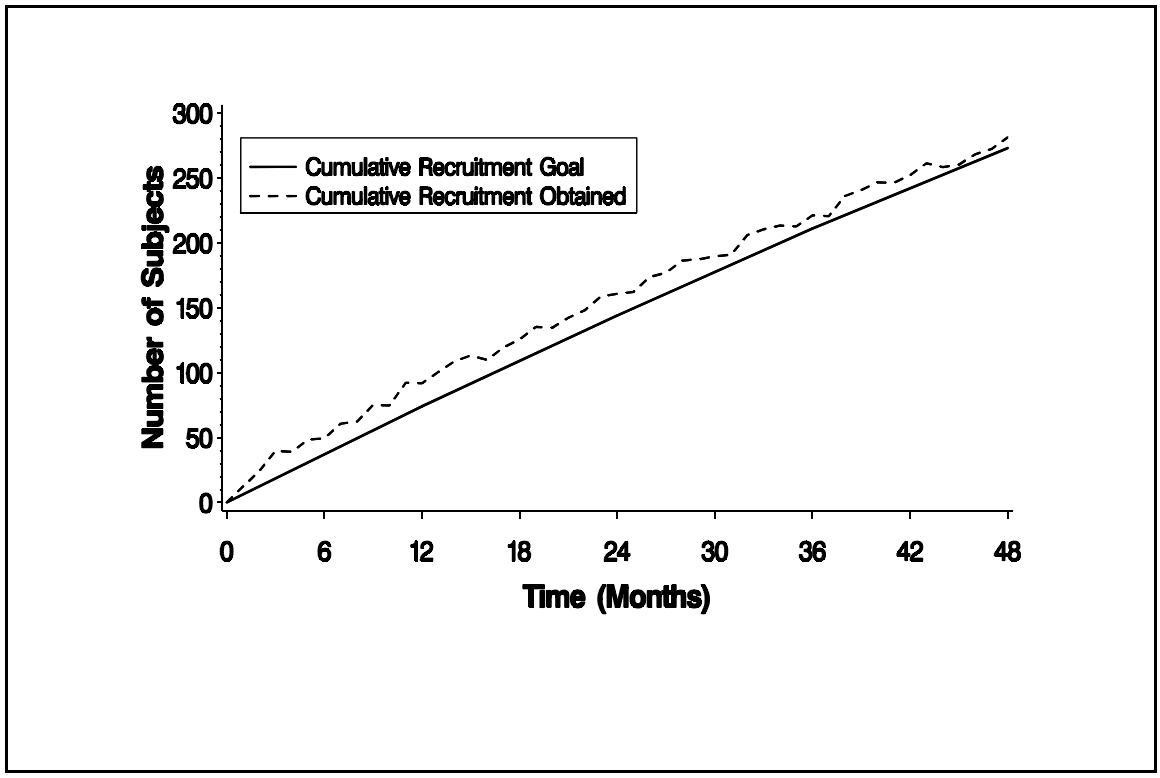


Figure 5.1. An example of a Recruitment Status Plot for a Clinical Center consistently meeting its recruitment goal.

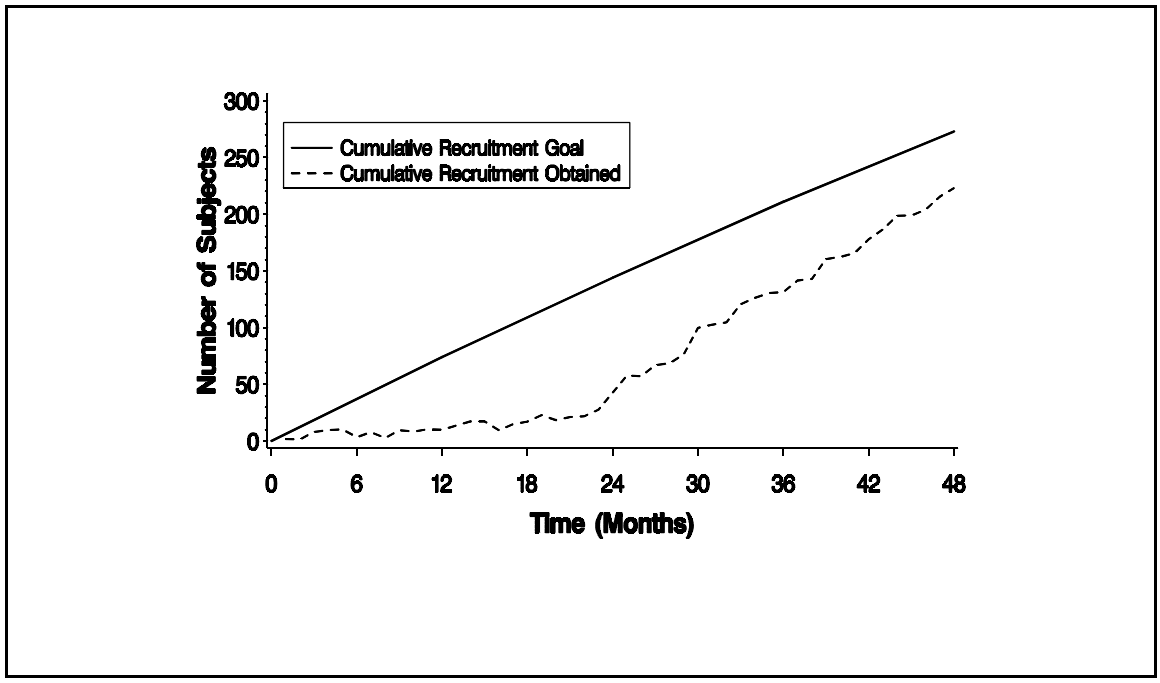


Figure 5.2. A Recruitment Status Plot for a Clinical Center whose recruitment started out slowly and subsequently increased.

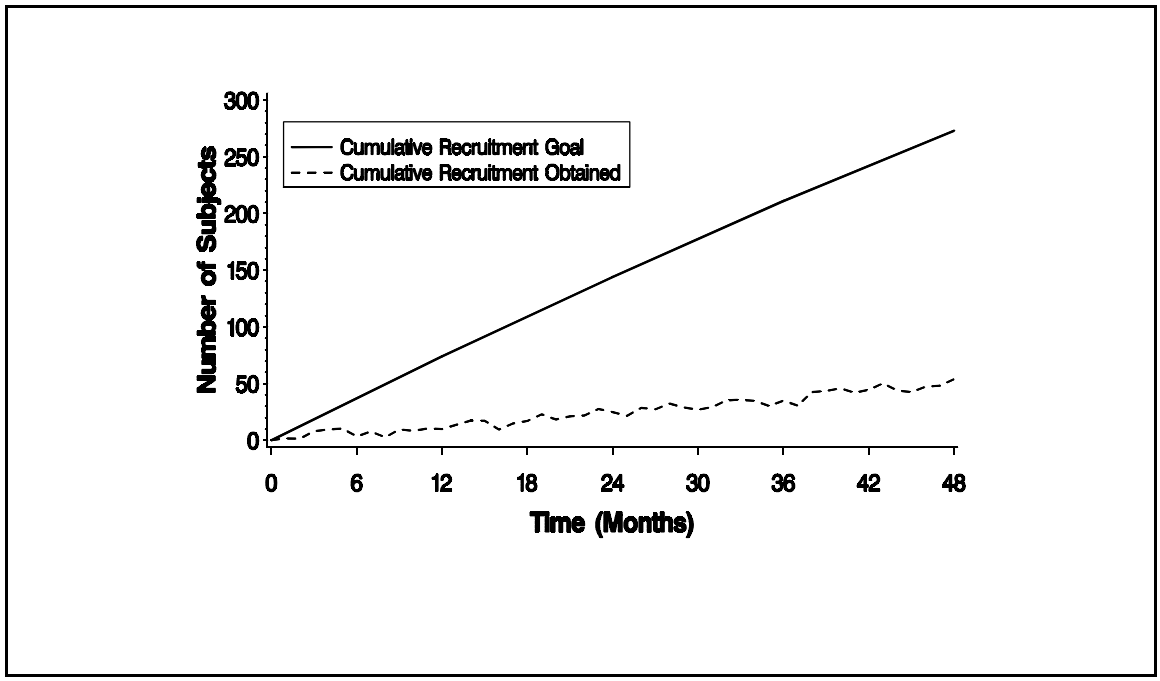


Figure 5.3. A Recruitment Status Plot for a Clinical Center which never reached its recruitment goals.

The Recruitment Status Plot and Accrual Report provide each Clinical Center with the necessary information to evaluate its current recruitment strategies. Because nonconstant recruitment can result in uneven workloads throughout follow-up, Clinical Centers should strive for constant recruitment as illustrated in Figure 5.1. If a Clinical Center's Recruitment Status Plot looks like either of those illustrated in Figure 5.2 or Figure 5.3, the Clinical Center should consider alternative recruitment techniques.

Patient recruitment projection shortfall

If study-wide recruitment projections are not met, the DCC will research the causes for the shortfall and propose solutions to the Steering Committee to correct the problem(s). If a large number of potential study participants fail to meet a specific eligibility criterion, the Steering Committee will evaluate the scientific implications of relaxing the entrance criterion. Alternatively, the Steering Committee, in conjunction with the NIDDK Project Officer, will assess the viability of increasing the sources of potential study subjects via the addition of another Clinical Center or the extension of the study time period.

5.2. ADMINISTRATION OF INFORMED CONSENT

The informed consent form must be the first form administered to all ICDB Study patients. The informed consent form should be administered in a comfortable setting where the patient is able to make a free choice in the absence of additional pressure. The informed consent should be presented in a way to allow the patient to have time to process the information *alone* and to have all questions answered before she/he is asked to make a decision regarding enrollment. *When possible*, the informed consent process should be carried out in two separate visits with at least a day or more between the two visits. During the first visit, the RC should acquaint the patient with the study and its requirements, and during the second visit the RC should answer questions raised by the patient and review the patient's responsibilities. The consent statement should be signed at the end of the second visit and must be signed in the presence of a third party. A patient should not be asked to sign the consent statement if she/he has any doubts about enrolling or if the clinic staff believes she/he does not understand what her/his participation would involve. Under no circumstances is any study information to be collected or study procedures performed for the specific purpose of the ICDB Study before the patient has signed the informed consent form.

5.3. PATIENT REGISTRATION

Every potential study patient must be registered immediately following the informed consent process and prior to the completion of any screening forms or procedures. A patient is registered by her/his completion of the Patient Registration Form (REG). The patient's assigned study ID number is in the shaded box at the bottom of the first page of the Registration Form.

Because all communication with the DCC regarding individual patients must be via the patient's ID number, each Clinical Center needs a mechanism to cross-reference patient's names and ID numbers. Therefore, the registration process should be completed by entering the patient into the Clinical Center's *Patient Log* (Figure 5.4). The Patient Log, whether an electronic database or simply a notebook, should contain a list of the names and ID numbers of all patients **registered** into the ICDB Study. Ordered by patient ID numbers, the Patient Log provides quick and easy access to patient's names.

The Patient Registration Forms and Patient Log should be stored in a secure, locked filing cabinet. A backup copy of this log should be made at the end of every other week and the copy stored in a separate, secure location.

ID Number	Patient Name
210001	Doe, Jane
210002	Johnson, Mary
210003	Smith, John
210004	Holtz, Beth
210005	Robson, Deb
210006	Bland, Margaret

Figure 5.4. An example of a Patient Log.

5.4. PATIENT ELIGIBILITY

5.4.1. **Study Eligibility Criteria**

Every potential study patient must be screened in order to confirm that she/he meets the necessary criteria to be eligible to participate in the ICDB Study. The *study eligibility criteria* consist of a set of *inclusion criteria*, a set of *exclusion criteria*, and a set of *deferral criteria:*

- If the patient meets all of the inclusion criteria, then the patient proceeds to the next stage of screening.
- If the patient meets any of the exclusion criteria, then the patient is not eligible to participate in the ICDB Study.
- If the patient meets any of the deferral criteria, then the patient is temporarily deferred from entry into the ICDB Study. Deferred patients must meet the requisite *re-entry criteria* to be eligible for ICDB study participation.

Inclusion criteria that a patient must meet to be considered a candidate for the ICDB Study:

1) At least 18 years of age;

2) Having had symptoms of urinary urgency or frequency or pain for at least the past 6 months;

3) Scoring at least 1 on the frequency scale, or at least 1 on the pain scale, or at least 1 on the urgency scale (see Appendix C).

***Exclusion criteria that, if met, preclude patients from participating in the ICDB Study*:**

1) Unwilling to undergo a cystoscopy under general or regional anesthesia, when indicated, during the course of the study;

2) Having a history of genito-urinary tuberculosis, or having a positive culture for tuberculosis;

3) Having a history of bladder cancer, as reported by the patient, or having a bladder biopsy positive for malignancy, high-grade dysplasia, or carcinoma *in situ*;

4) If a male patient, showing clinical suspicion of prostate cancer and having a positive biopsy for cancer;

5) Having had lower urinary tract or gynecologic cancer (vaginal, uterine, cervical, ovarian or fallopian tube) within the last 3 years;

6) Having been previously treated with cytoxan/cyclophosphamide, as reported by the patient;

7) Having prior pelvic radiation therapy, as reported by the patient;

8) Having neurogenic bladder dysfunction (e.g. due to a spinal cord injury, a stroke, Parkinson's disease, multiple sclerosis, spina bifida, or diabetic cystopathy), as reported by the patient or as determined during a neurologic exam;

9) If a male patient, having a bladder outlet obstruction, as determined by the physician or as defined during a urodynamic investigation by a voiding detrusor pressure > 100 cm H_2O and a peak flow rate < 10 cc/sec with a minimum voiding volume of 125 cc;

10) If a female patient, having a bladder outlet obstruction, as determined by the physician or as defined during a urodynamic investigation by a voiding detrusor pressure > 60 cm H_2O and a peak flow rate < 10 cc/sec with a minimum voiding volume of 125 cc;

11) Having augmentation cystoplasty, as reported by the patient;

12) Having undergone a cystectomy, as reported by the patient;

13) Having previously had a cystolysis or any bladder denervation procedure, as reported by the patient;

14) Having previously had any neurectomy affecting bladder function, as reported by the patient;

15) Having a urethral stricture of less than 12 French.

***Deferral criteria that, if met, temporarily defer patients from participating in the ICDB Study*:**

1) If a urinalysis indicates more than 10 WBC/HPF, a urine culture for bacteria is negative, and waiting for the results of a Tb urine culture;

2) If a patient had a positive urine culture for bacterial cystitis in the past 3 months (as reported by the patient), or had a positive urine culture (>10^5 colonies/ml) for bacterial cystitis at presentation;

3) If a female patient has symptoms of vaginitis and a positive wet prep for bacteria, clue cell, trichomonas, or a positive KOH test for yeast;

4) If a patient has active herpes at presentation, or has had active herpes in the past 3 months (as reported by the patient);

5) If a male patient has a positive culture for bacterial prostatitis within the past 6 months (as reported by the patient);

6) If a male patient experiences painful ejaculation or is suspicious for prostatitis, then if an expressed prostatic secretions (EPS) or a VB3 culture for bacterial prostatitis is positive;

7) If a patient has bladder, ureteral, or urethral calculi;

8) If a female patient presents with urethritis (urethral redness, tenderness, or discharge);

9) If a male patient presents with urethritis (first glass pyuria, as defined by more than 2 WBC/HPF, or urethral discharge, itching or urethral burning, or red, edematous meatus);

10) If, within the past 3 months, a patient has undergone a cystometrogram, a bladder cystoscopy under full anesthesia, or bladder biopsy under full anesthesia;

11) If a patient has had a urethral dilation in the past 3 months.

Unfortunately, patients can be very poor historians and/or have a very limited understanding of their health problems and corresponding treatments. Therefore, it is prudent to verify the responses to those questions denoted as "as reported by the patient" with their medical records wherever possible. If there is a discrepancy, then the information in the patient's medical records should be considered correct. For example, if the patient indicated that she/he has not had active herpes during the past 3 months, but her/his medical records clearly indicate that she/he was seen in the office with active herpes approximately 2 months ago, then the medical records should be considered correct and the patient deferred until they have been free of the herpes outbreak for 3 months.

Re-entry criteria that deferred patients must meet to be eligible for ICDB Study participation
Table 5.1 contains the re-entry criteria for each of the deferral criteria that a patient must meet to be eligible to take part in the ICDB Study.

Deferral Criteria	**Re-entry Criteria (Patient is deferred until....)**
(1) Suspicious for Tb, and waiting for culture results	Results of urine culture for Tb are available and prove negative
(2) Positive culture ($>10^5$) for bacterial cystitis	Absent of condition for 3 months
(3) Symptoms of vaginitis and positive wet prep	Asymptomatic
(4) Active herpes at presentation or in past 3 months	Absent of condition for 3 months
(5), (6) Positive EPS or VB3 culture for bacterial prostatitis in past 6 months	Absent of condition for 6 months
(7) Bladder, ureteral, or urethral calculi	Absent of calculi for 3 months
(8), (9) Urethritis	Absent of symptoms for 3 months
(10) CMG, bladder cystoscopy/biopsy under full anesthesia in past 3 months	3 months since date of procedure
(11) Urethral dilation in past 3 months	3 months since date of procedure

Table 5.1. Re-entry Criteria for patients who are deferred.

5.4.2. **Eligibility Checking**

Procedures for eligibility criteria confirmation:
In order to evaluate whether a patient is eligible to participate in the ICDB Study, the following forms must be completed: Inclusion Checklist (INCL), Exclusion Checklist #1 (EXCL1), Exclusion Checklist #2 (EXCL2), Exclusion Checklist #3 (EXCL3), Deferral Checklist #1 (DEF1), and Deferral Checklist #2 (DEF2). Refer to Chapter 8: *Data and Administrative Forms Procedures* for instructions for completing these forms.

The Inclusion Checklist (INCL), Exclusion Checklist #1 (EXCL1), and Deferral Checklist #1 (DEF1) forms take a total of 10-15 minutes (and no invasive procedures) to complete, and therefore must be completed at the patient's first screening visit. Exclusion Checklist #2 (EXCL2) and Deferral Checklist #2 (DEF2) cannot be completed in full until the results of a urine culture, physical exam, and urodynamic evaluation are obtained, and therefore must be completed after these procedures are done. Exclusion Checklist #3 (EXCL3) must be completed by only those patients undergoing a cystoscopy/hydrodistention/biopsy (CHB) at baseline.

Procedures for ineligible patients:
The Completed Screening forms should not be sent to the DCC but should be filed in the ICDB Patient Study Book at the clinic. If the patient is re-screened and deemed eligible for the study, then the new complete screening packet should be copied and the originals mailed to the DCC.

Procedures for eligible patients:
If a patient is determined eligible and completes all of the required screening forms and procedures for the ICDB Study, then the patient should be scheduled for her/his 1-Month Follow-Up Contact. The completed screening packet should be copied and the originals mailed to the DCC.

5.4.3. Screening and Re-screening Requirements

Every potential study patient must complete all of the screening phase requirements indicated in Chapter 6: *Visit Scheduling and Administration.* If a patient was previously screened and determined "deferred" or "on-hold", then the patient must be re-screened to confirm her/his eligibility for the study. Patients previously **excluded** from the ICDB Study can not be re-screened.

Re-screening requires re-completing all screening forms and procedures, except for the Patient Registration (REG) form. A re-screened patient should **not** be given a new ID number. When a patient is re-screened she/he retains her/his previously assigned ID number.

Tracking patient status
The Patient Status (STAT) Form is an optional tool that the RC may use to track a patient's ICDB study status. The STAT form should be filed in the patient's medical chart and updated each time the patient's study status changes. Refer to Chapter 8: *Data and Administrative Forms Procedures* for more instructions for the completion of this form.

5.5. ENROLLMENT

Every potential study participant is considered enrolled in the follow-up phase of the ICDB Study when the patient completes **all** of the required screening procedures **and** is confirmed eligible. If a patient no longer meets all of the eligibility criteria after they are enrolled in the ICDB Study, then the patient is no longer eligible to continue in the study. The Patient Withdrawal (WITH) form should be completed and sent to the DCC.

5.6. PATIENT TRANSFERS

It is possible for an ICDB Study patient to transfer from one Clinical Center to another during the course of the study. However it is preferable from a scientific, as well as operational, point of view that a patient complete the entire study at the same Clinical Center. One of the RC's responsibilities during the screening phase is to evaluate a patient's commitment to the study, including her/his stability within the geographic region. This should be done to ensure that the patient is able to meet the demands of the follow-up visit schedule and to determine the likelihood of the patient moving during the course of the study.

5.6.1 **Transfer of a Patient during Follow-Up**

An enrolled (or "complete") patient is one who has successfully completed the screening phase and has entered the follow-up stage. It is essential that an enrolled patient retain her/his **original** patient identification number and ICDB Study file during the **entire** study. If a patient indicates her/his desire to transfer to another Clinical Center after she/he is officially enrolled in the follow-up phase, then the guidelines listed below must be followed to ensure the accurate and timely recording and tracking of this patient's information.

- The RC at the originating center (originating RC) must notify the patient of the time window of her/his next follow-up visit and the name of the RC to contact at the receiving center (receiving RC).

  The patient must be informed that:

  - It will be the responsibility of the patient to make the initial contact with the receiving RC to schedule the next follow-up visit.

  - Upon notification by the receiving RC that the next follow-up visit has been scheduled at the receiving center, the originating center will send a copy of the patient's ICDB study

records to the receiving center.

