

Chapter 1: General Study Information

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1.1 WELCOME

Welcome to Predicting Response to Standardized Pediatric Colitis Therapy (PROTECT); a multicenter open-label study designed to evaluate the efficacy and safety of standardized initial therapy for the treatment of children and adolescents newly diagnosed with ulcerative colitis. The study is funded by the National Institute of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health.

PROTECT is based at Connecticut Children's Medical Center where the Clinical Coordinating Center (CCC) is located. They, along with the University of North Carolina's Collaborative Studies Coordinating Center which functions as the Statistical and Data Coordinating Center (DCC), will manage the study. We look forward to working with you on this important study.

1.2 ORIENTATION TO CONTENTS

This Study Reference Manual is your resource throughout the course of this project. Before beginning the study, please read through the documents provided in this manual which include:

- The PROTECT Protocol
- The PROTECT Manual of Procedures Chapters, describing all study procedures, including participant eligibility determination, study medication and measures of adherence, participant follow-up visit schedules, adverse event collection, and bio-specimen collection and processing.
- Forms and QxQ's provide paper copies of all data collection forms with accompanying question-by-question instructions for completing each form.
- Quick Reference Guides (Appendix A-E) offer helpful tools about the study medication and installing and using the MEMs caps
- Other Reference Guides in the SRM (some laminated worksheets) to offer helpful tools for recruitment, daily dosage recommendations and steroid tapering_

The DCC will provide each site with one copy of the complete Study Reference Manual, the Study Coordinator's copy is considered an official study document; all materials are also available for downloading on the study website <http://www.protectstudy.com>.

Amendments to the Study Reference Manual (MOP)

Please note that study documents may be amended during the course of the study. Current versions will be posted on the PROTECT study website and study coordinators will be notified via email of any modifications via an official Numbered Memo (this process is described in more detail in Chapter 10 Data Management and Administrative Procedures).

1.3 GETTING HELP

1.3.1 For General Study Questions

Please call the toll-free "help-line" at **1-800-472-2595**. Your call will be triaged to the appropriate person to help answer your questions. If someone is not available to answer your

call, please leave a voicemail and a DCC staff member will respond to your call within 24 hours. Typical questions for the DCC include:

- Study procedures
- Form completion questions
- Data entry problems
- Label Supplies or resupply
- Reporting protocol violations

The Project Medical Officer or the Project Safety Officer will be available to you for help concerning the protocol/treatment and safety issues, respectively. General questions that do not require an immediate response or that do not need telephone communication can be sent to the DCC's "help-line" email at **PROTECT@UNC.EDU**.

1.3.2 Project Medical Officer

Specific areas of responsibility for the Project Medical Officer (PMO) include:

- Address protocol questions
- Address protocol violations
- Assist with determining eligibility
- Provide assistance to mitigate the risk of illness worsening

Clinical questions for the Project Medical Officer **should whenever possible come from the study physician**.

The on-call Project Medical Officer (PMO) can be determined by checking the call schedule on the calendar found on the PROTECT study website.

1.3.3 Project Safety Officer

The Project Safety Officer is an independent physician with responsibility to review significant adverse events (SAE):

- The site clinician's assessment of the relationship of study drug to the event, and the expectedness of the event.
- Review the event narrative for a clear, concise, and complete description of the event for eventual DSMB and NIDDK review.
- Work with the DCC and the clinical site consulting on any FDA event reporting.

If a clinical question arises on SAE reporting it **should come from the study physician** and should be directed to the Project Safety Officer. Contact information for the Project Safety Officer is available on the study website in the **NEED STUDY HELP** box on the research staff home page. .

1.3.3 PROTECT Website

URL: <http://www.protectstudy.com>

The PROTECT study website includes a public page of general information, a participant's page which will include the links needed for the participant/family self-report questionnaires, and the study operations page which contains documents, policies, manuals, data forms, contact information (directory), and other important study information necessary for sites.

Each site's Study Coordinator will be given a site-specific username and password for the protected study operations pages from the DCC; they are responsible to distribute the username and password information to site staff as needed.

Each site's Study Coordinator will also be provided with a site-specific participant/family username and password. Information for study participants regarding the participant page will be included in the Participant Passport (refer to MOP Chapter 4).

1.3.4 Data Management Systems (DMS)

URL: <https://cdart.csc.unc.edu/PROTECT>.

For any questions regarding the PROTECT DMS please call the help-line number **1-800-472-2595** or help-line email PROTECT@UNC.EDU. All web browsers work with our DMS, though Firefox and Chrome are recommended. Study Coordinators will be sent a username and password for the DMS from the DCC.