- The patient must follow the originating center's institution guidelines for transferring her/his medical records.

- The originating RC should then notify the receiving RC of the impending patient transfer. Pertinent information includes the patient's current ICDB Study patient number and status, and the patient's study history, if necessary.

- The originating RC must complete the Patient Withdrawal (WITH) Form, indicate "patient transfer" as the reason for withdrawal and send it to the DCC.

- The receiving RC should wait until the transferring patient has contacted her/him to process any forms or create any records in the event that the patient decides not to reenter the study at the receiving center.

- Once the patient schedules the next follow-up visit at the receiving center, the receiving RC:

  - must complete the Patient Reinstatement (REIN) Form, indicate "patient transfer" as the reason for reinstatement, and send it to the DCC.

  - should create a new ICDB Patient Study Book for the patient, retaining the patient's **original** patient identification number. This is critical for the DCC's ability to track and store the patient's complete ICDB Study information.

  - should contact the originating RC to obtain a photocopy of the patient's ICDB study records only. The patient should request a transfer of her/his medical records from the originating center to the receiving center.

- Before any ICDB study forms or procedures are completed at the scheduled follow-up visit, the receiving RC **must** have the patient complete the receiving center's Informed Consent Form.

- All correspondence from the DCC regarding the transfer patient will be sent to the originating center, since the patient's ID number identifies that Clinical Center. The originating RC will forward the correspondence to the receiving center. It is the receiving center's responsibility to resolve queries or any other correspondence with the DCC. If the correspondence applies to data collected by the originating RC, it will be the responsibility of the receiving RC to contact the originating RC to resolve the problem.

- It will be the joint responsibility of both originating and receiving RCs to ensure the

completeness and accuracy of the patient's ICDB Study records.

5.6.2. **Transfer of a Patient during Screening**

If a patient indicates her/his desire to transfer to another Clinical Center during the screening phase, then the patient should be strongly encouraged to immediately suspend the screening process at the originating center and to start anew at the receiving center. If a patient transfers during the screening process, they must be re-screened from the beginning at the receiving center (except for the urine culture and the hematology test which do not need to be redone unless they were collected earlier than 28 days or 26 weeks, respectvely, from the date of the new Inclusion Checklist (INCL)). Again, it is preferable for a patient to be fully screened and followed up at one Clinical Center to ensure that all data are collected and procedures performed as consistently as possible. If this is not possible for some reason, then the patient should complete screening at the originating center and transfer during follow-up according to the guidelines in Section 5.6.1.

If a patient transfers during the screening phase, then the guidelines listed below must be followed to ensure the accurate and timely recording and tracking of this patient's information.

- The RC at the originating center (originating RC) must notify the patient of her/his current screening status, and the name of the RC to contact at the receiving center (receiving RC). The patient must be informed that:
    - It will be the responsibility of the patient to make the initial contact with the receiving RC to schedule the next screening visit.
    - Upon notification by the receiving RC that the next screening visit has been scheduled at the receiving center, the originating center will send a copy of the patient's ICDB study records to the receiving center.
    - The patient must follow the originating center's institution guidelines in transferring the patient's medical records.
- The originating RC should notify the receiving RC of the impending patient transfer. Pertinent information includes the patient's current ICDB Study patient number and status, and the patient's study history, if necessary.
- The receiving RC should wait until the transferring patient has contacted her/him to process any forms or create any records in the event that the patient decides not to reenter the study at

the receiving center.

- Once the patient schedules the next screening visit at the receiving center, the receiving RC:
  - should create a new ICDB Patient Study Book for the patient, and assign a **new** receiving center patient identification number. Assignment of a new ICDB Study patient number is correct in this situation because the patient is starting the screening process over and no data for this patient has been submitted or processed by the DCC.
  - should contact the originating RC to obtain a photocopy of the patient's ICDB study records only. The patient should request a transfer of her/his medical records from the originating center to the receiving center.
- The receiving RC should begin the screening process with Informed Consent and treat the transfer patient as a new patient being screened for the first time.

5.6 Introductory Paragraph

It is possible for an ICDB Study patient to transfer from one Clinical Center to another during the course of the study. However it is preferable from a scientific, as well as operational point of view that a patient complete the entire study at the same Clinical Center. One of the RC's responsibilities during the screening phase is to evaluate a patient's commitment to the study, including her/his stability within the geographic region. This should be done to ensure that the patient is able to meet the demands of the follow-up visit schedule and to determine the likelihood of the patient moving during the course of the study.

5.6.1 Introductory Paragraph

If a patient indicates her/his desire to transfer to another Clinical Center after she/he is officially enrolled in the follow-up phase, then the guidelines listed below must be followed to ensure the accurate and timely recording and tracking of this patient's information.

5.6.2 Introductory Paragraph

If a patient indicates her/his desire to transfer to another Clinical Center durgin the screening phase, then the patient should be strongly encouraged to immediately suspend the screening process at the originating center and to start anew at the receiving center. Again, it is preferrable for a patient to be fully screened at one Clinical Center to ensure that all data are collected and procedures performed as consistenly as possible during the screening phase. If this is not possible for some reason, say insurance restrictions, then the guidelines listed below must be followed to ensure the accurate and timely recording and tracking of this patient's information.

6.1. SCREENING PHASE

Before a patient is enrolled in the ICDB Study, the patient must complete a series of screening procedures. This screening phase, which enables the RC to evaluate the patient's study eligibility and to collect baseline data on the patient, must be completed in no more than 13 weeks from the date of the Inclusion Checklist to the date of the last screening phase visit as reported on the SCR form. At least one, but likely two to four, clinic visits will be necessary in order to carry out the requisite screening procedures. Any clinic visit which takes place during the patient's screening phase is referred to as a *screening visit.*

Screening phase procedures:
During their screening phase, all patients must complete all of the data forms and/or diagnostic procedures indicated in Table 6.1. Details on completing each of the data forms are provided in Chapter 8: *Data and Administrative Forms Procedures*, while details on each of the diagnostic procedures or bladder specimen handling procedures are provided in Chapters 9 and 10: *Clinical Diagnostic Procedures* and *Bladder Biopsy Handling*, respectively.

- Informed Consent
- Registration (REG)
- Patient Log
- Inclusion Checklist (INCL)
- Pain and Urgency Scales (PURG)
- Exclusion Checklist #1 (EXCL1)
- Deferral Checklist #1 (DEF1)
- Background Information (BACK)
- Symptom Questionnaire (SYMPTS)
- Quality of Life (QUL)
- Dietary Habits (DIET)
- Physical Exam (PHS)
- Urine Specimen Tests
  - Urine Culture
  - Macroscopic Urinalysis (URN)
- Patient Medical History (MEDHX)
- Pregnancy History (PREG), if applicable
- Family History (FHX)
- Prior Diagnoses and Treatments (PRIOR)
- Symptom History (SYMHX)
- Concomitant Medications (CMED)
- Physician's Treatment and Evaluation Plan (PHYTRT)
- Deferral Checklist #2 (DEF2)
- Exclusion Checklist #2 (EXCL2)
- Serum Specimen Test -- Hematology (HEM)
- Voiding Log (VOID)
- Urodynamic Evaluation (UROD)
- Screening Phase Sign-Off (SCR)
- Screening Phase Checklist
- Patient Status (STAT), optional

Table 6.1. Screening Phase Forms and Procedures

If clinically indicated at baseline, a patient must undergo a cystoscopy, hydrodistention, and biopsy under full anesthesia (CHB). For patients warranting a CHB at baseline, the data forms and/or diagnostic procedures identified in Table 6.2 must also be completed. The home institutional Biopsy Slide Consent form should be completed and placed in the patient file. *If a cystoscopy is warranted and can not be completed in the 13 week time frame, then the cystoscopy should be processed as part of the 1 Month follow-up visit.*

- Cystoscopy (CYST)
- Exclusion Checklist #3 (EXCL3)

Table 6.2. Screening forms and procedures for patients undergoing a cystoscopy, hydrodistention and biopsy under full anesthesia.

Patients whose symptoms do not warrant a CHB at baseline must undergo these procedures when clinically indicated during the course of the study. When a CHB is performed on a patient enrolled in the follow-up phase of the ICDB Study, the Exclusion Checklist #3 (EXCL3) should be eliminated. See Section 6.3.4: Cystoscopy During Follow-Up Visits.

Data forms and diagnostic tests order

The required screening phase procedures can be completed in an order that is amenable to both the patient and the clinical center staff. *However*, in order to protect the scientific integrity of the study, the subsequent guidelines must be followed:

- The Informed Consent form, assignment of the patient ID number (patient log), the eligibility checklists to identify patients easily determined as ineligible (INCL, EXCL1, DEF1), and the Background Information (BACK) form must be completed at the patient's first screening visit. The Informed Consent form must be signed in ink by the patient who is agreeing to participate in the study and witnessed by one of the Clinical Center staff prior to collecting any information or performing any procedures specifically for the ICDB Study. The Patient Registration Form (REG) must be completed after obtaining informed consent and before any other screening forms or procedures.

- Because diagnostic procedures or treatments may alter a patient's assessment of her/his baseline status, the Symptom Questionnaire (SYMPTS), Quality of Life (QUL), and Prior Diagnoses and Treatments (PRIOR) forms must be completed prior to administering any such procedure or treatment (i.e., cystoscopy or urodynamics).

- A Voiding Log (VOID) must be completed during the screening period. No patient may be enrolled into the follow-up phase of the ICDB Study without a screening phase voiding log.

- Because diagnostic procedures or treatments may alter a patient's baseline symptoms or assessment of her/his baseline status, the Voiding Log (VOID) must be completed before performing the Urodynamic Evaluation. If this is not possible, then it may be completed equal to or greater than 7 days following an urodynamic evaluation.

- Because diagnostic procedures or treatments may alter a patient's baseline symptoms or assessment of her/his baseline status, the Voiding Log (VOID) must be completed before performing any type of cystoscopic procedure.

- Because the Patient Medical History (MEDHX) form comprises data collected on a patient's medical history, it should be completed at the patient's first screening visit.

- The completion of the Dietary Habits (DIET) form may alter a patient's eating behavior and subsequently her/his symptoms. Therefore, if the Symptom Questionnaire (SYMPTS), Quality of Life (QUL), and Dietary Habits (DIET) forms must be completed on separate screening visits, the Symptom Questionnaire and Quality of Life forms must be completed on the former visit and the Dietary Habits form on the latter.

- The Exclusion Checklist #2 (EXCL2) and Deferral Checklist #2 (DEF2) can not be completed in full until the results of the urine culture, physical exam and urodynamic evaluation are obtained. Therefore, the Exclusion Checklist #2 and Deferral Checklist #2 must be completed after these diagnostic procedures are completed.

- The Urodynamic Evaluation (UROD) must be performed before the Cystoscopy (CYST).

- The Physician's Treatment & Evaluation Plan (PHYTRT) and the Concomitant Medications (CMED) forms must be completed at least once during the screening phase and should be completed at every screening visit which results in any significant change from the previous form.

- The required urine culture may be waived in favor of a urine culture collected prior to Informed Consent if it was obtained no earlier than 28 days prior to the date of the Inclusion Checklist (INCL).

- The required serum specimen test may be waived in favor of a serum specimen test collected prior to Informed Consent if it was obtained no earlier than 26 weeks prior to the date of the Inclusion Checklist (INCL).

- The Screening Phase Sign-Off (SCR) must be signed by the Research Coordinator and the attending Physician after the patient's final screening visit to confirm the patient's eligibility for the ICDB Study.

Preferred screening phase visit schedule

Each Clinical Center can arrange to complete the required screening phase procedures in as many or as few visits as necessary. However, because 1) the eligibility criteria should be checked in an efficient manner, 2) the diagnostic procedures and/or treatments may alter a patient's baseline data, and 3) the patient's load should be spread out across as few screening visits as necessary, the screening visit schedule outlined in Table 6.3 is preferred.

Preferred Screening Phase Visit Schedule

Screening Visit #1:

- Informed Consent, Registration (REG)
- Inclusion Checklist (INCL), Pain and Urgency Scales (PURG)
- Exclusion Checklist #1 (EXCL1), Deferral Checklist #1 (DEF1)
- Patient Symptom Questionnaire (SYMPTS)
- Quality of Life (QUL)
- Prior Diagnostic Tests and Treatments (PRIOR)
- Background Information (BACK)
- Dietary Habits (DIET)
- Patient Medical History (MEDHX)
- Pregnancy History (PREG)
- Physical Exam (PHS)
- Urine Specimen Tests -- Urinalysis (URN) and Urine Culture
- Voiding Log distributed (VOID)
- Physician's Evaluation and Treatment Plan (PHYTRT)
- Concomitant Medications (CMED)

Screening Visit #2:

- Exclusion Checklist #2 (EXCL2)
- Deferral Checklist #2 (DEF2)
- Family Medical History (FHX)
- Symptom History (SYMHX)
- Urodynamic Evaluation (UROD)
- Serum Specimen Test -- Hematology (HEM)
- Voiding Log collected (VOID)
- Physician's Evaluation and Treatment Plan (PHYTRT)
- Concomitant Medications (CMED)
- Screening Phase Sign-Off (SCR), if applicable

Screening Visit #3:

This visit need only be completed by patients warranting a CHB at baseline.

- Cystoscopy (CYST)
- Exclusion Checklist #3 (EXCL3)
- Physician's Evaluation and Treatment Plan (PHYTRT)
- Concomitant Medications (CMED)
- Screening Phase Sign-Off (SCR)

Table 6.3: Preferred Screening Phase Visit Schedule

Alternative screening phase visit schedules

Although the screening phase schedule outlined in Table 6.3 is the preferred visit schedule, alternative visit schedules are permissible providing the guidelines identified above are followed. One alternative screening phase schedule (Table 6.4) entails 3-4 clinic visits, while a second alternative schedule (Table 6.5) entails 1-2 clinic visits.

If the screening phase is completed in less than 3 visits, then the forms and procedures outlined in Table 6.3 should be completed in the visit order as they are listed. For example, if the screening phase is completed in 2 visits, then the forms and procedures listed under Screening Visit 1 should be completed before proceeding with those outlined under Screening Visit 2.

Alternative Screening Phase Visit Schedule I

Screening Visit #1:

- Informed Consent, Registration (REG)
- Inclusion Checklist (INCL), Pain and Urgency Scales (PURG)
- Exclusion Checklist #1 (EXCL1), Deferral Checklist #1 (DEF1)
- Background Information (BACK)
- Symptom Questionnaire (SYMPTS)
- Quality of Life (QUL)
- Prior Diagnoses and Treatments (PRIOR)
- Physician's Evaluation and Treatment Plan (PHYTRT)
- Concomitant Medications (CMED)

Screening Visit #2:

- Patient Medical History (MEDHX)
- Dietary Habits (DIET)
- Physical Exam (PHS)
- Urine Specimen Tests -- Urinalysis (URN) and Urine Culture
- Voiding Log -- collected (VOID)
- Physician's Evaluation and Treatment Plan (PHYTRT)
- Concomitant Medications (CMED)

Screening Visit #3:

- Exclusion Checklist #2 (EXCL2), Deferral Checklist #2 (DEF2)
- Family History (FHX)
- Symptom History (SYMHX)
- Urodynamic Evaluation (UROD)
- Serum Specimen Test -- Hematology (HEM)
- Physician's Evaluation and Treatment Plan (PHYTRT)
- Concomitant Medications (CMED)
- Screening Phase Sign-Off (SCR), if applicable

Screening Visit #4:

This visit need only be completed by patients warranting a CHB at baseline.

- Cystoscopy Form (CYST), Exclusion Checklist #3 (EXCL3)
- Physician's Evaluation and Treatment Plan (PHYTRT)
- Concomitant Medications (CMED)
- Screening Phase Sign-Off (SCR)

Table 6.4. Alternative Screening Phase Visit Schedule I

Alternative Screening Phase Visit Schedule II

Screening Visit #1:

- Informed Consent, Registration (REG)
- Inclusion Checklist (INCL), Pain and Urgency Scales (PURG)
- Exclusion Checklist #1 (EXCL1), Deferral Checklist #1 (DEF1)
- Background Information (BACK)
- Symptom Questionnaire (SYMPTS)
- Quality of Life (QUL)
- Prior Diagnoses and Treatments (PRIOR)
- Dietary Habits (DIET)
- Patient Medical History (MEDHX)
- Physical Exam (PHS)
- Urine Specimen Tests -- Urinalysis (URN) and Urine Culture
- Exclusion Checklist #2 (EXCL2)
- Deferral Checklist #2 (DEF2)
- Family Medical History (FHX)
- Symptom History (SYMHX)
- Urodynamic Evaluation (UROD)
- Serum Specimen Test -- Hematology (HEM)
- Voiding Log (VOID)
- Physician's Evaluation and Treatment Plan (PHYTRT)
- Concomitant Medications (CMED)
- Screening Phase Sign-Off (SCR)

Screening Visit #2:

This visit need only be completed by patients warranting a CHB at baseline.

- Cystoscopy Form (CYST)
- Exclusion Checklist #3 (EXCL3)
- Physician's Evaluation and Treatment Plan (PHYTRT)
- Concomitant Medications (CMED)
- Screening Phase Sign-Off (SCR)

Table 6.5. Alternative Screening Phase Visit Schedule II

6.2. Follow-Up Phase

Once a patient completes the screening phase and proves eligible, the patient moves into the follow-up phase of the ICDB Study. This phase consists of four (4) types of follow-up contacts: 1-Month Follow-Up Contact, Telephone Contacts, Brief Clinic Visits, and Extensive Clinic Visits. The 1-Month Follow-Up Contact, which entails either a clinic visit or a telephone contact, should take place one month after the patient's final screening visit. The first Telephone Contact should take place 3 months after the patient's final screening visit, and subsequent Telephone Contacts every 6 months thereafter. Six (6) months into the patient's follow-up phase, and every 6 months thereafter, a clinic visit should take place. The patient's final clinic visit, as well as those visits taking place on months 24 and 48 are Extensive Clinic Visits, while all other visits in this sequence of clinic visits are Brief Clinic Visits. Details for scheduling patient follow-up visits are provided in Section 6.3: *Scheduling Visits*.

6.2.1. **1-Month Follow-Up Contact**

Each patient should have a follow-up contact one month after the completion of her/his final screening visit. Patients undergoing CHB at baseline should have a clinic visit, while patients not undergoing CHB at baseline should have either a clinic visit or a telephone contact as determined by the physician and patient.

Forms requirements

Table 6.6 identifies the forms that should be completed for the 1-Month Follow-Up Contact. The Address Update (ADDR) form need only be completed if the patient's address, phone number, or employer changed since the last contact. Every other form must be completed by all patients undergoing a 1-Month Telephone Contact.

Completion of data and administrative forms

Details on completing each of the forms are provided Chapter 8: *Data and Administrative Forms Procedures*. The patient should complete the Voiding Log (VOID) prior to the scheduled contact, while all other forms should be completed during the contact. If the contact is completed by telephone, then the RC should follow the *Completion of data and administrative forms* guidelines for telephone contacts provided in Section 6.2.2.

1-Month Follow-Up Contact

- Voiding Log (VOID)
- Pain and Urgency Scales (PURG)
- Symptom Questionnaire (SYMPH)
- Medical Events and Patient Treatment Evaluation (MED)
- Concomitant Medications (CMED)
- Physician's Evaluation and Treatment Plan (PHYTRT)
- Administrative Forms
  - Address Update Form (ADDR), if applicable
  - 1-Month Follow-Up Contact Checklist

Table 6.6. Data and Administrative Forms for the 1-Month Follow-Up Contact

6.2.2. Telephone Contact

During the follow-up phase, each patient should have a series of follow-up Telephone Contacts. The first Telephone Contact should take place 3 months after the patient's final screening visit, and subsequent Telephone Contacts every 6 months thereafter. That is, a Telephone Contact should take place during months 3, 9, 15, 21, 27, 33, 39, and 45 of each patient's follow-up phase. Section 6.3: *Scheduling Visits* provides details on scheduling a patient's Telephone Contacts.

Forms requirements

Table 6.7 contains the list of forms that should be completed for each of the Telephone Contacts. The Address Update (ADDR) form need only be completed if the patient's address, phone number, or employer changed since the last contact. Every other form must be completed by all patients undergoing a Telephone Contact.

Completion of data and administrative forms

The RC should complete the following data forms with the patient according to the instructions outlined in Chapter 8: *Data and Administrative Forms Procedures*: Pain and Urgency Scales (PURG), Symptom Questionnaire (SYMPH), Medical Events and Patient Treatment Evaluation (MED), Concomitant Medications (CMED) and Physician's Treatment and Evaluation Plan (PHYTRT). The RC should interview the patient and record her/his answers in order to complete each of the data forms.

Prior to the scheduled telephone contact, the RC must mail a copy of the PURG form to the patient (with the Voiding Log (VOID)) for the patient to refer to during the phone call. To complete the Pain and Urgency Scales (PURG), the RC should ask the patient to look at her/his copy of the pain

and urgency scales and indicate her/his ratings for the past four weeks. The RC should record the patient's ratings on the two scales on the original Pain and Urgency Scales (PURG) form.

At the conclusion of the phone call, if the RC has not already received the patient's completed Voiding Log (VOID), then the RC should remind the patient to mail it to the clinic as soon as possible. The Telephone Contact Checklist should be completed before ending the telephone contact.