1.3.5 Clinicaltrials.gov

URL: <http://clinicaltrials.gov/ct2/show/NCT01536535>

The National Institutes of Health (NIH) website provides patients, family members, health care professionals, and members of the public information on clinical trials sponsored primarily by the National Institute of Health and other federal agencies. All sites in the PROTECT study are listed on this website. The website provides the name, telephone number, and e-mail address of the Site Coordinator along with recruitment status (i.e., recruiting or not yet recruiting). As a result, your site may receive e-mails or phone calls inquiring about the PROTECT project. All PROTECT sites are listed on this website.

Please check the website for accuracy and provide the Study Administrator with updates as necessary.

1.4 CLINICAL SITE STUDY ROLES

Site Principal Investigator

The site Principal Investigator (PI) is responsible for the overall implementation of the study. All sites have a PI that abides by good clinical practices at their site. They work collaboratively with other study physicians to recruit patients, consent, perform physical examinations, perform diagnostic studies, obtain biospecimens, and work with study coordinators to ensure timely and accurate completion of case report forms.

Study Physician(s)

This includes the Principal Investigator as well as any other physician designated by the Principal Investigator to see patients. Study physician(s) will be the primary contact person for the Chief Medical Officer.

Study Coordinator

Study Coordinators (SC) are responsible for providing the thread of continuity from participant recruitment, evaluation and treatment through follow-up, and ultimately trial closeout. The SC will schedule patients, oversee the collection, processing, and shipment of blood, stool, and other samples to the appropriate local and Central Laboratories, and be responsible for accurate documentation and collection of the study's data at the clinic and its transfer to the DCC. An in-depth knowledge of all aspects of the protocol and MOP is required. The SC serves as the liaison with PI Committee, the DCC, the CCC, the Central Laboratories and the clinical site, and is the primary contact for the DCC, the CCC and the Research Laboratories.

Data Entry Person(s)

Data for this study will be captured on paper source documents, provided on the Study Website. The data must then be entered into the PROTECT Data Management System (DMS)(web-based electronic data capture system). The data entry person will have the primary responsibility for entering the study data into the Data Management System (DMS) within 5 working days of data collection. DMS specific training will be provided to the person(s) designated for this role. Study Coordinators often fill this role, or take responsibility to supervise and train another staff member.

Site Administrator

This person will be the main contact to discuss administrative issues such as payments and contracts. The Administrator should also be familiar with the research activities of this study. It is preferred that this person not be at the institutional level if they are not familiar with this study. Study Coordinators often fill this role.

1.5 START-UP REQUIREMENTS

Sites must satisfy the following requirements to be activated:

- Regulatory Study Documents
 - Documentation of IRB approval of the most current study protocol and informed consent and human subjects training
 - Completed FDA 1572
 - CV and License of Principal Investigator
 - Conflict of Interest (COI) Form signed by Principal Investigator
- Fully executed contract
- Completed Delegation of Duties log
- Have met Study Training Requirements

Upon completion of the start-up requirements listed above the site will be notified via email that they are activated to begin recruitment upon receipt of study supplies.

1.5.1 Where to send Regulatory Study Documents

If not already completed, refer to MOP Chapter 11 regarding regulatory documents.

1.6 TRAINING REQUIREMENTS

To protect the quality of the study results, data are to be collected by trained personnel only. Before the launch of the study a Central Investigator and Coordinator Training Meeting for Principal Investigators and Study Coordinators will have been conducted and include presentations and examples that will assure good quality assurance of study procedures and data collection, and continued adherence to standards. Each site will be responsible to train any additional staff using materials covered at the central meeting, and stored on the study website. Throughout the study training will continue through monthly PI-coordinator webinars , bi-monthly Study Coordinator trainings, and through clinic monitoring.

1.6.1 New Staff

When a new staff member is added to your site please review the “To-Do” List below.

1. Notify the Study Project Manager and the DCC Project Manager of any changes to your staff using the Delegation of Duties Log and fax to CCC and DCC
 - ✓ All study personnel and contact information must be included on the delegation of Duties Log regardless of role.
 - ✓ Any added study personnel needs to be added to the Log as they join the project.
 - ✓ For sites utilizing a pharmacy to distribute study medication to patients, the pharmacy director/overseer’s name is to be included on the List of Study Personnel for the site.
 - ✓ If the pharmacy has multiple personnel distributing study medication to patients, then a supplemental list must be provided that lists all pharmacy staff that dispense medication to/for PROTECT participants.
 - ✓ For sites utilizing a pathologist who will be completing data forms, the pathologist’s name is to be included on the List of Study Personnel for the site.
 - ✓ An updated copy of this log must be forwarded to CCC and DCC each time someone joins or leaves the study team.
2. Ensure that the new staff member has completed the required Human Subjects Training for your institution.
3. Ensure that the new staff member completes any required study training by completing the Coordinator Training Checklist in the Training section of the PROTECT website. Training can be done by the onsite Coordinator, or the DCC can make arrangements for additional training. The study coordinator should distribute the PROTECT website username and password to new personnel or request new/separate logins from the DCC.