Telephone Contact

- Voiding Log (VOID)
- Pain and Urgency Scales (PURG)
- Symptom Questionnaire (SYMPH)
- Medical Events and Patient Treatment Evaluation (MED)
- Concomitant Medications (CMED)
- Physician's Evaluation and Treatment Plan (PHYTRT)
- Administrative Forms
  - Address Update Form (ADDR), if applicable
  - Telephone Contact Checklist

Table 6.7. Data and administrative forms for Telephone Contacts.

6.2.3. **Brief Clinic Visits**

During the follow-up phase, each patient should complete a series of Brief Clinic Visits taking place 6, 12, 18, 30, 36, and 42 months after the patient's final screening visit. Details for scheduling a patient's Brief Clinic Visits are provided in Section 6.3: *Scheduling Visits*.

Forms requirements

Table 6.8 contains the list of forms that must be completed for each of the patient's Brief Clinic Visits. The Physical Exam (PHS) need only be completed as indicated by the physician. The Address Update Form (ADDR) need only be completed if the patient's address, phone number, or employer changed since the last contact. Every other form must be completed by all patients undergoing a Brief Clinic Visit.

Completion of diagnostic procedures and data and administrative forms

The RC should collect the Voiding Log (VOID) that the patient completed at home. Details on

completing each of the required forms are provided in Chapter 8: *Data and Administrative Forms Procedures.* The Brief Clinic Visit Checklist should be completed by the RC before the patient leaves the clinic.

Brief Clinic Visit

- Voiding Log (VOID)
- Pain and Urgency Scales (PURG)
- Symptom Questionnaire (SYMPTS)
- Quality of Life (QUL)
- Dietary Habits (DIET)
- Physical Exam (PHS)
- Urine Specimen Test -- Macroscopic Urinalysis (URN)
- Medical Events and Patient Treatment Evaluation (MED)
- Concomitant Medications (CMED)
- Physician's Evaluation and Treatment Plan (PHYTRT)
- Administrative Forms
  - Address Update Form (ADDR), if necessary
  - Brief Clinic Visit Checklist

Table 6.8. Data and administrative forms for the Brief Clinic Visits.

6.2.4. **Extensive Clinic Visits**

During the follow-up phase, each patient should complete at least two Extensive Clinic Visits. The patient's final follow-up study visit, as well as those clinic visits taking place 24 and 48 months after the patient's final screening visit are Extensive Clinic Visits. Details for scheduling a patient's Extensive Clinic Visits are provided in Section 6.3: *Scheduling Visits*. The Extensive Clinic Visits are very important study time points for the ICDB statistical analyses. Therefore, it is imperative that every effort is made to obtain all data for all enrolled ICDB patients for these visits.

Form requirements

Table 6.9 contains the list of forms and procedures that must be completed for each of the patient's Extensive Clinic Visits. The Physical Exam (PHS) need only be completed as indicated by the

physician. The Address Update Form (ADDR) need only be completed if the patient's address, phone number, or employer changed since the last contact. Every other form must be completed by all patients undergoing an Extensive Clinic Visit.

Completion of diagnostic procedures and data and administrative forms
The RC should collect the Dietary Habits (DIET) form and Voiding Log (VOID) that the patient completed at home. Details on the completion of the remaining forms are provided in Chapter 8: *Data and Administrative Forms Procedures.* The Extensive Visit Checklist should be completed by the RC before the patient leaves the clinic.

Extensive Clinic Visit

- Voiding Log (VOID)
- Background Information (BACKF)
- Patient Medical History (MEDHX)
- Pregnancy History (PREG)
- Pain and Urgency Scales (PURG)
- Symptom Questionnaire (SYMPTS)
- Quality of Life (QUL)
- Dietary Habits (DIET)
- Physical Exam (PHS)
- Urine Specimen Test -- Macroscopic Urinalysis (URN)
- Medical Events and Patient Treatment Evaluation (MED)
- Concomitant Medications (CMED)
- Physician's Evaluation and Treatment Plan (PHYTRT)
- Administrative Forms
  - Address Update Form (ADDR), if applicable
  - Extensive Clinic Visit Checklist

Table 6.9. Data and administrative forms for Extensive Clinic Visits.

6.3. SCHEDULING VISITS

6.3.1. Screening Visits

If the patient has not completed the screening phase at the end of a particular screening visit, then the Research Coordinator (RC) should schedule the patient for her/his next screening visit. The total elapsed time for the screening phase for each patient should take no longer than 13 weeks (from the date of the INCL form to the date of the SCR form). Therefore, the screening visits should be scheduled as close together as possible.

At the patient's final screening visit, the RC should schedule the patient's 1-Month Follow-Up Contact to take place in approximately 30 days. The RC should not wait for receipt of the Follow-Up Contact Schedule before scheduling the 1-Month Follow-Up Contact. Although the 1-Month Follow-Up Contact ideally should take place 30 days after the final screening visit, the Contact can take place anywhere from 16-45 days after the final screening visit. If the patient's final screening visit entailed a cystoscopy, hydrodistention and biopsy (CHB), then the patient's 1-Month Follow-Up Contact must be a clinic visit. For patients not undergoing a CHB during their screening phase, the type of contact (phone contact or clinic visit) is left to the discretion of the physician and patient.

6.3.2. Follow-Up Visits

The Follow-Up Contact Schedule

Once a Clinical Center (CC) confirms that a patient is eligible for the ICDB Follow-up Phase by signing the Screening Phase Sign-Off (SCR), the Data Coordinating Center (DCC) will generate, and mail to the CC, a Follow-Up Contact Schedule for the patient (Figure 6.10). The Follow-Up Contact Schedule indicates the sequence of visits, with their possible dates, that a patient must complete in order to adhere to the study protocol. The schedule contains the date and type of contact, as well as the permissible time window in which the patient must complete the indicated type of contact.

Follow-Up Contact Schedule

Id Number: 210109
Final Screening Visit Date: 12/03/92

The indicated contacts should be done within the time window specified and as close to the desired date as possible.

Type of Contact	Desired Date	Time Window: First Possible Date	Time Window: Last Possible Date	Actual Visit Date
1 Month Contact	01/02/93	12/19/92	01/16/93	_____
3 Month Phone	03/03/93	02/01/93	04/02/93	_____
6 Month Brief Visit	06/01/93	05/02/93	07/01/93	_____
9 Month Phone	08/30/93	07/31/93	09/29/93	_____
12 Month Brief Visit	11/28/93	10/29/93	12/28/93	_____
15 Month Phone	02/26/94	01/27/94	03/28/94	_____
18 Month Brief Visit	05/27/94	04/27/94	06/26/94	_____
21 Month Phone	08/25/94	07/26/94	09/24/94	_____
24 Month Ext. Visit	11/23/94	10/24/94	12/23/94	_____
27 Month Phone	02/21/95	01/22/95	03/23/95	_____
30 Month Brief Visit	05/22/95	04/22/95	06/21/95	_____
33 Month Phone	08/20/95	07/21/95	09/19/95	_____
36 Month Brief Visit	11/18/95	10/19/95	12/18/95	_____
39 Month Phone	02/16/96	01/17/96	03/17/96	_____
42 Month Brief Visit	05/16/96	04/16/96	06/15/96	_____
45 Month Phone	08/14/96	07/15/96	09/13/96	_____
48 Month Ext. Visit	11/12/96	10/13/96	12/12/96	_____

Figure 6.10. An example of a Follow-Up Contact Schedule.

Determination of the Follow-Up Contact Schedule

The *desired date* for any follow-up contact is determined by adding the appropriate number of days to the date of the patient's final screening visit. The appropriate number of days is determined by the number of months, based on a 30.4 day month, after the patient's final screening visit in which the follow-up contact should occur.

The *time window* for any follow-up contact is the permissible time period in which the contact can occur. The time window for the 1-Month Follow-Up Contact is defined as the interval of time starting 14 days before and ending 14 days after the desired date of the visit, while the time window for all other visits is defined as the interval of time starting 30 days before and ending 30 days after the desired date of the visit. All dates are determined from the date of the final screening visit without regard to whether they fall on a weekend or holiday.

Example:

Figure 6.10 contains the Follow-Up Contact Schedule of Patient 210109 whose final screening visit took place on December 3, 1992.

The desired date of the 12-Month Brief Clinic Visit, November 28, 1993, is determined by adding 360 days (12 months times 30 days per month) to the date of the patient's final screening visit.

The first possible date of the visit, October 29, 1993, is the date 30 days prior to the desired date. The last possible date of the visit is the date falling 30 days after the desired date, or December 28, 1993.

Therefore, the permissible time window for this patient's 12-Month Brief Clinic Visit is from October 29, 1993 to December 28, 1993.

Use of the Follow-Up Contact Schedule

The Follow-Up Contact Schedule is designed to assist the RC in scheduling all follow-up contacts. When a patient's Follow-Up Contact Schedule is received from the DCC, the RC should place it in the front of the patient's study book. At the end of every completed contact, the RC should refer to the patient's schedule in order to schedule the next contact. The RC should write down the date of the contact just completed under the column titled "Actual Visit Date", and then refer to the next line to determine the type and desired date of the next contact.

When to schedule the next contact in the permissible time window depends largely on the patient's tendency to adhere to scheduled contacts. If the patient tends to keep scheduled appointments, then the contact should be scheduled as close as possible to the desired date. If the patient tends to re-schedule contacts (although this should be discouraged), the next contact should be scheduled as early as possible in the permissible time window in order to increase the chances of re-scheduled contacts falling within the window. If the RC is not sure when to schedule the next contact, it should be scheduled as early as possible in the time window.

The RC should consult the Follow-Up Contact Schedule whenever *any* appointment is scheduled for a study patient. Depending on the date of the appointment, the contact could qualify as one of the patient's follow-up study contacts. The RC should adhere to the following guidelines to schedule a future appointment or to determine whether one of the required follow-up contacts should be completed during an appointment:

- If the patient has just completed one of the follow-up contacts, the next follow-up contact indicated on the patient's schedule should be scheduled in the permissible time window.

Example:

Jane Smith's Follow-Up Contact Schedule is illustrated in Figure 6.10.

Assume today's date is 11/25/93, and Jane Smith has just completed her 12-Month Brief Clinic Visit. For the 12 Month Brief Visit, record "11/25/93" under the "Actual Visit Date" Column.

Schedule her 15-Month Phone Contact for some day between 01/27/94 and 03/28/94. Since Jane has tended to keep her scheduled appointments over the past year, the phone contact should be scheduled as close to 02/26/94 (the desired date) as possible.

- If a patient calls to reschedule a study follow-up visit, the RC should attempt to reschedule the visit within the remaining allowable time window. If the visit cannot be scheduled within the time window, the visit should be scheduled and completed **before** the first possible date of the next study visit.

Example:

(See Figure 6.10.)

Assume today's date is 10/31/95, and Jane Smith has called to cancel her appointment for her 36-Month Brief Clinic Visit scheduled 11/14/95.

Since the last possible date of her 36-Month Brief Visit is 12/18/95, the RC attempts to reschedule the appointment prior to 12/18/95. Jane and the RC agree to reschedule the appointment for 12/04/95.

When Jane calls on 12/01/95 to reschedule the appointment again due to extenuating circumstances, Jane and the RC are unable to schedule an appointment prior to 12/18/95.

Since the appointment can not be completed within the specified time window, Jane and the RC attempt to reschedule the appointment to take place **before** the beginning of the time window for the 39 Month Phone Contact, 02/16/96. Therefore, they schedule the appointment for 01/4/96, on which Jane completes the 36-Month Brief Clinic Visit.

- If a patient calls to schedule an appointment within the time window of a brief clinic visit, and the brief clinic visit in this window has not already been completed, then a brief clinic visit should be completed. Similarly, if a patient calls to schedule an appointment within the time window of an extensive clinic visit, and the extensive clinic visit in this window has not already been completed, then an extensive clinic visit should be completed.

Example:

(See Figure 6.10).

Assume today's date is 05/05/93, and Jane Smith has called to schedule an appointment, because her symptoms have worsened and she would like some relief. The RC and Jane Smith schedule an appointment for her on 05/12/93.

Because Jane's newly scheduled appointment falls in the permissible time window of the 6-Month Brief Clinic Visit, which was previously scheduled for 06/02/93 and has not yet been completed, this follow-up study visit should be completed during her new appointment on 05/12/93.

The 06/02/93 appointment need not be kept for study purposes.

6.3.3 **Missed Study Visits**

If a follow-up visit cannot be completed in the allowable time window, the visit should be scheduled and completed before the first possible date of the next study visit. If the visit cannot be completed before the first possible date of the next study visit, then that visit must be considered missed.

Example:

Cathy Brown's Follow-Up Contact Schedule is illustrated in Figure 6.10.

Assume today's date is 12/20/94, and Cathy Brown has called to cancel her appointment for her 24-Month Extensive Visit scheduled for 12/23/94.

Since the last possible date of her 24-Month Extensive Visit is 12/23/94, the RC attempts to reschedule the appointment before 01/22/95, the first possible date of the 27-Month Phone Contact. Cathy and the RC agree to reschedule the appointment for 01/20/95.

On 01/15/95, Cathy calls to cancel her 01/20/95 appointment due to extenuating circumstances. The RC attempts to reschedule the appointment before 01/22/95, the first possible date of the 27-Month Phone Contact but is unable to reschedule the appointment.

The 24-Month Extensive Visit is considered as a missed visit.

When a patient misses a follow-up visit, the RC should explain to the patient the importance of collecting follow-up data. If a patient misses multiple follow-up visits, the RC should consider withdrawing the patient from the study.

6.3.4 Cystoscopy During Follow-Up Visits

To the extent possible, the cystoscopy should be scheduled in the visit time window and completed on the same day as the remainder of the follow-up visit. When a cystoscopy is performed during the follow-up phase, the same procedures must be followed as with a cystoscopy completed during the screening phase. The Cystoscopy (CYST) form must be completed and the biopsy specimens must be sent to the home institution pathology lab and the Anatomic Pathology Laboratory (APL). For more information on bladder biopsy handling, refer to Chapter 10 of this manual. However, an Exclusion #3 Checklist (EXCL3) should not be completed.

If the cystoscopy is performed in between scheduled ICDB Study visits, the Cystoscopy (CYST) form should be submitted to the DCC with the forms packet of the patient's nearest study visit in the patient's sequence of visits. Additionally, Question #3 on the Physician's Evaluation and Treatment Plan (PHYTRT) form for that study visit must indicate whether or not a cystoscopy will be, or has been, performed.

Example:

Mary Johnson's Follow-Up Contact Schedule is illustrated in Figure 6.10.

Assume it is 05/27/94 and Mary is completing her 18-Month Brief Visit today. During her visit, Mary's physician determines that Mary needs to have a cystoscopy with hydrodistention and biopsy.

Mary and the RC agree to schedule the cystoscopy for 06/30/94, in between the 18 Month and 21 Month Contact windows. Because the date of the cystoscopy is closer to the 18-Month Brief Visit time window than the 21-Month Phone Contact time window, the RC uses Question #3 of the 18-Month Brief Visit PHYTRT form to indicate that Mary will be having a cystoscopy with hydrodistention and biopsy on 06/30/94.

On 06/30/94, Mary has a cystoscopy. The RC completes the CYST form and sends the biopsy specimens to the home institution pathology lab and the APL. The CYST form and pathology report are included in the 18-Month Brief Visit forms packet to be submitted to the DCC.

Example:

Linda Tyler's Follow-Up Contact Schedule is illustrated in Figure 6.10.

Assume it is 05/27/94 and Linda is completing her 18-Month Brief Visit today. During her visit, Linda's physician determines that Linda needs to have a cystoscopy with local anesthesia.

Linda and the RC agree to schedule the cystoscopy for 07/15/94, in between the 18 and 21 Month Contact windows. Because the date of the cystoscopy is closer to the time window of the 21-Month Phone Contact than the 18-Month Brief Visit, the RC does not indicate the cystoscopy on Question #3 of the PHYTRT form for the 18-Month Brief Visit. The 18-Month Brief Visit forms packet is submitted to the DCC.

On 07/15/94, Linda has a cystoscopy and the RC completes the CYST form.

Linda completes her 21-Month Phone Contact on 08/15/94. The RC indicates that a cystoscopy was performed on 07/15/94 in Question #3 of the 21-Month Phone Contact PHYTRT form. The CYST form is included in the 21-Month Phone Contact forms packet to be submitted to the DCC.

6.3.5 **Additional Visits**

There may be times when additional visits or contacts are made with the patient, but the data forms need not be completed. However, during any non-study visit which results in a change in concomitant medications or urinary treatments, the RC must record the changes in the patient's chart. These changes should then be subsequently recorded on the Concomitant Medications (CMED) and Physician's Evaluation and Treatment Plan (PHYTRT) forms at the next required study visit.

Under the following circumstances, the RC need not complete data forms:

- If a patient calls to schedule an appointment within the time window of a clinic visit or phone contact and the requisite visit has already been completed in that window, then no data forms should be completed. If there is a change in the patient's concomitant medications or urinary treatments, it must be noted in the patient chart and recorded on the appropriate data forms at the next required study visit.

Example:

Jeff Miller's Follow-Up Contact Schedule is illustrated in Figure 6.10.

Jeff Miller completed his 6-Month Brief Visit on 05/12/93.

Assume it is 05/25/93 and Jeff Miller calls to schedule an appointment to seek relief for an increase in severity of his symptoms. The RC and Jeff schedule an appointment for 06/02/93.

Because the 06/02/93 appointment falls in the time window of the 6-Month Brief Clinic Visit which was already completed during his 05/12/93 appointment, no data forms are completed. However, the RC notes any changes in Jeff's medications and treatments and records them in his patient chart so that they can be indicated on the CMED and PHYTRT forms at his next required study visit.

- If a patient calls to schedule a visit at a time in between study contact time windows, and the last visit in the patient's sequence of visits was completed in its required time window, then no data forms should be completed. If there is a change in the patient's concomitant medications or urinary treatments, it must be noted in the patient chart and recorded on the appropriate data forms at the next required study visit.

Example:

(Continued from previous example).

Jeff Miller is still seeking relief for his symptoms, and calls to schedule another appointment.

The RC is able to schedule an appointment for him on 7/05/93, which does not fall inside the time window of any study follow-up visit.

Because the previous follow-up visit, the 6-Month Brief Clinic Visit, was completed in its permissible time window, no data forms are completed during this appointment. However, the RC records any changes in Jeff's medications and treatments in his patient chart so that they can be indicated on the CMED and PHYTRT forms at his next required study visit.

- If a patient and RC have telephone contact outside of the patient's required sequence of phone contacts, there is no need to complete any data forms. However, if there is a change in the patient's concomitant medications or urinary treatments, it must be noted in the patient chart and recorded on the appropriate data forms at the next required study visit.

Example:

(Continued from previous example.)

On 07/10/93, Jeff Miller called his physician to discuss negative side effects he is experiencing due to his treatment for IC.

The physician recommends changing his treatment. The RC notes the change of treatment in the patient chart on 07/10/93.

Jeff completes his 9-Month Phone Contact on 08/28/93. At that time, the RC notes the 07/10/93 treatment change on the PHYTRT form.

6.4. VISIT REMINDERS

Two (2) weeks before any scheduled clinic visit or phone contact, the RC should mail the patient a packet containing a visit reminder and any forms that need to be completed by the patient for that study visit. The contents of the packet depend on whether the scheduled appointment is a clinic visit or a phone contact.

For a ***phone contact***, the packet should contain:

1) a phone contact reminder indicating the date and time of the scheduled telephone call;
2) a Voiding Log (VOID);
3) a copy of the Pain and Urgency Scales (PURG); and,
4) an envelope, stamped and addressed to the RC at the urology clinic.

For a ***clinic visit***, the packet should contain:

1) a clinic visit reminder indicating the date and the time of the scheduled clinic visit;
2) a Voiding Log (VOID); and,
3) a Dietary Habits Form (DIET), *except 1-Month Follow-up Visits.*

The phone contact and clinic visit reminders also provide the patient with directions for preparing for her/his scheduled appointment. Sample visit reminders are included in the Administrative Forms section of this manual.

In addition to the mailed clinic visit reminder, a telephone call should be placed to the patient 1-2 days prior to the scheduled appointment reminding her/him of the date and time of the scheduled visit. Reminder phone calls for patients with appointments on Monday should be placed on Thursday or Friday of the previous week.

6.5. VISIT PREPARATION

Before the telephone call is placed for a phone contact or before the patient arrives at the clinic for a study visit, the RC should prepare for the visit. This section contains information on preparing for any type of study visit.

6.5.1. First Screening Visit

Assembly of the patient's Study Book

Prior to each patient's first screening visit, the RC should start a *Study Book* for the patient. The patient's Study Book, which will be used to hold the patient's complete set of ICDB Study data and administrative forms, should be created using a 3-inch 3-ring binder. To start the Study Book prior to the patient's first screening visit, the RC should place a Patient Status Form (optional), an Informed Consent Form, the **next available** Patient Registration Packet and a Screening Phase Packet in a 3-ring binder. The forms should not be dated ahead of time as the patient may not complete the screening phase during this visit.

Labelling of the patient's Study Book

The Study Book should be labelled on the outside with the patient ID number that appears on the first page of the Patient Registration Form (REG). Because the patient may be determined ineligible for the study, and the RC subsequently desire to move the patient's data forms to a smaller binder, the RC may prefer to label the binder temporarily with a Post-It™ note. Once the patient is confirmed eligible for the study, the RC should permanently label the Study Book with a sticker label.