Removal of Staff Member

- ✓ Notify the Project Manager of the change using the Delegation of Duties and fax to CCC and DCC.
- ✓ If someone leaves the study team, a stop date should be provided noting the date of termination. The staff member should not be crossed out or deleted from the signature log.

- ✓ New site usernames and passwords may need to be provided for the study website and/or DMS with employee terminations.

1.7 START-UP STUDY SUPPLIES

Sites will be supplied with all necessary study documents, specimen collection kits and instructions for clinical laboratory specimen collection, and study medication supplies including MEMS caps and necessary software. A summary of all supplies is listed below.

All study supplies should be received within 10 business days of site activation. A copy of the study supply checklist sent upon site activation will list all that is to be expected. Notification of receipt of all study supplies must be made to the DCC. Notification of all medication supplies must be made to the Study Project Manager.

Item	Source	Supplies
<i>Study Medication</i>	<i>Connecticut Children's Medical Center</i>	<i>Start-up Supply</i>
<i>MEMS caps, software, instructions, PROTECT bags, brochures, Passports</i>	<i>Connecticut Children's Medical Center</i>	<i>Start-up Supply</i>
<i>Central Laboratory Kits</i>	<i>Emory University</i>	<i>Start-up Supply including containers for biospecimens and labels for containers</i>
<i>Study Documents</i>	<i>Data Coordinating Center, University of North Carolina</i>	<i>Study Reference Manual Participant ID Labels</i>
<i>DMS and other web address Usernames and Passwords</i>	<i>Data Coordinating Center, University of North Carolina</i>	<i>To Study Coordinator</i>

1.8 SUPPLY ORDERING

<https://redcap.emory.edu/surveys/?s=TvPcJbP3Qp>

To order supplies, coordinators should log into the above website and request supplies. This website allows PROTECT personnel to order supplies, see when packages have been shipped, etc. this link is also posted on the PROTECT website's main resource page.

Upon entering the site, coordinators must input the date the request is being made, a contact name and e-mail address and select “PROTECT” from the drop down study menu before hitting “submit.” Sites will then be brought to the next page where they must specify the institution requesting supplies and then choose the inventory of needed items (lab kits come from Emory, recruitment supplies come from CT Children’s, participant ID labels come from UNC). Once the ordering is complete, a confirmation page and confirmation e-mail sent to the requesting individual’s address will allow the requestor to review the supply order. Once supplies are shipped, the requestor will receive updated details with a tracking number.

1.9 INVOICING

Sites are responsible for invoicing Connecticut Children’s Medical Center on a quarterly basis for reimbursement of completed, enrolled patient visits and specimens. Sites are reimbursed according to the attached NIH approved per-patient visit schedule.

Study coordinators or designated staff at each site’s institution should prepare invoices as visits are completed detailing a list of patient identification numbers for each enrolled patient for which reimbursement is requested.

Invoices should be submitted utilizing the attached template for the appropriate period covered. Payments are linked to CRF completion in the data management system ([DMS](#)), the Confirmation of Diagnosis (COD) and Site Biopsy Histology (SBH) forms must be complete in the DMS in order to receive payment for baseline visits, screen failed patients/specimens are not reimbursable, week 2 is mandatory for all patients; weeks 6, 8 and 10 are reimbursable visits for steroid patients only. Coordinators or designated staff should print the template on their institutional letterhead (with information on where payments should be directed), include the site’s subcontract number (located at the top of the PROTECT contracts), a description of expenditures (please reference specimen number), please be sure totals from pages 1 and 2 match page 3 and please have the site PI and/or grants/accounts sign the invoice.

A suggested patient stipend of \$25 per specimen collected (for enrolled patients only) is site-specific and is included in the amount awarded to the sites (for example, at baseline visits patients have the potential to earn \$75 if all 3 specimens are obtained (\$25 each for blood, stool and biopsy), PROTECT reimburses sites \$50 for each specimen collected. However, if the child is a screen failure, we cannot reimburse your site, or if only biopsy and blood are collected and not stool, we will only reimburse you for what is actually collected (in this example we would pay for the biopsy and blood but not stool if no stool was collected). Some sites do not provide stipends to their patients.

PROTECT will reimburse sites for Week 52 optional flexible sigmoidoscopies. Standard of care colonoscopy will be billed to the participant’s insurance carrier. If the endoscopy procedure is done under the study then PROTECT will pay a stipend to your center. If the procedure is done as standard of care it should be billed through normal insurance. Week 52 Flexible Sigmoidoscopies should be invoiced separately from the main invoice (see template). If the participant's insurance was billed for a standard of care colonoscopy at week 52 at the request of their doctor, the study cannot reimburse the \$1200 stipend as this is only billed if it is done for research purposes only. If it's standard of care, you should re-consent the participant with the Standard of Care consent form (from the version 4 protocol amendment dated March 11, 2013)

to request standard of care biopsies (versus the week 52 consent) and invoice CT Children's Medical Center for the \$50 biopsy charge.

PROTECT will not be providing information from the biopsies collected. If your institution wants to independently send specimens to your pathology department, then it will be charged to insurance. PROTECT can only reimburse week 52 flexible sigmoidoscopies up to a maximum of \$1200 if the patient qualifies.

For patients who undergo a colectomy, CRFs will be entered closest to where the visit would fall if they were a regular participant following the normal follow up schedule so invoices will be entered the same way. Example: if they were last seen at week 12 and then they come in every 6 months, their next visit may be closest to week 39.

PERIOD COVERED:

Period 1 = May 1 - July 31: Invoice Due August 31

Period 2 = August 1 - October 31: Invoice Due November 30

Period 3 = November 1 - January 31: Invoice Due February 28

Period 4 = February 1 - April 30: Invoice Due May 31

Per Patient Cost - Payment to the Sites

430 Patients

Schedule of Visits and Assessments	Screening Baseline	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	SOC*	Total
		2	4	6	8	10	12	26	39	52	78	104	156			

Total Payment to Site for each visit \$605 \$25 \$80 \$25 \$55 \$25 \$80 \$190 \$190 \$85 \$50 \$50 \$50

that is completed including suggested pt stipend

Invoiceable Costs for each Collection if occurs

Biopsy	\$50									\$50					\$50	
Stool	\$50	\$50				\$50				\$50						
Blood	\$50	\$50				\$50				\$50						\$500

*Flex Sig at Wk 52

*If performed site will be reimbursed up to \$1200 for procedure

* \$1,200

Visit	Baseline	Wk 4	Wk 12	Wk 52	SOC
Patient Stipends					
Stool	\$25	\$25	\$25	\$25	-
Blood	\$25	\$25	\$25	\$25	
Biopsy	\$25			\$25	\$25

*Standard of Care Biopsies can occur at anytimepoint during the follow up period

Sample Invoice Template:

TITLE OF PROJECT:

Predicting Response to Standard Pediatric Colitis Therapy: The PROTECT Study

INSTITUTION NAME:

PERIOD COVERED:

- Period 1 = May 1 - July 31: Invoice Due August 31, Year _____
- Period 2 = August 1 - October 31: Invoice Due November 30, Year _____
- Period 3 = November 1 - January 31: Invoice Due February 28, Year _____
- Period 4 = February 1 - April 30: Invoice Due May 31, Year _____

Sub-Contract Number

12-179296-XX

EXPENDITURES:

<u>New Patient Enrollment</u>	CURRENT
<i>Number of Patients</i>	
Screening/Baseline	_____
	[\$605]
Biopsy	_____
	[\$50]
Stool	_____
	[\$50]
Blood	_____
	[\$50]
<u>Patient Follow-up Payments</u>	
<i>Number of Patients</i>	
Week 2	_____
	[\$25]
Week 4	_____
	[\$80]
Week 4 Stool	_____
	[\$50]
Week 4 Blood	_____
	[\$50]
Week 6	_____
	[\$25]
Week 8	_____

		[(\$55)]
	Week 10	_____
		[\$25]
	Week 12	_____
		[\$80]
	Week 12 Stool	_____
		[\$50]
	Week 12 Blood	_____
		[\$50]
	Week 26	_____
		[\$190]
	Week 39	_____
		[\$190]
	Week 52	_____
		[\$85]
	Week 52 Biopsy	_____
		[\$50]
	Week 52 Blood	_____
		[\$50]
	Week 52 Stool	_____
		[\$50]
	Week 78	_____
		[\$50]
	Week 104	_____
		[\$50]
	Week 156	_____
		[\$50]
	SOC biopsy	_____
		[\$50]
Total Requested	\$	_____

INVESTIGATOR or Department Head Signature

Grants Office Signature

**Attach list of patient identification numbers for each patient for which reimbursement is requested at each stage on attached table.

** Please submit a separate invoice for any flexible sigmoidoscopy procedures that are completed in Week 52. If performed, the site will be reimbursed up to \$1,200 per patient procedure. Be sure to include institution name, patient ID, date of flex sig procedure and cost of reimbursement (up to a maximum of \$1,200).

Please ensure itemized expenditures on pages 1 and 2 equal amounts listed on page 3.