6.5.2. Follow-Up Visits

Two (2) weeks before any scheduled clinic visit or phone contact, the RC should mail the patient a visit reminder packet. Section 6.4: *Visit Reminders* provides information on the necessary contents of each visit reminder packet. When the RC prepares to send the visit reminder packet to the patient, she/he should take out one packet of forms from her/his supply of forms packets for the appropriate follow-up visit. The forms needed for the visit reminder packet should be removed from the forms packet. The remaining forms in the forms packet should be placed in the patient's Study Book for completion at the follow-up visit.

Chapter 7 has been absorbed into Chapter 6: *Visit Scheduling and Administration* and Chapter 8: *Data and Administrative Forms Procedures.*

8.1. ACQUISITION OF FORMS FROM THE DCC

8.1.1. Transmission of forms to Clinical Centers

It is important that each RC keep a careful inventory of her/his forms supply to ensure that she/he does not run out of forms. When the Clinical Center needs additional forms, the RC should complete a Clinical Center Request for Forms (FREQ) according to the instructions outlined in Section 8.4: *Instructions for the Completion of Administrative Forms.* The FREQ form must be used to request visit packets and may be used to request administrative forms and extra copies of data forms. The RC should allow 10-15 business days to receive the forms.

Templates of all administrative and data forms are provided in Appendix D so that the RC may make photocopies of forms. If the RC photocopies forms, she/he must be careful to use the *current* version of the form.

8.1.2. Identifying forms

The data collection forms are clipped together in packets that relate to when the data on the forms should be collected. For example, there is a Screening Phase packet, a Brief Clinic Visit packet, a Telephone Contact packet, etc. The first page of each packet is a blue sheet of paper identifying the type of packet and the forms contained in the packet. A list of all data forms, who should complete them, and when they should be completed is contained in Appendix E.

All ICDB Study forms are identified by both a form title and a form code. The table in Appendix E lists each data form and Section 8.4: *Instructions for the Completion of Administrative Forms* lists each administrative form both by title and by form code. The form code, which is the primary identification, is found on each form in the shaded box at the bottom right hand corner of each page of every form. The form code is the primary identifier for a form since there may be two forms with the same title that collect slightly different information. For example, the forms that collect the patient's background information are collected both during the screening phase and at Extensive Clinic Visits and the information collected at these two time periods is different. Thus, the form code is different. The form codes are BACK and BACKF for the screening phase and Extensive Clinic Visits, respectively.

There are basically three different types of data forms. There are (1) those administered to the patient by the RC, (2) those completed by the patient alone, and (3) those completed by the Clinical Center staff. Each type of form is printed on a different color of paper. Those administered to the patient by the RC are printed on green paper, those completed by the patient alone are printed on orange paper, and those completed by the Clinical Center staff are printed on yellow paper.

All administrative forms are completed by the RC. Query forms (QDC and QMD), the Clinic-Initiated Data Correction (CIDC) form, and the Clinical Center Request for Forms (FREQ) form are printed on white paper. All other administrative forms are printed on blue paper.

8.2. GENERAL INSTRUCTIONS FOR THE COMPLETION OF DATA FORMS

8.2.1. General instructions for all data forms

Instructions for specific data forms are contained in Section 8.3. The items below are guidelines to be followed when completing any of the data forms.

The RC should always check the forms in a visit packet against the visit checklist to ensure that all forms are available **before** the patient arrives for her/his scheduled visit. If a form is missing in a visit packet, the RC should make a copy of the form to use for the visit. The templates of the forms contained in Appendix D can be used for making photocopies. The RC must ensure that the current version of the form is used.

Before each data form is completed, the RC should put the patient ID and the visit date in the spaces provided at the top of the first page of the form. The RC should also copy the patient ID onto the top right hand corner of **every** page of the form. If the pages of the form are separated, then each can be identified.

All data forms should be completed in **black** ink. Do not use pencil, blue ink, or red ink. Black ink is required because xerox copies of the forms will be made and black ink is the most easily copied.

All responses should be printed legibly. When making changes to answers or correcting mistakes on incorrectly recorded information, put a single line through the middle of the incorrect information. Record the correct information, and initial and date the correct answer. Circle the correct answer for clarification, if necessary.

All dates should be recorded using two digits for the month, two digits for the day (if applicable), and two digits for the year. If the patient does not know the exact date, prompt the patient for the month and the year. If the patient cannot recall the day, leave the day blank; if the patient cannot recall the month, leave the month and day blank; if the patient cannot recall the year, leave the entire date blank, indicating that the patient cannot recall the date.

8.2.2. Forms administered to the patient by the RC

These forms must **not** be completed by the patient. They are designed to be administered to the patient by the RC.

These forms are completed by interviewing the patient and asking the specific questions found on the form. Any text in ***bold italic*** print, in a shaded box or set off by a pointing hand ( ) are instructions to the interviewer only and should not be read to the patient.

The questions should be read **exactly** as written and in the order that they appear on the form. A natural conversational tone should be used when asking questions. All possible responses should be read before the patient answers. Do not rush through the interview and keep interruptions to a minimum.

If the patient provides an answer to a question that is unclear, incomplete, or irrelevant, it is the RC's responsibility to work with the patient to get an appropriate response to the question. This must be done without leading the patient or biasing her/his answer in any way. The most commonly used method of doing this is 'probing.' Probing is a technique used by interviewers to refocus and redirect the patient's attention to the question. It requires the interviewer to get the patient to elaborate or reconsider an incomplete or inappropriate answer without influencing the content of the answer. Use the following rules when using probing techniques:

Rule #1: Keep it neutral. Be sure not to probe in a way that is leading or directive.
Rule #2: Use only probes similar to those on the list of standard probes provided in Appendix F.

Some of the data collected on the data collection forms touch particularly sensitive areas. If the patient shows reluctance to answer a particular question, try to reassure the patient regarding the confidentiality of the response and explain the importance of the question. However, don't argue and don't push the issue to the point of alienating the patient. If the patient does not provide a response, make a note in the left margin indicating that the patient refused to answer the question.

After the interview is complete, the RC should review the form for completeness and legibility. This should be done before the patient leaves the clinic so that if additional information or clarification is needed it can be obtained. After reviewing the form, the RC should place her/his ID number in the space provided for the Interviewer ID on the upper right hand corner of the first page of the form.

8.2.3. **Forms that the patient completes on her/his own**

The RC should supervise the completion of any forms that the patient completes on her/his own. This includes any special instruction necessary for a given form as well as being available for questions while the patient is completing the form. Be sure that the patient has a quiet comfortable place to sit. Although you should be available for questions, don't hover over the patient while she/he is completing the form. Allow her/him some privacy.

After the patient has completed a form, the RC should review the form for completeness and legibility. This should be done before the patient leaves the clinic so that if additional information or clarification is needed it can be obtained. After reviewing the form, the RC should place her/his

ID number in the space provided for the Reviewer ID on the upper right hand corner of the first page of the form.

Some of the data collected on these data collection forms touch particularly sensitive areas. If the patient shows reluctance to answer a particular question, try to reassure the patient regarding the confidentiality of the response and explain the importance of the question. However, don't argue and don't push the issue to the point of alienating the patient. Make a note in the left margin indicating that the patient refused to answer the question.

If the patient is uncomfortable about completing these forms alone or if the RC feels that the patient may have trouble reading the forms, the RC may interview the patient to complete the forms. The RC should ask the patient, *'Would you like to complete these forms alone, or would you prefer for me to read them to you?'*. Since the patient may find some of the information on these forms to be sensitive, whenever possible the patient should be encouraged to complete the forms alone.

8.2.4. **Forms completed by the physician or other CC staff**

The RC should review all forms completed by other Clinical Center staff. The RC should ensure that the ID of the *person completing the procedure or questionnaire* is indicated in the space provided on the upper right hand corner of the first page of the form.

8.2.5. **Review of completed forms**

The RC should review *all* forms for legibility, accuracy, and completeness *before* they are submitted to the DCC, preferrably while the patient is still available to clarify questionnable responses or to provide missing information.

Several of the ICDB Study data collection forms are administered during multiple patient contacts. It is important to review each form at every visit not only for legibility, accuracy, and completeness, but also for comparison against all previously administered forms of the same type. Some answers should not change (i.e. began menstruating at age 11 should not change from contact to contact) or may only change in certain directions (i.e., previous pregnancy could change from "no" to "yes" from one contact to another but should not change from "yes" to "no").

If information is in question between forms collected at different patient contacts, the RC should review the discrepancy with the patient to determine which answer is correct. If the answer on the current form is correct, the RC should complete a CIDC, staple a photocopy of the applicable page(s) of the original data form and indicate all corrections on the photocopy in **red** ink. The RC should then ensure that the error is corrected on the previous form(s) in the patient study book by crossing out the error with a single line in **black** ink, entering the correct information, and initialing and date the change. If the previous information is correct, the error should be corrected on the

current form by crossing out the error with a single line in **black** ink, entering the correct information, and initialing and date the change.

When making changes to answers or correcting mistakes on incorrectly recorded information, put a single line through the middle of the incorrect information. Record the correct information, and initial and date the correct answer. Circle the correct answer for clarification, if necessary.

8.3. SPECIFIC INSTRUCTIONS FOR THE COMPLETION OF DATA FORMS

This section provides specific instructions for the correct completion of data forms. The forms are listed in alphabetical order.

For each data form, the following information is provided: the purpose of the form, who completes the form, when the form should be completed, and specific instructions. Appendix E also contains a list of all data forms, when they should be completed, and who should complete them.

If you are unable to find specific information that you need to complete the form, please contact the ICDB Data Manager.

8.3.1 Background Information (BACK)

Purpose: To collect demographic and other background information.

Who: Completed by the patient and reviewed by the RC.

When: Screening Phase.

Instructions:

Q4: If the patient has more than one address, use the zip code of the address where she/he receives her/his mail.

Q5: The races listed on this form are defined as follows:

Aleut, Eskimo or American Indian: A person having origins in any of the original peoples of North America, who maintains cultural identification through tribal affiliation or community recognition.

*Asian or Pacific Islande*r: A person having origins in any of the original peoples of the Far East, Southeast Asia, the Indian subcontinent, or the Pacific Islands. This area includes, for example, China, India, Japan, Korea, the Philippine Islands, and Samoa.

Black: A person having origins in any of the black racial groups of Africa.

White: A person having origins in any of the peoples of Europe or the Middle East.

Q6: *Latino/Hispanic:* A person of Mexican, Puerto Rican, Cuban, Central or South American or other Spanish culture of origin, regardless of race.

Q7: The religions listed on this form are defined as follows:

Protestant: The Protestant religions include denominations such as Baptist, Episcopalian, Lutheran, Methodist United Church of Christ, etc.

Q8: This question should indicate the patient's most recent marital status. For example, if the patient is widowed and remarried, mark married.

8.3.2 Background Information (BACKF)

Purpose: To collect updated demographic and other background information.

Who: Completed by the patient and reviewed by the RC.

When: Extensive Clinic Visits.

Instructions:

Q1: If the patient has more than one address, use the zip code of the address where she/he receives her/his mail.

Q3: This question should indicate the patient's most recent marital status. For example, if the patient is widowed and remarried, mark married.

8.3.3 Concomitant Medications (CMED)

Purpose: To collect information regarding medications that a patient is currently taking for reasons *other than her/his urinary symptoms.* This includes both prescription and over-the-counter drugs.

Who: Administered to the patient by the RC.

When: Screening Phase and all follow-up visits.

Instructions:

This form consists of two sections. The first section, "Prior medications stopped since last visit or contact", should be used to record any medications that the patient stopped taking since her/his last ICDB study visit. The second section, "New medications started since last visit or contact", should be used to record any medications that the patient started taking since her/his last ICDB study visit.

Prior medications stopped since last visit or contact: First, indicate the study visit. If this is the first screening visit, check the "none" box and proceed to the "New medications started since last visit or contact" section. For any other visit type, follow the instructions below.

Review the CMED forms from the patient's previous visits. Ask the patient if she/he has stopped any medications since her/his last visit. If she/he has not stopped any medications since the last visit, check the "none" box and proceed to the "New medications started since last visit or contact" section. If she/he has stopped any medications since the last visit, record these changes in the table.

Instructions for completing the table:

Drug Name: Record the name of the drug exactly as it appeared on the original CMED form where it was recorded as a new medication.

Start Date: Obtain the start date from the original CMED form where the drug was recorded as a new medication.

Stop Date: Ask when the patient stopped taking the drug and record only the month and year of the stop date.

Reason: Record the reason exactly as it appeared on the original CMED form where the drug was recorded as a new medication.

New medications started since last visit or contact: First, indicate the study visit. If this is the first screening visit, record all current concomitant medications in the table or check the "none" box if the patient is not currently taking any concomitant medications. For any other visit type, follow the instructions below.

Review the CMED forms from the patient's previous visits. Ask the patient if she/he has started any new medications since her/his last visit. If she/he has not started any new medications since the last visit, check the "none" box and stop. If she/he has started any new medications since the last visit, record these changes in the table.

Instructions for completing the table:

Drug Name: Record the name of the drug exactly as it appears on the label provided by the patient or as reported by the patient. Verify the accuracy of the drug name, including spelling, with a drug handbook (i.e., *Physician's Desk Reference*).

Start Date: Ask when the patient started taking the drug and record only the month and year of the start date. If the patient does not know the month, record only the year.

Stop Date: If the patient is no longer taking the drug, ask when the patient stopped taking the drug and record only the month and year of the stop date. If the patient is still taking the drug, do not record a stop date and check the "continuing" box.

Reason: Ask the patient why she/he is/was taking this medication and record a brief explanation.

8.3.4 Cystoscopy (CYST)

Purpose: To collect information obtained during the cystoscopy procedure.

Who: Completed by the physician performing the cystoscopy procedure and reviewed by the RC.

When: Any study visit, when clinically indicated.

Instructions:

Q9-Q10, Q15-Q19: The locations of all Hunner's patches, scars, localized glomerulations, and biopsies should be indicated on the bladder map on page 4.

Q12-Q16: These questions should be completed only if a hydrodistention is performed.

Q17-Q19: These questions should be completed only if a biopsy is performed.

The pathology report must be submitted for any screening or follow-up visit packet when a biopsy is performed. Any patient identifying information (i.e., name or hospital ID number) must be removed or covered. The report must contain the red ink laboratory report stamp in the upper or lower right hand corner of the front of the first page. This stamp must indicate the patient ID number, the date that the specimen was *collected*, and the form code "PATH".

8.3.5 Deferral Checklist #1 (DEF1)

Purpose: To assess the patient's eligibility for the study according to a subset of the study deferral criteria.

Who: Administered to the patient by the RC.

When: Screening Phase.

Instructions:

Q1: This refers to positive cultures for bacterial cystitis only. Self-diagnoses or diagnoses by a physician without a culture do not apply.

Q3: This question, for men only, refers to positive cultures for bacterial prostatitis only. Self-diagnoses or diagnoses by a physician without a culture does not apply.

Q4: If the patient has never heard of the procedure and does not know if she/he has had one, check "unknown".

Eligibility Question: If the patient is deferred, refer to Section 5.4: *Patient Eligibility* for the length of the deferral period. Record the approximate date that the patient will be eligible for the study.

8.3.6 Deferral Checklist #2 (DEF2)

Purpose: To assess the patient's eligibility for the study according to a subset of the study deferral criteria.

Who: Completed by the RC.

When: Screening Phase, after the physical exam and all clinically indicated tests have been performed.

General Instructions:

The visit date on this form should correspond to the date of the last physical exam or clinically indicated test required to complete the form.

Q2: This question cannot be completed until after the urine culture result is known.

The urine culture report must be submitted with the packet of screening phase data forms. Any patient identifying information (i.e., name or hospital ID number) must be removed or covered. The report must contain the red ink laboratory report stamp in the upper or lower right hand corner of the front of the first page. This stamp must indicate the patient ID number, the date that the specimen was *collected*, and the form code "UCULT".

Eligibility Question: If the patient is deferred, refer to Section 5.4: *Patient Eligibility* for the length of the deferral period. Record the approximate date that the patient will be eligible for the study.

8.3.7 Dietary Habits (DIET)

Purpose: To collect information regarding the effect of certain foods on a patient's urinary symptoms.

Who: Completed by the patient and reviewed by the RC.

When: Screening Phase, Brief Clinic Visits, and Extensive Clinic Visits.

Instructions:

The patient should indicate how each food affects her/his urinary symptoms, *if* they eat the food. If the patient marks more than one response for a question, ask the patient to choose the *one* response that *best* answers the question.

8.3.8 Exclusion Checklist #1 (EXCL1)

Purpose: To assess the patient's eligibility for the study according to a subset of the study exclusion criteria.

Who: Administered to the patient by the RC.

When: Screening Phase.

Instructions:

Q5: If the patient has never heard of the procedure and does not know if she/he has had one, check "unknown".

8.3.9 Exclusion Checklist #2 (EXCL2)

Purpose: To assess the patient's eligibility for the study according to a subset of the study exclusion criteria.

Who: Completed by the RC.

When: Screening Phase, after the physical exam and all clinically indicated tests have been performed.

Instructions:

The visit date on this form should correspond to the date of the last physical exam or clinically indicated test required to complete the form.

Q6: This question cannot be completed until after the CMG has been performed.

8.3.10 Exclusion Checklist #3 (EXCL3)

Purpose: To assess the patient's eligibility for the study according to a subset of the study exclusion criteria.

Who: Completed by the RC.

When: Screening Phase, *if* a cystoscopy, hydrodistention, and biopsy is performed.

Instructions:

The visit date on this form should correspond to the date that the biopsy specimen was collected.

Q1: This question cannot be completed until after the pathology report is completed.

8.3.11 Family History (FHX)

Purpose: To collect information regarding the patient's family medical history.

Who: Administered to the patient by the RC.

When: Screening Phase.

Instructions:

Blood relatives also include half-brothers and half-sisters. Non-blood related family members, including step- and adopted children and siblings, should not be included in the patient's responses.

8.3.12 Hematology (HEM)

Purpose: To collect information obtained from the hematology test.

Who: Completed by the RC.

When: Screening Phase.

Instructions:

The visit date on this form should correspond to the date that the blood specimen was collected.

Hematology results should be transcribed from the laboratory report to the data form. If the "units" from the laboratory report are not the same as the "units" listed on the HEM form, then the RC should convert the values to the units requested on the HEM form. If necessary the RC should contact the laboratory for assistance. Make a note on the lab report that the values have been converted to those recorded on the HEM form.

The hematology report must be submitted with the packet of screening phase data forms. Any patient identifying information (i.e., name or hospital ID number) must be removed or covered. The report must contain the red ink laboratory report stamp in the upper or lower right hand corner of the front of the first page. This stamp must indicate the patient ID number, the date that the specimen was *collected*, and the form code "HMRPT".

8.3.13 Inclusion Checklist (INCL)

Purpose: To assess the patient's eligibility for the study according to the study inclusion criteria.

Who: Administered to the patient by the RC.

When: Screening Phase.

Instructions:

Q1: The patient *must* sign the Informed Consent before the screening process can continue. Do not continue with the rest of the form unless the patient has signed the Informed Consent.

Q2: Do not continue with the rest of the form if the patient is not 18 years of age or older.

Q5-Q8: These questions cannot be completed until the Pain and Urgency Scales (PURG) form is completed and reviewed.

Eligibility Question: If the patient is not eligible ("on-hold"), record the approximate date that the patient will be eligible for the study.

8.3.14 Medical Events and Patient Treatment Evaluation (MED)

Purpose: To collect the patient's assessment of her/his overall health and treatment effectiveness; to collect information regarding medical events and treatment effectiveness since the patient's last study visit or contact.

Who: Administered to the patient by the RC.

When: All follow-up contacts.

Instructions:

Q7: If the patient has had a period within the last 12 months, then check "no"; otherwise, check "yes".

Q9: If the patient does not know the exact date of her last menstrual period, record the month and year.

8.3.15 Patient Medical History (MEDHX)

Purpose: To collect information regarding the patient's medical history.

Who: Administered to the patient by the RC.

When: Screening Phase and Extensive Clinic Visits.

Instructions:

Q1-Q5: Do not complete these questions for male patients.

Q6-Q35: These questions should be answered based only on a physician's diagnosis.

Pap Smear Recommendation: If the patient's last pap smear was abnormal or more than one year ago, you *must* recommend that the patient see her gynecologist for another pap smear.

8.3.16 Physical Exam (PHS)

Purpose: To collect information obtained during the patient's physical examination.

Who: Completed by the physician performing the physical examination and reviewed by the RC.

When: Screening Phase. This form should also be completed during Brief Clinic Visits and Extensive Clinic Visits, when a physical examination is clinically indicated.

Instructions:

Q13-Q16: These questions should be completed only if a neurologic exam is indicated.

8.3.17 Physician's Evaluation and Treatment Plan (PHYTRT)

Purpose: To collect the physician's assessment regarding the patient's overall health and treatment effectiveness; to collect information regarding treatments that a patient is currently using for her/his urinary symptoms.

Who: Completed by the physician performing the evaluation and reviewed by the RC.

When: Screening Phase and all follow-up visits.

Instructions:

The first page of this form collects the overall health assessment, treatment effectiveness and whether or not a cystoscopy will be performed within this visit window.

Q3: This question should be marked "yes" if a cystoscopy has already been performed during this visit window or will be performed during this visit time window. For more details regarding the handling of cystoscopies between follow-up visits, see Section 6.3.4: *Cystoscopy During Follow-Up Visits*.

The last two pages of this form consist of two sections. The first section, "Prior treatments stopped since last visit or contact", should be used to record any treatments that the patient stopped taking since her/his last ICDB study visit. The second section, "New treatments started since last visit or contact", should be used to record any treatments that the patient started taking since her/his last ICDB study visit.

Prior treatments stopped since last visit or contact: First, indicate the study visit. If this is the first screening visit, check the "none" box and proceed to the "New treatments started since last visit or contact" section. For any other visit type, follow the instructions below.

Review the PHYTRT forms from the patient's previous visits. Ask the patient and review the patient's medical chart to determine if she/he has stopped any treatments since her/his last visit. If she/he has not stopped any treatments since the last visit, check the "none" box and proceed to the "New treatments started since last visit or contact" section. If she/he has stopped any treatments since the last visit, record these changes in the table.

Instructions for completing the table:

Treatment: Record the name of the treatment exactly as it appeared on the original PHYTRT form where it was recorded as a new treatment.

Start Date: Obtain the start date from the original PHYTRT form where the treatment was recorded as a new treatment.

Stop Date: Ask when the patient stopped using the treatment and record only the month and year of the stop date.

New treatments started since last visit or contact: First, indicate the study visit. If this is the first screening visit, record all current treatments in the table or check the "none" box if the patient is not currently using any treatments for her/his urinary symptoms. For any other visit type, follow the instructions below.

Review the PHYTRT forms from the patient's previous visits. Ask the patient and review the patient's medical chart to determine if she/he has started any new treatments since her/his last visit. If she/he has not started any new treatments since the last visit, check the "none" box and stop. If she/he has started any new treatments since the last visit, record these changes in the table.

Instructions for completing the table:

Treatment: Record the name of the treatment exactly as it appears on the label provided by the patient or as reported by the patient. Verify the accuracy of all drug names, including spelling, with a drug handbook (i.e., *Physician's Desk Reference*).

Start Date: Determine when the patient started taking the treatment and record only the month and year of the start date. Record only the year if the month is not known.

Stop Date: If the patient is no longer using the treatment, determine and record only the month and year of the stop date. If the patient is still using the treatment, do not record a stop date and check the "continuing" box.

If a treatment is started and stopped on the same day, i.e., a cystoscopy with hydrodistention, then record the start date and stop date as the date of treatment.

8.3.18 Pregnancy History (PREG)

Purpose: To collect information regarding the patient's pregnancy history.

Who: Administered to the patient by the RC.

When: Screening Phase and Extensive Clinic Visits.

Instructions:

Q1: If the patient has had a hysterectomy and had both ovaries removed, then check "yes". If the patient has had a hysterectomy and still has at least part of one ovary and has experienced menopausal symptoms such as hot flashes, vaginal dryness, and/or discomfort when engaging in sexual relations, then check "yes". If the patient has had a hysterectomy and still has at least part of one ovary and has not experienced any menopausal symptoms, then check "no".

If the patient has not had a hysterectomy and has experienced **any** menopausal symptoms, then check "yes"; otherwise check "no". If the patient has not experienced any symptoms, but has had very irregular periods, with the last period within the last 12 months, then check "no". If her last period was greater than 12 months previously, check "yes".

Q2: If the patient has been pregnant at least one time, complete *all* rows in the "Number of Each" column, using zeroes where applicable. Complete the due date only if the patient is currently pregnant.

Q3-Q8: Complete these questions *only* if the patient has been pregnant at least one time.

Q7-Q8: Complete these questions *only* if any of the pregnancies resulted in live births or stillbirths.

8.3.19 Prior Diagnoses and Treatments (PRIOR)

Purpose: To collect information regarding prior diagnostic tests and treatments for the patient's urinary symptoms.

Who: Administered to the patient by the RC.

When: Screening Phase.

Instructions:

Q2-Q10: If the patient had a particular diagnostic test more than once, record the result of the most recent test.

Q13-Q18, Q20-Q26, Q28-45, Q47-51: If the patient has used multiple episodes of a particular treatment, record the effectiveness of the most recent episode.

8.3.20 Pain and Urgency Scales (PURG)

Purpose: To measure the patient's pain and urgency.

Who: Completed by the patient and reviewed by the RC or administered to the patient by the RC.

When: Screening Phase and all follow-up visits.

Instructions:

One number should be circled on each scale. If the patient responds using a range of numbers, ask her/him to clarify the answer by providing *one* number that best describes her/his pain or urgency.

8.3.21 Quality of Life (QUL)

Purpose: To collect information regarding the quality of the patient's life.

Who: Completed by the patient and reviewed by the RC.

When: Screening Phase, Brief Clinic Visits, and Extensive Clinic Visits.

Instructions:

Because this form is a standardized questionnaire (the SF-36), the procedures created by the developers of this form must be *strictly* adhered to when administering this form. These procedures are as follows:

- This form should be administered *before* the patient sees a provider, so that the interaction between the patient and the provider will not influence the patient's answers.

- If the patient asks for clarification of specific questions on the form, assist the patient by rereading the question *word for word*. Do not try to explain what the question means, but suggest that the patient use her/his own interpretation of the question. A patient should answer the questions *based on what she/he thinks* the questions mean.

- A patient may have trouble with the response choices, such as wanting to respond "does not apply" or "I don't know". In these instances, it is important to guide the patient to select one of the categories by saying something like: "I know that it may be hard for you to think this way, but which of these categories most closely expresses what you are thinking". Do not, however, assist the patient in her/his selection of the response. If the patient does not feel comfortable selecting one of the responses, leave the question blank and indicate the reason in the left margin next to the question.

The following list of "Dos and Don'ts" has been created by the developers of this form. It is *very* important that you adhere to these guidelines:

- Do have the patient complete the form before she/he completes any other health data forms and before she/he sees the physician.

  Do **not** discuss the patient's health, health data, or emotions with her/him before she/he completes this form.

- Do be warm, friendly, and helpful.

  Do **not** force or command the patient to complete the form.

- Do request and encourage the patient to complete the form.

Do **not** accept an incomplete form without first encouraging the patient to complete unanswered questions.

- Do read and repeat a question verbatim for the patient.

  Do **not** interpret or explain a question.

- Do tell the patient to answer a question based on what they think the question means.

  Do **not** force or command the patient to complete a particular question.

- Do have the patient complete the form by herself/himself.

  Do **not** allow spouses or family members to help the patient complete the form.

- Do encourage the patient to complete all questions.

  Do **not** minimize the importance of the form.

- Do thank the patient for completing the form.

- Do inform the patient that she/he will be asked to complete the same form again at other clinic visits.

8.3.22 Screening Sign-Off (SCR)

Purpose: To ensure that the Research Coordinator and the Principal Investigator have verified all screening phase data and that the patient is eligible for the ICDB study; to notify the DCC that the screening phase is complete and a Follow-Up Visit Contact Schedule (FVCS) should be generated.

Who: Completed by the Research Coordinator and the Principal Investigator.

When: Screening Phase.

Instructions:

The last screening phase visit date should be the date of the last screening phase visit where data were collected. This date should correspond to the latest visit date on any of the screening data forms.

8.3.23 Symptom History (SYMHX)

Purpose: To collect information regarding the patient's symptom history.

Who: Completed by the patient and reviewed by the Research Coordinator.

When: Screening Phase.

Instructions:

Q5: For the ICDB study, a remission must be a period without symptoms no less than 3 months.

Q18: If the patient has had a hysterectomy and had both ovaries removed, then check "yes". If the patient has had a hysterectomy and still has at least part of one ovary and has experienced menopausal symptoms such as hot flashes, vaginal dryness, and/or discomfort when engaging in sexual relations, then check "yes". If the patient has had a hysterectomy and still has at least part of one ovary and has not experienced any menopausal symptoms, then check "no".

If the patient has not had a hysterectomy and has experienced **any** menopausal symptoms, then check "yes"; otherwise check "no". If the patient has not experienced any symptoms, but has had very irregular periods, with the last period within the last 12 months, then check "no". If her last period was greater than 12 months previously, check "yes".

8.3.24 Symptom Questionnaire (SYMPH)

Purpose: To collect information regarding the patient's urinary symptoms.

Who: Administered to the patient by the Research Coordinator.

When: Month 1 Follow-Up Visit and Telephone Contacts.

Instructions:

Q1: One number should be circled. If the patient responds with a range of numbers, ask her/him to clarify the answer by providing *one* number that best describes her/his pain or urgency.

Q2, Q6: For each question, the patient should indicate one response. If the patient indicates multiple responses, ask the patient to choose the *one* response that *best* answers the question.

Q5: Make sure that the response to this question does not conflict with the responses to Q3 and Q4. Clarify any discrepancies with the patient.

Q6: The scale above the table is part of the instructions for the question. The numbers on this scale should *not* be circled.

8.3.25 Symptom Questionnaire (SYMPTS)

Purpose: To collect information regarding the patient's urinary symptoms.

Who: Completed by the patient and reviewed by the Research Coordinator.

When: Screening Phase, Brief Clinic Visits, and Extensive Clinic Visits.

Instructions:

General Instructions: Before giving the patient this questionnaire to complete, review with the patient the body parts described in questions 7-13. The RC should give the patient the laminated pictures depicting the body parts described in these questions for reference while completing this form. The patient will then be able to refer to the pictures while she/he is answering the questions.

Q1: One number should be circled. If the patient responds using a range of numbers, ask her/him to clarify the answer by providing *one* number that best describes her/his pain or urgency.

Q2, Q6: For each question, the patient should indicate one response. If the patient indicates multiple responses or leaves a question blank, ask the patient to choose the *one* response that *best* answers the question.

Q5: Make sure that the response to this question does not conflict with the responses to Q3 and Q4. Clarify any discrepancies with the patient.

Q11-Q12: Q11 is a female-only question and Q12 is a male-only question. Make sure that these questions are completed or left missing appropriately.

Q14: The scale above the table is part of the instructions for the question. The numbers on this scale should *not* be circled.

Q24: If the patient has had a hysterectomy, then check "no". If the patient has not had a hysterectomy and has had a period within the last 12 months, check "yes"; otherwise, check "no".

8.3.26 Urinalysis (URN)

Purpose: To summarize the information obtained from the dipstick analysis of the urine specimen.

Who: Completed by the Research Coordinator.

When: Screening Phase, Brief Clinic Visits, and Extensive Clinic Visits.

Instructions:

The visit date on this form should correspond to the date that the urine specimen was collected.

Urinalysis results should be transcribed from the dipstick to the data form.

8.3.27 Urodynamic Evaluation (UROD)

Purpose: To summarize the information obtained from the urodynamic evaluation.

Who: Completed by the physician or technician performing the urodynamic evaluation and reviewed by the RC.

When: Screening Phase.

Instructions:

The visit date on this form should correspond to the date that the urodynamic evaluation was performed.

The urodynamic trace must be submitted with the packet of screening phase data forms. Any patient identifying information (i.e., name or hospital ID number) must be removed or covered. The report must contain the red ink laboratory report stamp in the upper or lower right hand corner of the front of the first page. This stamp must indicate the patient ID number, the date that the urodynamic evaluation was *performed*, and the form code "TRACE".

8.3.28 Voiding Log (VOID)

Purpose: To collect information regarding the patient's voiding pattern over a 3-day period.

Who: Completed by the patient and reviewed by the RC.

When: Screening Phase and all follow-up visits.

Instructions:

All three days of the voiding log should be completed within the time window for the visit.

The instructions for the voiding log, listed on page 1 of the form, should be thoroughly reviewed with the patient before she/he completes her/his screening phase log and reviewed at each follow-up visit. If a patient cannot properly complete a screening phase voiding log, the RC should evaluate whether the patient can and/or will adhere to the protocol to warrant enrollment in the study.

All pages of the voiding log should be submitted to the DCC, including the instructions page (page #1). Ensure that the Reviewer ID is completed on page 1.

When a patient returns a voiding log, it should be reviewed thoroughly, in the presence of the patient.

- If the log was not completed for 3 three *consecutive* days (with *exactly one* weekend day), the instructions should be reviewed and the patient should be asked to repeat the log.

- If the returned voiding log is sloppy or difficult to read, it should be re-copied before being submitted to the DCC. The original patient log should be stapled to the back of the re-copied log. Label the copy "RECOPIED", with your initials and date re-copied.

- Any discrepancies or missing values (including dates, hours, *and* minutes) should be clarified and corrected, if possible. Ensure that the am/pm values are correct and that the times are not indicated on a 24-hour (military) clock.

- Only one number should be circled on each pain and urgency scale. If the patient circled a range of numbers, ask her/him to clarify the answer by providing *one* number that *best* described her/his pain or urgency.

- If the patient does not indicate *any* asterisks (*) for awakening to void, verify with her/him that she/he did not awaken to void.

8.4. INSTRUCTIONS FOR THE COMPLETION OF ADMINISTRATIVE FORMS

8.4.1 General Instructions for Administrative Forms

Instructions for specific administrative forms are contained in Section 8.4.2. The items below are guidelines to be followed when completing any of the administrative forms.

All administrative forms should be completed in **black** ink. Red ink should be used when making corrections to photocopies of forms during the completion of query forms (QDC and QMD) and the Clinic-Initiated Data Correction (CIDC) form.

All responses should be printed legibly. When making changes to answers or correcting mistakes or incorrectly recorded information, put a single line through the middle of the incorrect information. Record the correct information, and initial and date the correct answer. Circle the correct answer for clarification, if necessary.

8.4.2 Specific Instructions for Administrative Forms

This section provides specific instructions for the correct completion of administrative forms. The following information is provided for each form: the purpose of the form, when the form should be completed, and specific instructions. If you are unable to find specific information that you need to complete the form, please contact the ICDB Data Manager.

8.4.2.1. Address Update Form (ADDR)

The Address Update Form (ADDR) provides a simple tool for the RC to keep updated information on all patients involved in the ICDB Study. This form should be completed by the RC whenever the patient's address, phone number, or employer has changed. The form must not be sent to the DCC; it is for Clinical Center records only.

8.4.2.2. Informed Consent Form

The Informed Consent Form, developed by each of the individual Clinics, provides the mechanism for the patient to consent to participating in the ICDB Study. The form **must** be completed by the patient prior to collecting any information or performing any procedures for the specific purpose of the ICDB Study. The form must not be sent to the DCC; it is for Clinical Center records only.

8.4.2.3. Patient Registration Form (REG)

The Patient Registration Form (REG) assigns the patient ID number and provides the RC with a simple tool to keep a record of the addresses, phone numbers, and employers of all patients involved in the ICDB Study. The form must be completed by the patient at her/his first screening visit. The form must not be sent to the DCC; it is for Clinical Center records only.

8.4.2.4. **Patient Status Form (STAT)**

The Patient Status Form (STAT) is a simple tool designed to help the RC keep track of the status of each patient registered for the ICDB study. This form is optional and may be completed by the RC whenever a patient has a change in status. The form **must** not be sent to the DCC; instead it should be placed in the patient's medical records.

8.4.2.5. **Patient Withdrawal Form (WITH)**

The Patient Withdrawal Form (WITH) is designed to keep track of all patients who withdraw from the study. This form must be completed by the RC whenever a patient decides that she/he no longer wants to participate in the study or when a patient is lost-to-follow-up. A copy of the form should be placed in the patient's study book, and the original form should be sent to the DCC in the next mailing.

8.4.2.6. **Patient Reinstatement Form (REIN)**

The Patient Reinstatement Form (REIN) is designed to keep track of patients who previously withdrew from the study and want to be reinstated. This form must be completed by the RC whenever a patient who has been previously withdrawn from the study desires to participate in the ICDB Study again. A copy of the form should be placed in the patient's study book, and the original form should be sent to the DCC in the next mailing.

8.4.2.7. **Request for Forms (FREQ)**

The Clinical Center Request for Forms form (FREQ) should be used any time a Clinical Center wishes to request forms from the DCC. This form requires the Clinical Center ID and name, and the date of request. Forms packets may be ordered by box by contact type. Individual forms may also be ordered. The form should be signed by the requestor prior to being sent to the DCC. The RC should allow 10-15 business days to receive the forms.

8.4.2.8. **Visit Checklists**

A Checklist was created for each visit to provide the RC with a simple way of ensuring that all required data forms and diagnostic procedures were completed. The Visit Checklist should always be checked before a patient leaves the clinic or gets off of the phone. The checklist must accompany the forms packet for that visit when it is mailed to the DCC.

In the "Submitted to DCC?" column, indicate with a checkmark whether or not each form was completed at the clinic. If a form was completed and is in the attached packet, check the "Yes" column. If a form was not completed due to some extenuating circumstance, check the "No" column. If the form is not applicable (e.g. patient is male, so no pregnancy history is completed), then check the "N/A" column.

8.4.2.9. **Visit Reminders**

Visit Reminders should be sent to the patient two weeks before a scheduled visit. The visit reminders should be accompanied by any forms that must be completed by the patient prior to the study visit. Please refer to Section 6.4: *Visit Reminders* for more details.

8.4.2.10. **Biopsy Specimen Tracking Form (TRACK)**

The Biopsy Specimen Tracking Form (TRACK) is designed to track the shipment of the Database Biopsy specimens from the Clinical Center to the Anatomic Pathology Laboratory (APL) and to provide pertinent biopsy information to the APL pathologist. Please refer to the Bladder Biopsy Handling chapter (Section 10.4: *Relevant Biopsy Forms*) of this manual for more details.

8.4.2.11. **Biopsy Slide Tracking Form (SLTR)**

The Biopsy Slide Tracking Form (SLTR) is designed to track the shipment of the Home Institution Biopsy microscope slides from the Clinical Center to the APL and to provide pertinent biopsy information to the APL pathologist. Please refer to the Bladder Biopsy Handling chapter (Section 10.4: *Relevant Biopsy Forms*) of this manual for more details.

8.4.2.12. **Data Clarification Form (QDC)**

The Data Clarification Form (QDC) is a query form initiated at the DCC and sent to the Clinical Center to request clarification of an unclear, illogical, or problematic response on a form. The query form identifies the patient ID, visit type, date of visit, form code, date of query, and an explanation of the question(s) requiring clarification. A photocopy of the appropriate pages of the form are attached to the query form. The queried item should be clarified with the patient, the patient's Study Book, and/or the patient's medical records, as appropriate. The clarification should be indicated either on the query form or the attached photocopy of the form (in red ink). The completed query form should be signed and dated, photocopied for the patient's Study Book, and sent to the DCC in the next mailing. The patient's Study Book and/or the patient's medical records should be updated

to reflect the change indicated on the submitted query form so that the Clinical Center records match those maintained at the DCC. Changes to the patient's Study Book or medical records should be made by crossing out the error with a single line in black ink, entering the correct information, and initialing and dating the change.

8.4.2.13. **Request for Missing Data (QMD)**

The Request for Missing Data (QMD) is a query form initiated at the DCC and sent to the Clinical Center to request missing data on a form. The query form identifies the patient ID, visit type, date of visit, form code, date of query, and the question number(s) of the missing data. A photocopy of the appropriate pages of the form are attached to the query form. The queried items should be retrieved from the patient, the patient's Study Book, and/or the patient's medical records as appropriate. The missing data should be provided either on the query form or the attached photocopy of the form (in red ink). If the missing data cannot be obtained, the reason should be indicated on the query form. The completed query form should be signed and dated, photocopied for the patient's Study Book, and sent to the DCC in the next mailing. The patient's Study Book and/or the patient's medical records should be updated to reflect the change indicated on the submitted query form so that the Clinical Center records match those maintained at the DCC. Changes to the patient's Study Book or medical records should be made by crossing out the error with a single line in black ink, entering the correct information, and initialing and dating the change.

8.4.2.14. **Clinic-Initiated Data Correction Form (CIDC)**

The Clinic-Initiated Data Correction Form (CIDC) should be used to notify the DCC of any necessary corrections to data already submitted to the DCC. This form should be used for items which cannot be queried or have not been queried and is not intended to be used to record corrections already recorded on a query form. The form requires the patient ID, visit type, date of visit, form code, a brief description of the correction, and the reason for the correction. A photocopy of the applicable pages of the original form should be used to indicate the corrections in red ink and then stapled to the correction form. The completed correction form should be signed and dated, photocopied for the patient's Study Book, and sent to the DCC in the next mailing.

8.5. SUBMISSION OF COMPLETED FORMS TO THE DCC

8.5.1. **Preparing the completed forms to be sent to the DCC**

No forms for a visit should be submitted to the DCC until *all* forms in that visit packet are completed. For the screening phase, visit packets should only be submitted to the DCC if the patient is eligible and has completed the screening phase.

Once a visit packet is complete, a xerox copy of all forms contained in that visit packet should be made. The xerox copy should be placed in the study book and the original forms should be sent to the DCC.

The visit checklist should be completed (refer to Section 8.4: *Instructions for the Completion of Administrative Forms*) and the forms should be sorted in the same order as listed on the checklist. All multi-page forms should be stapled and the entire packet should be paper-clipped.

8.5.2. **Mailing Schedule**

All visit packets and administrative forms that were completed during the previous week should be sent to the DCC. It is very important that data are sent to the DCC as quickly as possible so that they can be entered into the study database and relevant accrual and summary reports can be generated.