Make check payable to:

Children's Hospital
123 Children's Way
Springfield, XX
06123

Please add in memo: Fund 123456

Predicting Response to Standard Pediatric Colitis Therapy: The Protect Study
Flexible Sigmoidoscopy Reimbursement

PERIOD COVERED:

- Year 2 Period 1 = May 1 - July 31: Invoice Due August 31, Year _____
- Year 2 Period 2 = August 1 - October 31: Invoice Due November 30, Year _____
- Year 2 Period 3 = November 1 - January 31: Invoice Due February 28, Year _____
- Year 2 Period 4 = February 1 - April 30: Invoice Due May 31, Year _____

INSTITUTION NAME:

Children's

SUBCONTRACT NUMBER:

12-179296-XX

Patient ID	Flexible Sigmoidoscopy Description	Flex Sig Date	Amount
PXX1234	Week 52 Flexible Sigmoidoscopy		1,200
		Subtotal	\$ 1,200.00

Total Requested

\$	<u>1,195.00</u>	Expenditures
\$	<u>1,200.00</u>	Flexible Sigmoidoscopy
\$	<u>2,395.00</u>	Total

INVESTIGATOR or Department Head Signature

Grants Office Signature

Chapter 2: Recruitment, Consent, Eligibility

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2.1 OVERVIEW

Recruitment and retention of an adequate number of study participants are critical to the success of any clinical trial. This chapter outlines the steps involved in the “process” of identifying, recruiting and consenting potential participants for further screening and potential enrollment into the PROTECT Study.

2.2 GENERAL RECRUITMENT STRATEGIES FOR CLINICAL CENTERS

Each participating clinical center will have developed its own preferred mechanism for identifying and recruiting potential participants by developing multiple strategies tailored to their center and the population served.

Investigators should consider sending brief information letters or study brochures to all gastroenterologists at their site and in the catchment area, describing the goals and methods of the study. It is critically important that referring physicians understand that patients need to be evaluated for potential study participation before commencement of therapy for ulcerative colitis. This should be done before the study starts, and periodically throughout the recruitment phase. Referring physicians should be supplied with materials that detail the study requirements for medical record documentation. It will be important to maintain a good relationship with referring physicians, keeping them informed of the study and their participants’ progress. In addition, educational presentations to medical, nursing and other health professional groups should be scheduled to help with recruitment.

2.3 PARTICIPANT RECRUITMENT

Study participants will be identified from patients who are evaluated, referred, and followed at the Clinical Sites for a potential new diagnosis of ulcerative colitis. A chart review may provide some pre-screening to identify potential patients for consenting. Many sites utilize three main avenues for screening and recruitment of study participants: 1) patients scheduled for endoscopy 2) inpatient admissions and 3) patients scheduled for clinic visits.

Those found to be potential participants should have their primary gastroenterologist consulted. If mutually agreed upon, the patient will be recruited for further screening and enrollment in the study.

Initial patient contact should be made by the principal investigator or the subject’s primary gastroenterologist, who may or may not be a co-investigator in the study. In some instances, initial contact will be made by the research coordinator/nurse after consulting with the patient’s primary gastroenterologist. The investigator, study physician, or clinical research coordinator will speak to the child and parent(s) or guardian(s) during a clinic visit, inpatient admission to the hospital, or prior to colonoscopy to discuss the study design, benefits and possible risks with the family. On rare occasions the initial conversation may take place after the diagnostic colonoscopy but before the initiation of any therapy. A brochure describing the study along with the required consent and assent forms will be given to the family and patient, respectively.

Participants should be recruited and consented before colonoscopy in order to allow collection of biospecimens. It is possible that recruitment would not take place until after colonoscopy but

before commencement of therapy for the disease state; in this case, approval should be sought from the medical monitor. As the goal of the study is to collect biospecimens prior to and at diagnostic colonoscopy every effort should be made to consent before colonoscopy to allow collection of these samples. Extreme importance should also be placed on obtaining stool prior to the start of colonoscopy cleanout. As such, subjects may need to be recruited and consented (see Section 2.4 below) prior to completing all the assessments and diagnostic requirements of the study necessary to confirm the new diagnosis of ulcerative colitis.

2.3.1 Recruitment Goals

The goal of recruitment is for each of the participating clinical centers to enroll a minimum of 8-12 patients per year over the course of the 24-36 month recruitment period; no site will be capped for maximum enrollment and sites are encouraged to recruit as many patients as possible. During recruitment, every attempt should be made to recruit consecutively diagnosed subjects from each participating site to reduce the potential for selection bias.

Enrollment will cease at all sites when a total of 430 subjects have entered into the study. There will be some sites that enroll less than 20 and some who enroll more than 20 subjects, and we anticipate this will balance out to meet the overall study goal of 430 participants.