All forms mailings and all correspondence to the DCC regarding forms should be addressed as follows:

If you are sending the forms via UPS or Federal Express the address is:

ICDB Data Manager
Center for Biostatistics and Epidemiology
Penn State University
M.S. Hershey Medical Center
500 University Drive
Hershey, Pennsylvania 17033

If you are sending the forms via the U.S. Mail the address is:

ICDB Data Manager
Center for Biostatistics and Epidemiology
Penn State University
M.S. Hershey Medical Center
P.O. Box 850
Hershey, Pennsylvania 17033

Each Clinical Center should mail forms once each week. If for some reason a Clinical Center does not have any completed visit packets to mail during a given week, the RC should send a fax to the DCC indicating that no mailing will be sent that week.

If visit packets are received at the DCC in a manner which is unsuitable for processing (form pages are missing, key information like patient ID number, visit type or visit date are missing, multi-page forms are not stapled, forms are not properly ordered and paper-clipped, visit checklist is not completed, etc.), they may be returned to the Clinical Center for resolution. The DCC will attempt to resolve any problems by telephone before visit packets are returned to the Clinical Center.

9.1. BLADDER CATHETERIZATION

When bladder catheterization is necessary, the professional nurse will follow the procedure outlined below using strict asepsis. Aseptic technique and the maintenance of a closed-drainage system in patients requiring catheterization is necessary to minimize the risk of nosocomial urinary tract infections. Universal Barrier Precautions should be observed for all contacts with patients' body fluids.

9.1.1. Equipment

A sterile catheter using aseptic technique is necessary to perform the bladder catheterization.

9.1.2. Procedure for Female Catheterization

1. Position the patient in a dorsal recumbent position with knees drawn up and slightly separated, feet flat on bed.

2. Assemble equipment and arrange sterile field.

3. Put on sterile gloves. Place sterile drape just under patient's buttocks and place disposable basin on sterile drape.

4. Soak cotton balls with antiseptic solution.

5. Lubricate catheter approximately 2-3 inches from the insertion tip and place catheter in sterile basin.

6. Spread labia and keep retracted with non-dominant hand until catheter is inserted. With dominant, sterile-gloved hand, pick up antiseptic-soaked cotton balls. With a new cotton ball each time, cleanse each side of labia minor, stroking from clitoris downward. Cleanse meatus by making stroke directly down center from clitoris to vagina.

7. Encourage the patient to breathe deep as a relaxation technique to prevent contraction of the urethra. A flashlight may help visualize urethra.

8. Pick up catheter 3-4 inches from the top; insert about 1-1/2 inches or until urine begins to flow, collecting it in the basin.

9. Slowly withdraw straight catheter after urine ceases to flow. If more urine starts to drain while withdrawing catheter, stop and allow urine to drain. Then proceed to remove the catheter slowly.

10. Document the date of catheter insertion and the size of catheter in the patient's chart.

9.1.3. **Procedure for Male Catheterization**

NOTE: Should the nurse encounter significant resistance while inserting the catheter, the nurse should stop the procedure and notify the physician.

1. Position the patient comfortably in a dorsal recumbent or semi-sitting position.

2. Assemble equipment and arrange sterile field.

3. Put on sterile gloves. Place a sterile drape over the patient with diamond-shaped opening exposing penis. Place sterile container on sterile drape.

4. Soak cotton balls with antiseptic solution.

5. Lubricate catheter approximately 7 inches from the insertion tip and place catheter in sterile basin.

6. Grasp shaft of penis with non-dominant hand and lift into an almost vertical position. This position straightens the urethra and helps prevent retraction and contamination.

7. With dominant, sterile-gloved hand, pick up each antiseptic soaked cotton ball and cleanse glans penis around meatus in a circular motion. If foreskin is present, strip back and gently wash off any smegma accumulation.

8. Encourage the patient to begin slow deep breathing as a relaxation technique.

9. Pick up catheter 3-4 inches from the end and slowly advance it about 7 - 10 inches. As you near the bladder outlet, resistance may be felt if the patient has an enlarged prostate. Have the patient take a deep breath and with a smooth constant motion, advance the catheter until urine begins to flow, collecting it in the basin. Advance one more inch to insure placement in the bladder.

10. Slowly withdraw straight catheter after urine ceases to flow. If more urine starts to drain while withdrawing catheter, stop and allow urine to drain. Then, proceed to remove catheter slowly.

11. Reposition foreskin at conclusion of procedure.

12. Document date of insertion and size of catheter in patient's chart.

9.2. URODYNAMIC EVALUATION

The urodynamic evaluation should be administered after the patient has completed data forms that require the patient to assess her/his baseline status, i.e., Patient Symptom Questionnaire (SYMPTS) and Quality of Life (QUL) forms. (Please refer to Section 6.1 of this manual for the preferred screening phase visit schedules.) For this reason, a urodynamic evaluation completed prior to the patient's enrollment in the ICDB study is not valid for the purposes of the study.

Every effort should be made for the urodynamic evaluation to be performed under the supervision of the Principal Investigator (PI) or a co-investigator according to the procedures outlined below. If this is not feasible, then the urodynamic evaluation may be done by a non-ICDB Study physician/hospital if and only if the following conditions are met.

- The ICDB Study physician knows and understands the non-ICDB Study physician/hospital's methods and results.
- The ICDB Study physician provides the non-ICDB Study physician with a copy of the ICDB Study protocol for the urodynamics evaluation and the ICDB Study Urodynamics (UROD) Form.
- The urodynamics evaluation is performed with water according to the protocol.

Results of this evaluation must be recorded on the Urodynamics Form (UROD).

1. Ask patient to void into the toilet and empty her/his bladder as well as she/he can.

2. ***Optional for all patients:*** Perform flowmetry. Record initial average uroflow rate (cc/sec), initial peak uroflow rate (cc/sec), and initial volume voided (cc).

3. ***Optional for females &:*** Pass a rectal catheter (lubricated with sterile water - soluble jelly) past the external sphincter. This records abdominal pressure.

4. Pass a urodynamic catheter equal to or less than 10 French using the technique described for sterile catheterization. Indicate whether the patient has an urethral stricture less than 12 French. Drain any remaining urine into a sterile graduated container and record the amount obtained as post-void residual urine. This records bladder pressure.

5. Connect the catheter(s) to the pressure transducers, using the procedure described for your specific urodynamic recorder.

6. Fill the bladder with sterile 0.9% saline or sterile water at a rate of 60 cc/min. Record the filling rate, and indicate if it differs from 60 cc/min.

7. Instruct the patient neither to void nor to inhibit voiding, but simply to report all sensations, including first sensation to void, strong desire to void, and inability to tolerate continued filling.

8. When the patient says she/he has the first sensation to void:
   a) Record the volume at first sensation to void.
   b) Ask the patient: *Does this feeling or sensation feel like your symptoms?* Record the patient's response.

9. Observe throughout filling for involuntary bladder contractions. Record whether the patient experiences any involuntary bladder contractions. If a contraction occurs, record the volume infused at the time of the contraction.

10. When the patient says she/he cannot tolerate any more filling:
    a) Turn off the water infusion.
    b) Record the volume infused when the patient is at maximal capacity and cannot tolerate any more filling.
    c) Record the bladder pressure (end filling pressure) and indicate whether it is subtracted or not subtracted.
    d) If applicable, record the detrusor pressure (bladder pressure minus abdominal pressure).
    e) Ask the patient: *Does this feeling or sensation feel like your symptoms?* Record the patient's response.

11. ***Optional for females &:*** Ask the patient to void, with catheters in place, into the uroflow commode.

    a) If the patient can void, record the peak and average uroflow rates. Record opening pressure, peak flow pressure, and maximum pressure. Also indicate whether each pressure is subtracted or not subtracted.

    b) If the patient cannot void, remove the catheters and ask her/him then to void into the uroflow commode. Record the peak and average flow rates.

    c) Record the volume voided.

9.3. CYSTOSCOPY, HYDRODISTENTION, AND BIOPSY

The Cystoscopy, Hydrodistention, and Biopsy should be administered after the patient has completed data forms that require the patient to assess her/his baseline status, i.e., Patient Symptom Questionnaire (SYMPTS) and Quality of Life (QUL) forms and the Voiding Log (VOID). (Please refer to Section 6.1 of this manual for the preferred screening phase visit schedules.) Results of this evaluation should be recorded on the Cystoscopy form (CYST).

1. Do a sterile preparation and draping in the usual manner for your institution.

2. Record the type of anesthesia (local, general or regional).

3. Use a lubricated cystoscope 15-25 French in size (for women, use a sheath with a flush end so the entire urethra can be inspected). Fill the bladder with sterile irrigant as needed for visualization.

4. Inspect the urethra for stones, diverticula or other lesions, and record the findings.

5. Inspect the orifices, and record whether they are normal or abnormal.

6. Inspect the bladder for pseudomembranous trigonal changes, calculi or tumors, and record the findings.

7. If a Hunner's ulcer is present, indicate its position by placing an "H" on the bladder map.

8. If scars are present, record the position(s) by placing an "S" on the bladder map.

9. Record whether the bladder vascularity is normal, increased or decreased.

10. Elevate the container of sterile irrigant to 80 cm above the bladder and leave the connections open for two to three minutes. Compress urethra if leakage occurs. Empty and record volume.

11. Drain the bladder fluid into a graduated container. Observe whether the effluent is bloody.

12. After emptying, record the degree of glomerulations and whether they are diffuse or localized. If localized, indicate the position(s) by placing a "G" on the bladder map.

13. If a therapeutic distention is planned, re-distend the bladder for 8-12 minutes at the same pressure (80 cmH_2O).

14. When performing biopsies, adhere to the following guidelines for the sampling of three sets of

bladder tissue (a set is defined by 2 samples of bladder tissue, one superficial and one deep):

- If the patient has a Hunner's patch, then sample 2 sets, not closer than 5 mm of each other, in the area of the patch.
- If the patient does not have a Hunner's patch, but does have glomerulations, then sample 2 sets, not closer than 5 mm of each other, in the area of the glomerulations.
- If the patient does not have a Hunner's patch or glomerulations, then 2 sets, not closer than 5 mm of each other, should be randomly sampled from the "normal" posterior bladder wall.
- The remaining set of tissue should be sampled in the area of the trigone.

Use cold-cup forceps and try to obtain muscle. The first set of tissue should be fixed in neutral buffered formalin for routine histology at your local laboratory. Mark the sampled site(s) by placing an "1" on the bladder map. The second and third sets should be placed in weak cross-linker fixative and sent to the Anatomic Pathology Laboratory for evaluation and storage. Mark a "2" on the bladder map to indicate the location of the first set, and a "3" to indicate the location of the second set. Coagulate bleeding sites according to your usual practice. See Section 10.3: *Biopsy Sampling and Handling Protocol* for further discussion of this topic.

9.4. PHYSICAL EXAMINATION

The results of the Physical Examination should be recorded in the patient's medical chart as well as on the Physical Examination form (PHS).

1. Inspect and palpate the abdomen for masses, tenderness or presence of a hernia and record findings.

2. *For Men:*

   a) Inspect the urethral meatus for discharge, size, and tenderness; and palpate the urethral course, including the perineum.

   b) Inspect and palpate the scrotal contents.

   c) Check for circumcision.

   d) Inspect the genital skin for lesions.

   e) Examine the prostate for size, nodules and tenderness.

   f) Check the rectum for abnormalities or masses.

   g) If a neurologic exam is indicated by the patient's symptoms, then assess rectal sphincter tone, voluntary contraction, bulbocavernosus reflex and perianal sensation.

3. *For Women*:

   a) With the patient in the dorsal lithotomy position, inspect for:
      1. Urethral caruncle
      2. Cutaneous lesions
      3. Vaginal discharge (if present, perform a wet prep to look for vaginitis).
      4. Atrophic vaginitis

   b) Palpate the urethra to check for masses, to observe if pus can be expressed, and to check for tenderness.

   c) Palpate the perineum to check for masses or tenderness.

   d) Check the rectum for abnormalities or masses.

   e) If a neurologic exam is indicated by the patient's symptoms, then assess rectal sphincter tone,

voluntary contraction, bulbocavernosus reflex and perianal sensation.

f) Palpate the urethra, bladder base, posterior vaginal wall, and right and left vaginal wall (levator muscles) for tenderness.

g) Inspect for cystocele and rectocele at rest and during valsalva.

h) Inspect for enterocele and prolapsed uterus.

i) Inspect for redness and tenderness of introitus.

j) Check for clinical diagnosis of vulvodynia.

9.5. URINALYSIS

The urinalysis will be completed using the CHEMSTRIP® urine test strips. This is a multi-parameter test strip useful for measuring certain constituents in the urine. These measurements are useful in the evaluation of renal, urinary and metabolic disorders. The parameters that will be assessed are Leukocytes, Nitrite, pH, Protein, Glucose, and Blood. The results should be recorded on the Urinalysis form (URN).

9.5.1. CHEMSTRIP® Storage

Store strips at temperatures under 30°C (86°F). Do not freeze. In order to avoid exposure to moisture, the vial must be closed immediately after removal of strips, using the original stopper.

9.5.2. Specimen Collection and Preparation

CHEMSTRIP® urine test strips may be used on any freshly voided urine specimen. A clean-catch urine specimen should be collected in a clean container in mid-stream for both males and females. The specimen should be tested as soon as possible after collection. Do **not** centrifuge or use preservatives. If for some reason testing cannot be performed within one hour after collection, the specimen should be immediately refrigerated at 2 to 8° C. The urine should be returned to room temperature before testing. Mix thoroughly before use. Urine should be collected in a container which will allow complete immersion of the reagent areas on the test strip.

9.5.3. Procedure

Required materials

The materials required are a fresh urine sample, 1 aluminum vial containing CHEMSTRIP® urine test strips and the visual comparison color scale for reading test results printed on the vial label.

Assay procedure

1. Briefly (no longer than 1 second) dip the test strip into the urine. Ensure that the chemically impregnated patches on the test strip are totally immersed.
2. Draw the edge of the strip along the rim of the specimen container to remove excess urine.
3. After the appropriate time, read the test as follows:
   Hold the strip close to the color blocks on the vial and carefully match ensuring that the strip is properly oriented to the color chart on the vial label. The minimum time from the immersion in the urine until the value for each parameter may be read is provided in Table 9.1. However, all values may be read between 1 and 2 minutes after immersion in the urine. The colors are stable for **only** 120 seconds (2 minutes) after immersion. Color changes that occur after 2 minutes from immersion are **not** of diagnostic value. Color changes that occur only along the edge of the test area should be ignored. Careful removal of excess urine (step 2) should eliminate this effect.

Leukocytes	60-120 seconds
pH	immediate
Nitrite	30 seconds
Protein	30-60 seconds
Glucose	60 seconds
Blood	60 seconds

Table 9.1. Minimum Time Required Before Reading Test Results

9.5.4. **Obtaining and Recording the Results**

The results are obtained by direct visual comparison with the color scale printed on the vial label. No calculations are necessary. The results should be recorded on the Urinalysis form (URN). Refer to Chapter 8: *Data and Administrative Forms Handling* for more information on recording the urinalysis results.

9.6. URINE CULTURE

Initially, a clean-catch urine specimen should be collected in mid-stream for both males and females. The specimen should be promptly sent to the Clinical Center's local laboratory for a urine culture. If the clean-catch urine specimen provides a negative urine culture, as defined by $< 10^5$ colonies/ml, no additional urine specimen is necessary. If, for females, the clean-catch urine culture proves positive, a catheterized urine specimen should be collected and analyzed to rule out infection.

The results of the urine culture should be recorded on Deferral Checklist #2 (DEF2), Question #2 (*"Does this patient have bacterial cystitis?").* The urine culture laboratory report should be sent to the Data Coordinating Center (DCC) with the DEF2 form. See Chapter 8: *Data and Administrative Forms Procedures* for more information on completing the DEF2 form and submitting the laboratory report.

10.1. BLADDER BIOPSIES

If, and when, it is clinically indicated, a study patient should undergo a cystoscopy, hydrodistention, and biopsy under full anesthesia. The bladder biopsy specimens should be handled according to the protocol outlined in the following sections.

Any questions concerning bladder biopsy handling should be addressed to the Anatomic Pathology Laboratory (APL) at the University of Pennsylvania. The primary contact at the APL is Ms. Li-Ping Wang, who may be reached at one of the following numbers:

Ms. Li-Ping Wang (Research Assistant)	(215) 662-6503 (Voice Mail)
	(215) 662-6529 (Voice Mail)
	(215) 401-9765 (Beeper)

In the case of an emergency, if you are unable to reach Ms. Wang, the APL Director, Dr. John Tomaszewski, may be reached at one of the following numbers:

Dr. John Tomaszewski (APL Director)	(215) 662-6503
	(215) 308-3685 (Beeper)

10.2. BIOPSY KIT

A biopsy kit, which should be kept refrigerated at 4ºC until use, is provided for each patient biopsied. Each kit should contain:

- Three (3) color-coded vials containing pre-measured reagents, labelled:
  "Vial A" (violet label) containing stock paraformaledhyde fixative
  "Vial B" (orange label) containing lysine buffer
  "Vial C" (red label) containing periodate crystal

- Two (2) empty, color-coded vials, labelled:
  "Sample 2" (blue label)
  "Sample 3" (yellow label)

- Red tape for sealing the styrofoam box prior to mailing the specimens

- A pre-addressed mailer

- A Federal-Express envelope addressed to the Anatomic Pathology Laboratory

- A slide mailer

- Two (2) identifying labels for vials labelled "Sample 2" (blue) and "Sample 3" (yellow)

- Six (6) identifying labels for microscope slides

- A Biopsy Specimen Tracking Form (TRACK)

- A Biopsy Slide Tracking Form (SLTR)

If a biopsy kit does not contain all of the above items, then the APL should be notified immediately so that the problem can be rectified.

10.3. BIOPSY SAMPLING AND HANDLING PROTOCOL

Three sets of biopsies should be taken from each patient. A *set* is defined by two (2) samples of bladder tissue. The first specimen should be sampled superficially and the second specimen of the set should be sampled from deep bladder tissue including muscularis propria. A biopsy which contains both superficial and deep tissue is also considered a set. In total, three (3) sets--six samples of tissue, 3 superficial and 3 deep; or three samples, each including both superficial and deep material--should be collected from each patient.

The following guidelines should be adhered to in the sampling of the bladder tissue:

1) If the patient has a Hunner's patch, then 2 sets, not closer than 5 mm of each other, should be sampled in the area of the patch;

2) If the patient does not have a Hunner's patch, but does have glomerulations, then 2 sets, not closer than 5 mm of each other, should be sampled in the area of the glomerulations.

3) If the patient does not have a Hunner's patch or glomerulations, then 2 sets, not closer than 5 mm of each other, should be randomly sampled from the "normal" posterior bladder wall.

4) The remaining set of tissue should be sampled in the area of the trigone.

Use cold-cup forceps and attempt to obtain muscle. The first two sets, which are sampled in the most diseased area, are processed differently. The first set, which is referred to as S*ample 1: Home Institution Biopsy*, should be handled according to standard operating procedures for pathology specimens at the home institution. The second set, which is referred to as *Sample 2: Database Biopsy*, should be sent to the APL. The third set of tissue, which is sampled in the area of the trigone and is referred to as *Sample 3: Database Biopsy*, should also be sent to the APL. See Section 9.3 for further discussion of this topic.

10.3.1. Sampling and Handling the Home Institution Biopsy (Sample 1)

The Home Institution Biopsy (Sample 1) should be sampled according to the guidelines described above in Section 10.3. The Research Coordinator, or her/his designate, should be present at the time of the cystoscopy. When the urologist hands off the biopsy specimen, it should be **processed according to standard operating procedures for pathology specimens at the home institution. DO NOT SEND THIS SPECIMEN TO THE APL!!!**

Arrangements have been made to obtain **between 6 and 10** microscope slides from the Home Institution Biopsy from the pathologist at each of the Clinical Centers. Prior to the biopsy procedure, the Research Coordinator should contact this pathologist to let him/her know that the

patient is an "IC Protocol Biopsy". The local pathologist will provide a report to the attending urologist according to their usual procedure. Once the urologist receives this report, the Research Coordinator should contact the pathologist to make arrangements to pick up the 6-10 microscope slides for the ICDB Study. When the slides are obtained from the pathologist, the Research Coordinator should affix one completed slide label to each slide. In order to preserve the confidentiality of the database patients, the labels should be placed directly over any identifiers used by the local pathology laboratory.

10.3.2. **Sampling and Handling the Database Biopsies (Samples 2, 3)**

Immediately prior to use, the three color-coded vials containing pre-measured fixative reagents must be mixed. To prepare the fixative, the contents of Vial A (violet label) should be poured into Vial C (red label). Then, the contents of Vial B (orange label) should also be poured into Vial C. The contents of Vial C should then be shaken until the crystal is completely dissolved. Finally, the contents of Vial C should be split into equal parts, pouring half of the contents into the empty, blue vial labelled "Sample 2" and the remaining half into the empty, yellow vial labelled "Sample 3". Once the fixative is prepared and placed in the "Sample 2" and "Sample 3" vials, it is ready to receive the biopsy specimens.

The Database Biopsies (Samples 2, 3) should be sampled according to the guidelines described above in Section 10.3. The Research Coordinator, or her/his designate, should be present at the time of the cystoscopy. When the urologist hands off the second biopsy specimen from the same diseased area as the first specimen, it should be placed immediately in the blue vial labelled "Sample 2". When the urologist hands off the third and final biopsy specimen from the area of the trigone, it should be immediately placed in the yellow vial labelled "Sample 3". The Research Coordinator should affix one completed vial label to each of the vials. If the urologist samples the biopsy specimens in a different order than assumed here, then the Research Coordinator must be very careful to ensure that the specimens get placed in the appropriate vials.

10.4. RELEVANT BIOPSY FORMS

10.4.1. Slide Release Form

The local pathologists at the Clinical Centers will not release the microscope slides from the Home Institution Biopsy (Sample 1) to the Research Coordinator without a signed "Slide Release Form". A Slide Release Form, when signed by the patient, is the patient's informed consent to having the slides released from the local pathology laboratory. Slide Release Forms are particular to each institution and should therefore be obtained from the local pathology laboratory. The Slide Release Form should then be signed by the patient *at the time of the cystoscopy*.

10.4.2. Biopsy Specimen Tracking Form (TRACK)

The Biopsy Specimen Tracking Form (TRACK) is designed to track the shipment of the Database Biopsy specimens from the Clinical Center to the APL and to provide pertinent biopsy information to the APL pathologist. The Biopsy Specimen Tracking Form (TRACK) should be completed at the time of the procedure. The patient's date of birth and the date of biopsy should be indicated in MM/DD/YY format. The attending urologist and the site and associated pathology of each of the two Database Biopsies (Samples 2 and 3) should also be indicated. Note that although additional options are provided for the site of Sample 3, it should be from the area of the trigone.

The Research Coordinator should print and sign her/his name. The information below the dotted line should **not** be completed by the Research Coordinator; the APL will complete this section upon receipt of the specimens. A copy of the TRACK form should **not** be sent to the DCC.

10.4.3. Biopsy Slide Tracking Form (SLTR)

The Biopsy Slide Tracking Form (SLTR) is designed to track the shipment of the Home Institution Biopsy microscope slides from the Clinical Center to the APL and to provide pertinent biopsy information to the APL pathologist. The Biopsy Slide Tracking Form (SLTR) should be completed at the time of the procedure. The patient's date of birth and the date of the biopsy should be indicated in MM/DD/YY format. The attending urologist and the site and associated pathology of the home institution biopsy (Sample 1) should also be indicated.

The Research Coordinator should print and sign her/his name, and set the tracking form aside until the microscope slides are ready to be picked up from the local pathology lab. When the Research Coordinator picks up the slides (between 6 and 10 slides) from the local lab, she/he should record the number of slides sent to the APL on the Tracking Form. The information below the dotted line should **not** be completed by the Research Coordinator; the APL will complete this section upon receipt of the microscope slides. A copy of the SLTR form should **not** be sent to the DCC.

10.4.4. **Cystoscopy Form (CYST)**

The Cystoscopy Form (CYST) should be completed at the time of the procedure by the attending physician. Question 17 pertains to the Home Institution Biopsy, Sample 1, and Questions 18 and 19 pertain to the Database Biopsies, Samples 2 and 3, respectively. For each of these questions, the pathology associated with the sampled specimen should be indicated. On the bladder map provided on page 4 of 4 of this form, the location of each of the sampled specimens should be indicated.

A copy of the Cystoscopy (CYST) form should be placed as a record in the patient's Study Book. The original form should be sent to the DCC in the Research Coordinator's weekly data mailing.

10.5. LABELLING

10.5.1. **Vial Labels**

Labels, measuring 50mm x 32mm, are provided for the vials for the two Database Biopsies (Samples 2 and 3). The following is a sample vial label:

Patient I.D. # _____

Date of Birth m____/d____/y_____

Biopsy Date m____/d____/y_____

Site of Biopsy _____

The vial labels should be completed before adhering them to their respective vials. The patient's study ID number, the patient's birth date (in MM/DD/YY format), the date of biopsy (in MM/DD/YY format), and the biopsy site in the bladder should be indicated. It is very important to write very carefully and clearly in the small space provided. For the biopsy site, use the abbreviations provided on page 4 of 4 of the Cystoscopy form (CYST) for the bladder map.

10.5.2. **Microscope Slide Labels**

Labels, measuring 25mm x 18mm, are provided for the microscope slides obtained from the Home Institution Biopsy (Sample 1). The following is a sample slide label:

I.D. #_____
Birth m____/d____/y____
Biopsy m____/d____/y____
Site _____
APL #_____

The labels should be completed before adhering them to the slides. When the RC obtains the slides from the pathologist, one completed slide label should be affixed to each microscope slide. To preserve the confidentiality of the database patients, the labels should be placed directly over any identifiers used by the local pathology laboratory. The patient's study ID number, the patient's birth date (in MM/DD/YY format), the date of biopsy (in MM/DD/YY format), and the biopsy site in the bladder should be indicated. It is very important to write carefully and clearly in the small space provided. For the biopsy site, use the abbreviations provided on page 4 of 4 of the Cystoscopy form (CYST) for the bladder map.

The space provided for the APL # should not be completed; it will be completed by the APL upon receipt of the slides.

10.6 PACKAGING AND SHIPPING

10.6.1 **Packaging and Shipping Database Biopsies (Samples 2, 3)**

Samples 2 and 3 should be tightly capped and placed into the styrofoam mailer. The mailer should be sealed with the red tape provided and put into the pre-addressed Federal Express envelope along with the completed Biopsy Specimen Tracking Form (TRACK). The package should then be mailed *immediately* to the APL for overnight delivery. The APL will be open 6 days a week, Monday through Saturday, to receive the specimens. **However, if a Friday biopsy is planned, please notify the APL by telephone before 4:00 pm Friday Eastern Standard Time to expect a Saturday delivery. If a Friday biopsy is cancelled, notify the APL that the Saturday delivery will not be made.**

10.6.2. **Packaging and Shipping Home Institution Biopsy (Sample 1) Microscope Slides**

The labelled slides and the Biopsy Slide Tracking Form (SLTR) should be placed in the slide mailer provided. The slide mailer should be mailed via U.S. mail to the APL at the following address:

Dr. John Tomaszewski
Surgical Pathology
6 Founders Pavilion
Hospital of the University of Pennsylvania
34th and Spruce Streets
Philadelphia, PA 19104

11.1. PATIENT RECRUITMENT REQUIREMENTS

The Interstitial Cystitis Data Base Study is a multi-center, observational, longitudinal study. The patient population that will be recruited, and subsequently followed, by each of the Clinical Centers will consist of two distinct baseline subgroups:

i) the *mild symptom subgroup*, a group of patients with mild IC symptoms who at presentation have a total score of 3 or less on the Frequency, Urgency and Pain Scale (see Appendix C);

ii) the *severe symptom subgroup*, a group of patients whose IC symptoms are severe enough to result in a total score of at least 4 on the Frequency, Urgency, and Pain Scale.

If clinically indicated, patients in each of these subgroups will undergo, at baseline, a cystoscopy, hydrodistention and biopsy under full anesthesia (CHB). Patients whose symptoms do not warrant a CHB must be willing to undergo these procedures when clinically indicated during the course of the study. Thus, all patients enrolled in the IC Data Base must meet all the inclusion/exclusion criteria and be willing to undergo a CHB when clinically indicated.

During the course of the 4-year accrual period, a minimum of 1,365 patients will be enrolled into the study, such that

i) at most 530 patients will comprise the mild symptom subgroup at baseline entry; and

ii) at least 835 patients will comprise the severe symptom subgroup at baseline entry.

Each of 5 Clinical Centers will have the same target accrual of patients for the two baseline subgroups, varying by year of entry to compensate for anticipated attrition. In particular, each Clinical Center will enroll at least 74 patients (29 mild, 45 severe) in year 01, 70 patients (27 mild, 43 severe) in year 02, 67 patients (26 mild, 41 severe) in year 03, and 62 patients (24 mild, 38 severe) in year 04 (see Table below).

Annual Accrual Requirements for each Clinical Center (6% annual attrition)			
Year	Mild symptom subgroup (Total score # 3)	Severe symptom subgroup (Total score > 3)	Annual Total
01	29	45	74
02	27	43	70
03	26	41	67
04	24	38	62
Subgroup Total	106	167	273

Total score = Total score on the Frequency, Urgency, and Pain scale (Appendix C)

The annual attrition rate was estimated at 6%, because it is believed that the IC patient population is a group extremely motivated to aid in the collection of information about the disease, for which little is known. However, annual attrition rates could be much higher, as IC patients either get relief from their symptoms and lose interest, or worsen and search elsewhere for a workable treatment for their chronic condition. At the end of year 01, the attrition rate for each Clinical Center will be estimated, and the target accrual adjusted accordingly. The increased sample size requirements for a 20% annual attrition rate are indicated in the table below.

Annual Accrual Requirements for each Clinical Center
(20% annual attrition)

Year	Mild symptom subgroup	Severe symptom subgroup	Annual Total
01	39	61	100
02	34	54	88
03	29	46	75
04	24	38	62
Subgroup Total	126	199	325

11.2. PATIENT RETENTION

The success of the ICDB Study depends heavily on the ability of the Clinical Centers to retain enrolled patients throughout their follow-up phase. The onus of keeping patients interested in the study therefore resides in the hands of the Clinical Center staff. Potential ways of accomplishing this are:

- emphasizing advantage of having a dedicated RC available to answer phone calls;
- emphasizing advantage of receiving education about IC during participation in study and of having first access to any clinical trials;
- making a dedicated phone line and answering machine available to study patients;
- offering reduced fees to study patients; and,
- free Interstitial Cystitis Association (ICA) membership.

See Section 5.1.2: *Patient Incentives.*

11.3. STAFFING REQUIREMENTS

Each Clinical Center is responsible for staffing at least one Research Coordinator to coordinate all activities at the clinical center level required to achieve the goals of the ICDB Study. The Research Coordinators play an integral part in keeping the ICDB Study on course, and therefore every effort should be made to retain these individuals throughout the course of the study. If a Research Coordinator leaves the study, however, the Clinical Center investigator is responsible for hiring a replacement immediately to ensure overlap among the relevant individuals. The departing Research Coordinator is responsible for training the replacement on issues concerning the ICDB Study specific to the Clinical Center. Then, the Research Coordinator must be sent for 1-2 days to the Clinical Center at the University of Pennsylvania to be trained by its Research Coordinator and the Data Coordinating Center staff on general issues concerning the ICDB Study.

12.1 QUALITY CONTROL

12.1.1 Clinical Center Site Visits

The ICDB is a cooperative agreement study in which all investigators and the NIDDK have a shared responsibility for the overall quantity and quality of the data collection. The primary purpose of the ICDB Clinical Center (CC) site visits are to ensure to the Steering Committee, the ICDB External Advisory Committee, and the NIDDK the accuracy and quality of data which has been submitted for the Interstitial Cystitis Data Base and adherence of data collection to established protocol procedures.

The following issues will be assessed at each site visit:

i) CC organizational and administrative structure.
ii) Adequacy of support systems and environment.
iii) Quality control systems established within the CC.
iv) Data collection process.
v) Adherence to the protocol.

The site visit team will minimally consist of the Principal Investigator of the DCC, or his designee, and one Research Coordinator from a different CC (to be selected by the NIH Project Officer and/or the Steering Committee Chair). The CC will have at least four weeks written advance notice and the major determinant of scheduling will be the availability of the CC's Principal Investigator and Research Coordinator. The absence of other clinical personnel will not necessarily preclude a site visit. A detailed letter describing the requirements and expectations of the site visit team will be sent to the Principal Investigator, with a copy to the Research Coordinator, at least 3 weeks before the scheduled visit. An example of this letter is included in Appendix G. A Site Visit Report, following a general, standardized outline, will be submitted to the NIH Project Officer, the Chair of the Steering Committee, and the Principal Investigator, with copies to the site visit team and the CC Research Coordinator, within two weeks of the completion of the visit.

12.1.1.1 Initiation & Notification of Site Visits

Clinical Centers will be site visited for quality assurance purposes at least once a year, pending NIH funding, or as determined by the NIH Project Officer. The order of the site visits will be 1) San Diego, 2) Oklahoma, 3) Madison/Chicago, 4) Detroit, and 5) Philadelphia, unless revised by the NIH Project Office. The DCC Project Manager will work with the NIH Project Office to coordinate the visit dates. The DCC will be responsible for notifying the Principal Investigator and Research Coordinator at the selected CC, as well as members of the site visit team, of the scheduled site visit dates with at least one month's written notice.

12.1.1.2 Site Visit Activities

Each site visit will last 1-2 days. The site visit team will come prepared to evaluate the CC's day-to-day activities with respect to patient contact (including the CC's patient environment), patient scheduling, data collection, and organization and completeness of the patient's study records. Prior to evaluation of the patient study books, the site visit team will meet with the Principal Investigator to provide an overview of the visit and discuss patient confidentiality and privacy issues. The site visit will then proceed to include review of selected patient records, comparing key items with the source documents (i.e., patient's medical records), patient scheduling procedures, and organization and environment of the CC. Patient confidentiality will be maintained at all stages of the review process. In the event that conflicts exist between the source documents and the study documents, the reviewer will make a notation to this effect on the study document and initial and date the notation. A second reviewer will then be required to independently review the source and study documents to verify that the conflict does exist and also initial and date the notation on the study document. CONFIDENTIAL PATIENT RECORDS WILL **NOT** BE COPIED. The visiting Research Coordinator may also meet with the CC's Research Coordinator to discuss solutions/improvements of any data collection and/or patient record organizational problems.

The site visit team will meet with the CC's Principal Investigator at the end of the site visit to provide verbal feedback. All major issues will be discussed at that time. NOTE: The Site Visit Report should not include issues which have not been verbally discussed with the CC Principal Investigator prior to departure. This allows the CC Principal Investigator an opportunity to clarify any issues.

At the close of the site visit, the DCC Principal Investigator or his designee will complete the Site Visit Close-Out Form. This form should be signed by the DCC Principal Investigator or his designee and either the CC's Principal Investigator or the Research Coordinator. A copy of this form should be made for the CC and the original returned to the DCC for filing.

12.1.1.3 Site Visit Report

The DCC Principal Investigator or his designee will be responsible for writing and submitting an official Site Visit Report to the NIH Project Officer, the Steering Committee Chair, and the CC's Principal Investigator and Research Coordinator within two weeks of the completed site visit. These reports will be marked CONFIDENTIAL and released only to those listed in 12.1.1.

The Site Visit Report should include the following sections:

- A general overview of the purpose of the site visit.
- Assessment of protocol adherence.
- Data collection process.
- Clinic organization and environment.
- Recommendations, including a time frame for their implementation.

12.1.1.4 Grievance Process

If the CC Principal Investigator does not agree with the recommendations outlined in the Site Visit Report, a formal letter of grievance should be sent to the NIH Project Officer, with copies to the Chair of the Steering Committee and the DCC Principal Investigator, within one month of the submission of the Site Visit Report. The grievance will be reviewed by the NIH Project Officer and the Chair of the Steering Committee. The NIH Project Officer should provide a formal response to the grievance within 2 weeks, with copies to the Chair of the Steering Committee and the DCC Principal Investigator.

12.1.1.5 Follow-up Visit

A follow-up site visit may be performed in an appropriate time frame that allows for implementation of the Site Visit Report recommendations. The scope of the visit will include the activities listed in 12.1.1.2 as well as verification of implementation of the recommendations resulting from the initial site visit. The follow-up site visit should be completed within three months of the submission of the initial report. Requests for an exemption from the three month time limit should be made to the NIDDK Project Officer by the Principal Investigator.

12.1.2 Data Coordinating Center Site Visits

12.1.2.1 Internal Quality Control Procedures

(Under development)

12.1.2.2 External Site Visit of DCC

The ICDB is a cooperative agreement study in which all investigators and the NIDDK have a shared responsibility for the overall quantity and quality of the data collection. The primary purpose of the ICDB Data Coordinating Center (DCC) site visit is to ensure to the Steering Committee, the ICDB External Advisory Committee, and the NIDDK the accuracy and quality of data once it has been submitted and processed by the DCC.

The following areas will be assessed at each site visit:

i) Infrastructure and organization.
ii) Project management.
iii) Data management, including quality assurance (QA) monitoring.
iv) Data base management systems.
v) Statistical analysis plans.
vi) Administration and budget issues.

The NIH Project Officer will be responsible for assembling the site visit team. The DCC will have at least one month written advance notice and the major determinant of scheduling will be the availability of the DCC's Principal Investigator. The absence of other DCC personnel will not necessarily preclude a site visit. A detailed letter describing the requirements and expectations of the site visit team will be sent to the Principal Investigator, with a copy to the Project Manager, at least 3 weeks before the scheduled visit. A Site Visit Report will be submitted to the Chair of the Steering Committee and the Principal Investigator, with copies to the site visit team and the DCC Project Manager, within two weeks of the completion of the visit.

12.1.2.2.1 Initiation & Notification of Site Visits

The Data Coordinating Center will be site visited for quality assurance purposes at least once a year, pending NIH funding, or as determined by the NIH Project Officer. The NIH Project Office will work with the DCC's Project Manager to coordinate the visit dates. The NIH Project Officer will be responsible for notifying the Principal Investigator and the Project Manager, as well as members of the site visit team, of the scheduled site visit dates with at least one month's written notice.

12.1.2.2.2 Site Visit Activities

(Description of activities under development by NIDDK.)

The site visit team will meet with the DCC's Principal Investigator at the end the visit to provide verbal feedback. All major issues will be discussed at that time. NOTE: The Site Visit Report

should not include issues which have not been verbally discussed with the DCC Principal Investigator prior to departure. This allows the DCC Principal Investigator an opportunity to clarify the issues.

At the close of the site visit, the NIH Project Officer or his designee will complete the Site Visit Close-Out Form. This form should be signed by the NIH Project Officer or his designee and either the DCC's Principal Investigator or Project Manager. A copy of this form should be made for the DCC and the original returned to the NIH Project Office for filing.

12.1.2.2.3 Site Visit Report

The NIH Project Officer or his designee will be responsible for writing and submitting an official Site Visit Report to the Steering Committee Chair and the DCC's Principal Investigator and Project Manager within two weeks of the completed site visit. These reports will be marked CONFIDENTIAL and released only to those listed in 12.1.2.2.

This Site Visit Report should include the following sections:

- A general overview of the purpose of the site visit.
- Assessment of infrastructure, organization, and project management.
- Evaluation of data management and QA procedures.
- Evaluation of computing systems and network support, and backup and security procedures.
- Determination of adequacy of staff and budget.
- Recommendations, including a time frame for their implementation.

12.1.2.2.4 Grievance Process

If the DCC Principal Investigator does not agree with the recommendations outlined in the Site Visit Report, a formal letter of grievance should be sent to the NIH Project Officer, with copies to the Chair of the Steering Committee, within one month of the submission of the Site Visit Report. The grievance will be reviewed by the NIH Project Officer and the Chair of the Steering Committee. The NIH Project Officer should provide a formal response to the grievance within 2 weeks, with copies to the Chair of the Steering Committee.

12.1.2.2.5 Follow-up Visit

A follow-up site visit may be performed in an appropriate time frame that allows for implementation of the Site Visit Report recommendations. The scope of the visit will include the activities listed in 12.1.2.2.2 as well as verification of implementation of the recommendations resulting from the initial site visit. The follow-up site visit should be completed within three months of the submission of the initial report. Requests for an exemption from the three month time limit should be made to the NIDDK Project Officer by the Principal Investigator.

12.2 MAINTENANCE & DISPOSITION OF STUDY DOCUMENTS, DATA, AND MATERIALS

This section describes the procedures which will be employed for maintenance and disposition of study documents, data forms, tapes, results of analysis, and materials during and at the conclusion of the ICDB Study.

12.2.1 Internal Distribution of Study Documents

The DCC is responsible for maintaining a record of all documents, reports and meeting minutes pertaining to the ICDB Study. During the conduct of the ICDB Study, the DCC will be responsible for the distribution of the Protocol, Manual of Operations, and study reports to ICDB participants. At the end of the study, these documents will be archived by the DCC and forwarded to the National Technical Information Service (NTIS).

Minutes of all appropriate committee meetings, including minutes of the External Advisory Committee meetings, will be maintained in the files of the DCC. At the conclusion of the study, these minutes will be archived and forwarded to the NIDDK.

12.2.2 External Distribution of Study Documents

The NIDDK will be responsible for the distribution of study documents and manuscripts requested by individuals not associated with the ICDB Study. See Section 4.2.8: *Acknowledgement of Support and Reprint Addresses*.

12.2.3 Data Forms

The DCC will maintain a complete set of all study forms used in the collection of data. At the end of the study, these forms, without personal identifiers, will be archived and forwarded to the NIDDK. Clinical centers will maintain a file on each patient which will become a part of the individual's medical record at the conclusion of the ICDB Study.

12.2.4 Data Tapes and Analysis of Results

The DCC will prepare a computer tape of study data, results, and analyses at the conclusion of the study. This tape will be accompanied by appropriate documentation. One copy will be forwarded

to NIDDK and one to the NTIS, U.S. Department of Commerce, Springfield, Virginia so that the information may be generally available, at a small charge, to the scientific community.

The DCC will prepare a data tape of analysis pertaining to each major study paper. At the end of the Data and Analysis Phase (Phase 3), all of these tapes with appropriate accompanying documentation will also be submitted to NIDDK and NTIS.

The DCC will provide documentation of all formulas and statistical analyses used in the study or referred to in the study documents. This information will also be made available to NIDDK and NTIS.

12.2.5 Laboratory Specimens and Materials

All after thought specimens collected by the clinical centers will be kept for long-term storage until the end of the ICDB Study. At that time, the Steering Committee will decide as to the disposition of these specimens. All specimens and materials not claimed or undesignated by the Steering Committee will be destroyed.