All enrolled participants are planned to be followed for a minimum of 52 weeks for study outcome assessment, and will continue with additional annual follow-up visits to a minimum of 2 years from diagnosis and maximum of 5 years depending on time of recruitment into the study.

Participants will receive a small stipend (check, gift card, etc...) for bio-specimen collection as allowed by the site's institutional policy, and will be provided Pentasa (mesalamine) free of charge until the 52 week outcome assessment or until it is discontinued prior to 52 weeks.

To help facilitate a healthy competition between sites for enrollment, the PROTECT study instituted a Golden Scope Award (GSA). This award will be bestowed monthly on the center that enrolls the most patients between respective PI/coordinator calls. At the end of the PROTECT study the center that has the greatest number of GSAs will be sent \$100 for a celebratory lunch (courtesy of Jeffrey Hyams, MD).

2.3.2 Minority Recruitment

Study Coordinators and other personnel with whom the participants will have contact should be sensitive to different cultural and ethnic attitudes and practices. Sites may need to enlist the services of an interpreter to facilitate recruitment of non-English speaking participants.

2.3.3 Recruitment Monitoring

The PROTECT Data Management System (DMS) will have real time reporting features that provide the Clinical Site with tools useful in monitoring their site's screening, recruitment and enrollment numbers, including each screened participant's data collection status, participant scheduling, and each participants expected forms schedule.

The Data Coordinating Center (DCC) will provide Monthly Management Reports that will present screening, recruitment and enrollment numbers, including time trends, and data collection completeness, for overall study recruitment monitoring by the Executive Committee.

The study's Data and Safety Monitoring Board, is also charged with monitoring study progress, including recruitment, through review of bi-annual DSMB reports which include the study management tables. Following each bi-annual DSMB teleconference/webinar, the DSMB will

produce a letter which contains their recommendations regarding continuation of the study. These DSMB letters are available on the PROTECT website and should be printed for IRB/REB submission.

2.4 ELIGIBILITY

PROTECT's eligibility criteria are defined to reflect the typical patient population with ulcerative colitis for whom initial therapy with either mesalamine or corticosteroids followed by mesalamine is considered standard of care.

2.4.1 Protocol Inclusion Criteria

- Age ≥ 4 years and ≤ 17 years at initiation of therapy (achieved 4th birthday, not yet 18th)
- Weight ≥ 15 kg
- New diagnosis of ulcerative colitis established by standard clinical, endoscopic, and histologic features
- Colitis extending beyond the rectosigmoid (Paris classification E2, E3, or E4). If a patient is seriously ill and the clinician does not advance the colonoscope beyond the sigmoid colon but the clinical condition of the patient highly suggests more extensive disease then that patient is eligible for study.
- Disease activity by PUCAI of ≥ 10 at diagnosis
- No therapy previously initiated to treat newly diagnosed ulcerative colitis
- Stool culture negative for routine enteric pathogens (*Salmonella*, *Shigella*, *Campylobacter*, *E. coli 0157:H7*) and *Clostridium difficile* toxin. Recent successful treatment for *Clostridium difficile* does not exclude a patient if toxin now absent. However, the patient must be a minimum of 5 weeks from the time treatment was started at the time toxin is absent.
- Stool study negative for enteric parasites (ova and parasites) where appropriate
- Parent/guardian consent and patient assent
- Ability to remain in follow-up for a minimum of one year from diagnosis
- Female patients of child bearing age must have a negative urine pregnancy test and practice acceptable contraception (e.g., abstinence, intramuscular or hormonal contraception), two barrier methods (e.g., condom, diaphragm, or spermicide), intrauterine device, verbal report of the partner with history of vasectomy, or be surgically sterile. All female patients of childbearing potential (post-menarche) will undergo urine pregnancy testing at screening and must not be lactating.

2.4.2 Protocol Exclusion Criteria

- Clinical, endoscopic, radiologic, or histologic evidence suggesting CD consistent with Paris and NASPGHAN criteria
- A previous diagnosis of inflammatory bowel disease for which treatment was given
- Evidence of any active enteric infection at the time of study entry
-

- Use of any oral CS for non-gastrointestinal indication within the past 4 weeks (e.g., asthma). Use of inhaled CS does not exclude a patient.
- History of use of IM or anti-TNF α agent for other medical conditions (e.g., juvenile rheumatoid arthritis) within the past 6 months
- Use of Accutane within the past 4 weeks
- Use of any investigational drug within the past 4 weeks
- Use of any 5-aminosalicylate within the past 4 weeks
- Pregnancy
- Subjects with poorly controlled medical conditions (e.g. diabetes, congestive heart failure)
- Proctitis or proctosigmoiditis only (Paris classification E1) on colonoscopic evaluation
- Chronic renal disease (BUN and serum creatinine >1.5 times the upper normal limit)
- Hepatic disease (AST or ALP greater than 3 times the upper normal limit in the absence of concomitant liver disease associated with IBD following full evaluation)
- History of allergy or hypersensitivity to salicylates, aminosalicylates, or any component of the Pentasa capsule.
- History of coexisting chronic illness or evidence of significant organic or psychiatric disease on medical history or physical examination, which, in the Investigator's opinion, would prevent participation in the study
- History or presence of any condition causing malabsorption or an effect on gastrointestinal (GI) motility, or history of extensive small bowel resection (greater than half the length of the small intestine).
- The finding of *Helicobacter pylori* at the time of evaluation does not exclude the patient from the study. Whether to treat this patient for *Helicobacter pylori* and when will be left to the discretion of the site.

2.4.3 Pre-Screening Tool

A pre-screening process will help to identify potential study participants who appear to meet some of the PROTECT eligibility criteria and who should be consented for additional study screening and baseline data collection.

The PROTECT Eligibility Summary Card (Figure 2.1) will be distributed with the recruitment materials to each site prior to study start-up. The card (laminated and pocket sized) summarizes the PROTECT eligibility criteria as well as listing most of the exclusion criteria for study eligibility.

Figure 2.1. PROTECT Eligibility Summary Card



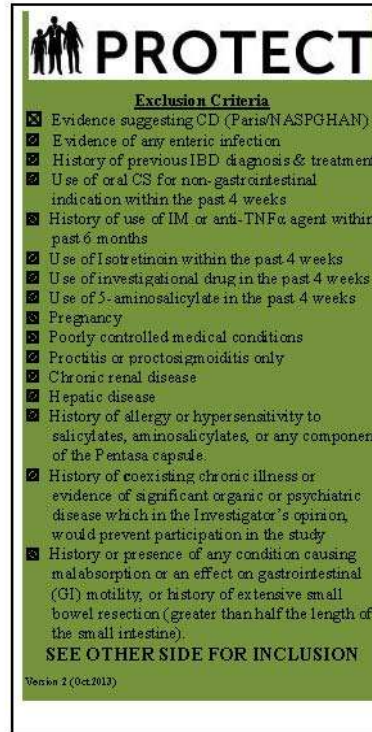
PROTECT

Inclusion Criteria

- Age \geq 4 years and \leq 17 years at initiation of therapy (achieved 4th birthday, not yet 18)
- Weight \geq 15 kg
- New diagnosis of ulcerative colitis
- Colitis extending beyond the rectosigmoid
- Disease activity by PUCAI of \geq 10 at diagnosis
- No therapy previously initiated to treat newly diagnosed UC
- Stool negative for routine enteric pathogens and Clostridium difficile toxin. Patient must be a minimum of 5 weeks from treatment
- Stool negative for enteric parasites
- Parent/guardian consent and patient assent
- Ability to remain in follow-up for a minimum of one year
- Negative urine pregnancy test and practice acceptable contraception

SEE OTHER SIDE FOR EXCLUSION

Version 2 (Oct 2013)



PROTECT

Exclusion Criteria

- Evidence suggesting CD (Paris/NASPGHAN)
- Evidence of any enteric infection
- History of previous IBD diagnosis & treatment
- Use of oral CS for non-gastrointestinal indication within the past 4 weeks
- History of use of IM or anti-TNF α agent within past 6 months
- Use of Isotretinoin within the past 4 weeks
- Use of investigational drug in the past 4 weeks
- Use of 5-aminosalicylate in the past 4 weeks
- Pregnancy
- Poorly controlled medical conditions
- Proctitis or proctosigmoiditis only
- Chronic renal disease
- Hepatic disease
- History of allergy or hypersensitivity to salicylates, aminosalicylates, or any component of the Pentasa capsule.
- History of coexisting chronic illness or evidence of significant organic or psychiatric disease which in the Investigator's opinion, would prevent participation in the study
- History or presence of any condition causing malabsorption or an effect on gastrointestinal (GI) motility, or history of extensive small bowel resection (greater than half the length of the small intestine).

SEE OTHER SIDE FOR INCLUSION

Version 2 (Oct 2013)

Prior to official study screening and data collection, all patients identified as potential participants must be consented.

2.5 CONSENT

The consenting process in PROTECT will usually occur prior to having a definitive diagnosis of ulcerative colitis, must occur before the commencement of therapy, and always before a final eligibility determination for study participation. Many of the procedures necessary for these determinations involve data and specimen collection that require consent.

Informed consent is a legal condition whereby a person can be said to have given consent based upon an appreciation and understanding of the facts and implications of an action. The individual needs to be in possession of all of his/her faculties, such as not being mentally retarded or mentally ill and without an impairment of judgment at the time of consenting. Impairments include illness, intoxication, drunkenness, using drugs, insufficient sleep, and other health problems.