12.2 DCC QUALITY ASSURANCE PROCEDURES

The Data Coordinating Center has implemented an extensive series of procedures in order to assure data quality for the ICDB Study. These procedures include: database management system that detects and prohibits entry of obvious data errors; computerized validation system that identifies missing values, out-of-range values, and inconsistent data; monitoring reports that detect protocol violations; use of protocol adherence aids, such as visit schedules and visit checklists; and site visits of the clinical centers in which patient files are compared to source documentation.

12.2.1. Database Monitoring Tools

12.2.1.1 "Up-front" Error Checking on Important Data Fields

The database management system prohibits data entry of:

- invalid patient IDs (i.e. 620001; '62' is not a valid hospital ID)
- invalid form codes (i.e. "PRUG" instead of "PURG")
- invalid visit types (i.e. can only enter 0,1,3,6,.....,48)
- invalid visit dates (i.e. month = 13)

12.2.1.2 Data Entry and Verification

Forms are entered by two different data entry clerks and conflicts between the two entries are resolved by a third person. This helps to ensure the accurate transfer of the data from the paper forms to the database.

12.2.1.3 Data Validation

The system checks for out-of-range values, missing values, incorrectly followed skip patterns, and inconsistent responses between forms during each visit, as well as from visit to visit.

Once these problem responses are identified, a query is generated by the data manager and sent to the appropriate research coordinator. A computer record is generated to identify that a query has been sent. The data manager reviews the list of validation errors on a regular basis.

12.2.1.4 Permissions on the Database

The database was created so that there are restrictions on access to the data. Within the DCC, there are different levels of access to the database. The data entry clerks have the ability to complete logging and data entry, the data managers can make changes and edits, and other DCC personnel only have the ability to browse the database.

12.2.1.5 Filing/Entry System

As the forms arrive at the DCC, they go through a series of processes involving manual reviews, logging, date stamping, entry, and filing.

The process is as follows:

1. Forms are date stamped with the date that they arrive at the DCC.

2. Forms are manually reviewed for serious problems that would prohibit entry.

3. Forms are logged so that a computer record of the forms' receipt exists. Fields that are entered during the logging process are patient ID, date received, visit date, visit type, and form code.

4. Data manager codes fields that are not precoded on the forms such as location of pain, location of biopsy, and other unique responses.

5. Each form is entered twice by two different data entry clerks.

6. The process of verification occurs next, which means a third person examines an conflicts that occur between the first and second entry. When possible, conflicts are resolved at this stage.

7. The validation process occurs next, which means all forms that are entered go through a series of error checks. These error checks include missing values, out of range values, and missed skip patterns. The data manager sends queries when required.

8. During steps 1-7 above, the paper forms move through a series of file folders, to indicate which stage of the entry system each form is at. After step 7, the forms are permanently filed according to hospital and patient ID.

12.2.2. ICDB Data Management Reports

Data Management has designed a series of reports for the purpose of accurately describing patient accrual, protocol violations, query rates, missing data, and other issues related to data quality. The following sections describe each of these reports.

12.2.2.1 Accrual Reports

- A series of graphs which illustrate the accrual of patients in the ICDB study. The graphs include an overall graph across all centers, and individual graphs for each center. The graph plots the net accrual of patients by time. It also plots the recruitment goal by time.

- A series of tables that illustrate the current accrual and retention patterns of the hospitals. These tables include the following: changes in complete patient accrual status; number and percent of patients completing each follow-up visit; number of patients withdrawn at each follow-up visit; race distribution across hospitals; age distribution across hospitals; sex distribution across hospitals; total of frequency, urgency and pain (t_score) distribution across hospitals; and biopsy study history.

12.2.2.2 Quality Reports

12.2.2.2.1 Biopsy

- A report which identifies biopsy protocol violations.

The biopsy protocol violations include:

- patient has at least one Hunner's patch, but at least one of the two pathologies of biopsies #1 and #2 does not come from the Hunner's patch

- patient does not have a Hunner's patch, but does have at least one glomerulation, and at least one of the two pathologies of biopsies #1 and #2 does not come from the glomerulation

- patient does not have a Hunner's patch or a glomerulation, and the locations of biopsies #1 and #2 are not the posterior wall

- biopsy #3 is not taken from the trigone

12.2.2.2.2 Screening

C A report which identifies protocol violations regarding the order of completion of forms and procedures during the screening phase.

C A report that identifies protocol violations regarding the maximum length of completion of the screening phase.

12.2.2.2.3 Queries

C A report containing the frequency of forms and fields queried for each hospital. These query rates are generated for all forms as well as for groups of similar forms.

12.2.2.2.4 Missing Data

C A report containing the frequency of missing forms and the average number of missing forms per visit completed. A second table includes the number of missing forms for groups of similar forms, listed by hospital.

C A report containing the frequency of missing values and the average number of missing values per visit completed for each hospital. A second table includes the number of missing values for groups of similar forms, listed by hospital.

C A report containing the frequency of missed visits, the number of visits that should have been completed, and the percent of visits missed for each hospital. These reports are also generated by type of visit contact: 1-month and telephone contacts and brief and extensive clinic visits.

12.2.2.2.5 Timeliness

- A report containing the mean arrival times of forms from the clinic to the DCC. The report generates these values in two tables: screening forms versus follow-up forms and track versus sltr forms.

- A report containing the number of follow-up contacts that fall outside of the visit window for each hospital. Three tables are created: one containing all follow-up visits, another which includes only 1-month follow-up visits and telephone contacts, and a third which contains only brief and extensive clinic visits.

12.2.2.2.6 Voiding Log

- A report that identifies violations in voiding logs of all patients that have completed screening. Violations include: completed out of the time window, not including exactly one weekend day, not completed on consecutive days, missing days, completed after a cystoscopy, and completed less than seven days after a urodynamic evaluation.

12.2.2.2.7 Site Visits

- A report which generates a listing of all forms that have been received (including visit type, visit date, form code, and date received) for a given subject, hospital, or center.

- A report which lists outstanding queries by hospital.

- A report which lists basic demographic characteristics of patients by hospital.

12.2.2.2.8 Additional Data Management Monitoring

- A report of incomplete baseline screenings and incomplete follow-up visits.

- A report of follow-up visits that were completed out of order.

- A report of visits completed on Saturdays, Sundays, and holidays.

- Several other reports to guarantee that data packets move efficiently

and correctly through the data processing queue once they are received by the DCC.

These reports perform the following functions:

- Check for timeliness of data processing by identifying records which have not completed data processing, but for which no processing has been done in the past ten days.

- Check for forms that are indicated as missing but for which some other processing (such as entry, verification, or validation) has been completed.

- Check for logical errors between data fields.

Examples of logical errors are:

- if the date of entry came before the visit date

- discrepancies between contact type (screen, 1 month, phone, and clinic) and type of form

- Check for missing values on any important data fields such as patient ID, visit date, or type of form.

- Check for problems with data entry such as: missing entry dates and records where only one of the two necessary data entries was completed.

- Check for out of range data values such as: patient ID, dates that occur before start of study, dates that occur after the current date, and invalid form names.

- Check for problems with verification (process which compares entry#1 to entry#2 and looks for conflicts).

12.2.3 Query Forms and Memos (see Chapter 8 for further details)

12.2.3.1 Request for Missing Data (QMD) Form

12.2.3.2 Data Clarification (QDC) Form

12.2.3.3 Clinic Initiated Data Corrections (CIDC) Form

12.2.3.4 APL Missing Tracking Forms Memo

12.2.4 Protocol Adherence Aids (see Chapter 8 for further details)

12.2.4.1 Patient Visit Schedules

12.2.4.2 Visit Reminders

12.2.4.3 Patient Status Form

12.2.4.4 Visit Checklists

12.2.5 Manual Error Detection

12.2.5.1 All forms received by the DCC are subjected to an extensive manual review process. The purpose of the review process is to identify missing values and inconsistencies on key fields that would prohibit entry into the database.

Examples of the items that are reviewed:

- Patient ID is completed on every data form and is consistent across all data forms for a given visit.

- Visit date is completed on every data form and is logical across all data forms for a given visit.

- Lab reports must contain the patient ID and the date of collection.

12.2.5.2 Reviewing returned query and data correction forms for logic and consistency.

12.2.5.3 Periodic data file reviews

Manual check for correct order of forms, order of visits, and consistency within and across forms.

12.2.5.4 Data Audits

Periodic random data reviews are conducted in order to evaluate the quality and accuracy of the data processing system. Further, on a random sample of the data, comparisons are made between records stored in the database and paper files of the patient records. At the completion of the data audit, any discrepancies that were found during the review are recorded and summarized in a report, and resolved when necessary. If the error rate exceeds a predetermined limit, a more extensive data audit is required.

12.2.5.5 Site Visits

Comparisons are made between the DCC's patient files and the site's patient files. Also, at the site, reviews are made between the patient's chart and the data on the forms, verifying that there are no obvious contradictions. Checks are made for consistency, organization, and a logical flow of the data.

13. Core APL Responsibilities — September 1, 1994

(To be developed)

[1] Hanno, P.M., Staskin, D.R., Krane, R.J., and A.J.Wein, Eds: *Interstitial Cystitis*. New York, Springer-Verlag, 1990.

[2] Meinert, C.L. *Clinical Trials: Design, Conduct, and Analysis*. New York, Oxford University Press, 1986.

[3] Pocock, S. J. *Clinical Trials: A Practical Approach.* New York, John Wiley & Sons, 1983.

[4] Friedman, L. M., Furburg, C. D., and DeMets, D. L. *Fundamentals of Clinical Trials.* Boston, Wright, 1981.

[5] Westat, Inc. *General Interviewing Techniques for In-Person and Telephone Interviewers.* Rockville, Westat Inc., 1991.

Appendix Listing

Appendix	Chapter Reference	Description
A	3	Subcommittees Listing
B	4	Statement of Understanding Form
C	5, 11	Scoring for Inclusion Criteria
D	8	Forms Schedule
E	8	Standard Probes
F	12	Initial Site Visit Notification Letter

Appendix A

ICDB Working SubCommittees

Active Committees

Publications, Presentations and Ancillary Studies
- LeRoy M. Nyberg, Ph.D., M.D., co-chair
- J. Richard Landis, Ph.D., co-chair
- Alan J. Wein, M.D.
- Aaron Kirkemo, M.D.
- C. Lowell Parsons, M.D.
- Michelle Fedon, R.N.

Access to ICDB Study Data and Patient Specimens
- J. Richard Landis, Ph.D., chair
- Aaron Kirkemo, M.D. (added 5/12/95)
- Gregory Broderick (removed 5/12/95)
- Robert Hurst, Ph.D.
- Lowell Parsons, M.D.
- John Tomaszweski, M.D.
- Lee Nyberg, Ph.D., M.D.

Patient Classification Working Group
- Philip Hanno, M.D., chair
- Edward Messing, M.D.
- C. Lowell Parsons, M.D.
- Deborah Erickson, M.D.
- Michael O'Leary, M.D., (DCC consultant)
- Camille Jones, M.D., M.P.H. (NIDDK staff)
- J. Richard Landis, Ph.D. and DCC staff
- Michelle Fedon, R.N.

Patient Outcomes Working Group
- Ananias Diokno, M.D. (chairman)
- Denise Nigro, M.D.
- Michael O'Leary, M.D., (DCC Consultant)
- John Kusek, Ph.D.
- J. Richard Landis, Ph.D. and DCC staff
- Mary Williams

Medications/Treatment Working Group
- Aaron Kirkemo, M.D. (chairman)
- Anthony Schaeffer, M.D.
- Leroy Nyberg, Ph.D., M.D.
- J. Richard Landis, Ph.D. and DCC staff
- Diane Pauk, B.S.

Committee Patient/Study Close-Out
J. Richard Landis, Ph.D., chair
John Kusek, Ph.D.
Yvonne Matthews, M.A.
Alan Wein, M.D.

Inactive Committees - Mission Completed

Committee on Data Coordination
Lowell Parsons, M.D., chair
Richard Landis, Ph.D.

Committee on the Use of a Control Group
Phil Hanno, M.D., chair
Lee Nyberg, Ph.D., M.D.
Richard Landis, Ph.D.

Patient Incentives Committee
Anthony Schaeffer, M.D., chair
Richard Landis, Ph.D.
John Kusek, Ph.D.
Marilou Foy, R.N.
Aaron Kirkemo, M.D.

Committee on Psychological Considerations
Kristine Whitmore, M.D., chair
Philip Lanzisera, Ph.D.
Richard Landis, Ph.D.
Debra Slade

ICDB Promotional Pamphlet
J. Richard Landis, Ph.D., chair
Vicki Ratner
Debra Slade
Mary Harris
Mary Nieweglowski

June 14, 1995

Appendix B

INTERSTITIAL CYSTITIS DATA BASE STUDY

Statement of Understanding of Policy Concerning Publications and Presentations

To assure that all professionals involved with the ICDB study know and understand the policies of the ICDB Study regarding publications and presentations, and to preclude the possibilities of misunderstandings after initiation of the Study, each professional member will be given a copy of the chapter of the Manual of Operations detailing these policies and will be asked to sign this form attesting to his/her acceptance of these policies, which are summarized here.

I. Material covered by these policies

All material to be presented orally or submitted for publication or dissemination by individuals associated with the ICDB Study and dealing with any aspect of the ICDB Study must receive prior review and approval by the Publications, Presentations and Ancillary Studies (PP&AS) Committee and the Steering Committee with the following exception:

Material prepared for publicity purposes either nationally or within the recruitment region of an ICDB Clinical Center, or presented orally or as handouts or posters to professional audiences solely for the purposes of informing the profession of the ICDB Study and its objectives, need not be reviewed by the PP&AS Committee. Such material must be limited to a background discussion of the issue of interstitial cystitis disease and a description of the ICDB Study organization, objectives, and entrance criteria, and to results of the study that have previously been presented to a scientific body or published in a scientific journal. It must <u>not</u> include discussion of any previously unpresented and unpublished ICDB Study outcomes or results, and must <u>not</u> itself result in publication of an abstract or other citable professional reference.

II. Assignment of writing committees for publications

The ICDB Study Chair will appoint writing committees to prepare <u>all</u> abstracts and papers for the ICDB Study, and will specify the subject material to be dealt with by each writing committee. All interested individuals will be given a chance to request appointment to the various writing committees, but the final appointments will be by the Study Chair.

III. Authorship

The ICDB policies specifies the authorship for each of the four different classes of publication or abstract (See Manual of Operations, Chapter 4.5 and 4.6 verify that these are correct). These policies are binding and must be followed in all publications derived from the ICDB Study.

IV. Review of Abstracts

All abstracts must be reviewed and approved by members of the PP&AS Committee before being submitted. These abstracts must be delivered to the reviewers at least seven (7) days before the submission deadline to permit time for this review. Abstracts not approved in this fashion will be withdrawn by the ICDB Study.

V. Review of Materials for Presentations

Approval for submission of an abstract does not automatically grant approval of the material ultimately to be presented. This material must also be submitted for review and approval by members of the PP&AS Committee at least seven (7) days prior to the scheduled oral or poster presentation.

VI. Review of Papers

All materials for which there is no explicit deadline, and all full papers that may result in a citable scientific reference, whether or not there is a deadline for submission, must be submitted to the Chair of the PP&AS Committee for formal review by the entire Committee. If there is a deadline for submission of a formal paper, it is the responsibility of the submitter to be certain that it is submitted to the Chair, PP&AS Committee, at least 30 days prior to the deadline, to permit such review.

VII. Certification by ICDB Study Participant

This is to certify that I have read the above statement of policies of the ICDB Study with regard to publications and presentations, understand it, and agree to abide by it in matters of all publications and presentations derived from the ICDB Study.

_____

(Name, *Please print*)

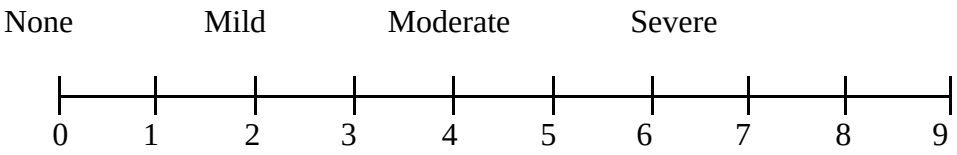
_____ _____

(Signature) (Date)

Appendix C

Summary of Scoring for Inclusion Criteria

Scale



Presence

Frequency

Score	Response
0	<7
*1	7-10
*2	11-14
*3	$15

Urgency

Score	Response
0	0
*1	1,2,3
*2	4,5,6
*3	7,8,9

Pain

Score	Response
0	0
*1	1,2,3
*2	4,5,6
*3	7,8,9

Duration

> 6 months	> 6 months	> 6 months

* Patients with a score of at least 1 on either the Frequency, Urgency, or Pain Scale are considered candidates to undergo the screening process to determine final eligibility.

Appendix D has not been included in this copy of the
ICDB Study Manual Operations.

Please refer to the ICDB Study Codebook for a copy of the
baseline screening forms and associated frequency distributions.

Appendix E

Form Summary

	Form Name	Form Code	Completed by*	Screening	1 Month Contact	Phone Contact	Brief Visit	Extensive Visit
1.	Inclusion Checklist	INCL	T	x				
2.	Deferral Checklist #1	DEF1	T	x				
3.	Deferral Checklist #2	DEF2	C	x				
4.	Exclusion Checklist #1	EXCL1	T	x				
5.	Exclusion Checklist #2	EXCL2	C	x				
6.	Exclusion Checklist #3	EXCL3	C	x				
7.	Voiding Log	VOID	P	x	x	x	x	x
8.	Dietary Habits	DIET	P	x			x	x
9.	Background Information	BACK	P	x				
10.	Background Information	BACKF	P					x
11.	Patient Symptoms	SYMPTS	P	x			x	x
12.	Patient Symptoms	SYMPH	T		x	x		
13.	Symptom History	SYMHX	T	x				
14.	Quality of Life	QUL	P	x			x	x
15.	Patient Medical History	MEDHX	T	x				x
16.	Pregnancy History	PREG	T	x				x
17.	Prior Diagnostic Tests and Treatments	PRIOR	T	x				
18.	Concomitant Medications	CMED	T	x	x	x	x	x
19.	Physical Exam	PHS	C	x			x#	x#
20.	Urinalysis	URN	C	x			x	x
21.	Family Medical History	FHX	T	x				
22.	Urodynamic Evaluation	UROD	C	x				

	Form Name	Form Code	Completed by*	Screening	1 Month Contact	Phone Contact	Brief Visit	Extensive Visit
23.	Cystoscopy	CYST	C	x#	x#	x#	x#	x#
24.	Hematology	HEM	C	x				
25.	Physician's Evaluation and Treatment Plan	PHYTRT	C	x	x	x	x	x
26.	Screening Sign-Off	SCR	C	x				
27.	Medical Events and Patient's Treatment Evaluation	MED	T		x	x	x	x
28.	Pain and Urgency Scale	PURG	P	x	x	x	x	x

* Patient=Patient, T=Administered to Patient by Research Coordinator, C=Clinical Center Staff
\# If indicated

June 14, 1995

Appendix F

List of Standard Probes

General Probes

1. Repeat question
2. Repeat part of question
3. Which would be closer (*repeat answer categories*)
4. So, would you say that it is (*repeat answer categories*)
5. Could you be more specific?
6. Could you say more about that?
7. Are there any other reasons?
8. What else?

Special Probes for 'Don't Know' Responses

1. Take a minute to think about it: (*repeat question, if appropriate*)
2. Your best estimate would be fine ...

Neutral Prefaces to Probes

1. Yes, but ...
2. Overall ...
3. But generally speaking ...
4. But, in general ...
5. No one knows for sure, but ...
6. We're just interested in your opinion ...

Data Coordinating Center
Center for Biostatistics & Epidemiology
Penn State University/M.S. Hershey Medical Center
Hershey, PA 17033

Voice: (717) 531-7178
Fax: (717) 531-5779

Appendix G

June 14, 1995

Principal Investigator, M.D.
ICDB Study Center
City, State ZIP

Dear PI:

In preparation for our ICDB Site Visit to ICDB Study Center, I would like to clarify some of our expectations and recommend a flexible timetable and agenda to accommodate our overall goals. I would like you to reserve a room with adequate table space so that we can conduct a review of selected study books and patient charts. For that purpose, please have each study book and supporting patient chart materials available, ordered by ICDB patient number sequence. Marilou Foy and I plan to arrive at your office area by 9:00 a.m. on Monday, August 1, 1994, and propose the following agenda:

Day 1, Date

9:00 a.m.	Meet PI & RC and discuss overall plans
9:15 a.m.	Ms. Foy & Dr. Landis review selected patient records in designated room (PI & RC need not be available)
noon	Lunch
1:00 p.m.	RC "on call" as needed to clarify questions
3:00 p.m.	PI and RC available for summary meeting

Day 2, Date

9:00 a.m.	Ms. Foy & RC meet to discuss findings in more detail, and identify areas for improvement in data collection procedures (Ms. Foy available for the entire day to work together on methods and procedures)

I look forward to a productive site visit, and want to assure you that we plan to make this entire process as positive and supportive as we possibly can. In that sense, we are all on the same team, promoting high quality data collection procedures for this important national research program.

With kind regards,

Sincerely yours,

J. Richard Landis, Ph.D.
Principal Investigator
Data Coordinating Center

JRL:skk
c.c. Dr. Leroy Nyberg, M.D., Ph.D.
Dr. Alan J. Wein, M.D.

/data/icdb/projmgt/document/mop/appendix/visitlet.wp6