Each site is responsible to follow the informed consent and assent requirements of their own institution's IRB. Canadian sites must follow the requirement of Health Canada and Public Health Agency of Canada.

Informed consent is an ongoing process, not just a form. It starts with the first contact with an individual and continues until the study is completed or a participant withdraws. Information must be presented to enable persons to voluntarily decide whether or not their child will participate as a research subject. It is a fundamental mechanism to ensure respect for persons

through provision of thoughtful consent for a voluntary act. The procedures used in obtaining informed consent should be designed to educate the subject population in terms that they can understand.

Included in the ‘informed’ process:

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

For pediatric ethics, informed consent is more properly understood as a combination of informed parental permission and (when appropriate) the assent of the child. In PROTECT the parent or guardian of the participant will be consenting for adolescents. A participant assent is also required among adolescents as required by your IRB. A child may refuse participation even if the parent has provided consent.

Each site’s trained Investigator, Project Coordinator, or other trained study staff member must perform the formal process of obtaining informed consent from the parent(s)/legal guardian of the child for enrollment. Failure to obtain informed consent, a signed consent form from the parent(s)/legal guardian of each potential participant before screening and/or before enrollment, and a signed assent form (if applicable) is a serious protocol violation. Note: Foster parents are not considered legal guardians.

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

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

2.5.1 Consent for Specimen Storage at the Repository

During this study, specimens of blood, tissue, and stool will be analyzed for indicators of inflammation. These specimens will be stored at the bio-repository at Emory University and

periodically shipped to other laboratories for specific analyses. Each year a part of each sample will be shipped to the NIDDK/NIH for storage in their bio-repository and become available for study through PROTECT Ancillary Studies. Some clinical sites may need a separate consent for specimen collection and storage; others may have this covered in the over-all study consent. If a family has any desire to limit the specimens to be stored, they should be free to do so without repercussion. Families and participants may also change their mind during the study about specimen collection and storage. The Informed Consent Tracking Form (ICT) provides documentation of specimen consent or restrictions.

2.5.2 Consent for Additional Clinically Indicated / Standard of Care Colonoscopy

If a patient undergoes a colonoscopy during the study course that the attending clinician deems needed for clinical care decisions, then consent will be sought to obtain 4 additional rectal mucosal biopsies for study purposes. Consent for this additional biopsy material may be separate from consent for the study. Procedures for this consenting process are described in MOP Chapter 6 ‘Follow-up’.

2.5.3 Consent for Week 52 Flexible Sigmoidoscopy

A flexible sigmoidoscopy will be offered to study subjects at end-of-study (week 52) to assess for mucosal healing if they are in clinical remission on Pentasa only and have not received rescue therapy with immunomodulators, calcineurin inhibitors, or anti-TNF alpha agents. Consent for the week 52 flexible sigmoidoscopy may be a separate section within the original study consent form or it may be a separate form. When the study is being described, it should be made clear that participation in the study does not imply consent for the week 52 flexible sigmoidoscopy, and that patients/parents may choose to refuse this consent at that time. Consent for the week 52 flexible sigmoidoscopy should be discussed prior to Week 52. Additional procedures for this consenting process are described in MOP Chapter 6 ‘Follow-up’.

2.5.4 Consent Modification

Any participant or parent may withdraw or modify their consent at any time in the study, for any reason, including:

- 1) Declining to provide any more data or specimens to the study but allow use of previously collected data and/or specimens.
- 2) Request to withdraw all their data from study databases and that any stored samples be destroyed.
- 3) Request to withdraw some portion of the data collected (i.e., participants may withdraw specimens but not examination data or vice versa).
- 4) Expansion of consent to include a week 52 flexible sigmoidoscopy or biopsies from a standard of care colonoscopy.

Documentation of consent modification is done on the Informed Consent Tracking Form (ICT).

2.5.5 Obtaining a Medical Release

Occasionally adverse event reporting requires review and abstraction of medical records for health care received outside the clinical site’s hospital. Study personnel must obtain a medical

record release form to obtain data from the outside care provider. Medical release forms should include the purpose of the request, the information that will be requested, and the time period related to the request. The release form should be reviewed with the participant during the informed consent process, prior to the participant signing the form.

2.5.6 Health Insurance Portability and Accountability Act (HIPAA)

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

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

Compliance for each clinical site will require that each participant read and sign a “HIPAA Authorization to Use and Disclose Individual Health Information for Research Purposes” form. These forms must receive IRB approval at the clinical site prior to their use and thus, prior to the enrollment of any PROTECT participant. The parent(s)/legal guardian of the participant should receive a copy of the signed authorization.

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

2.6 RECRUITMENT DATA COLLECTION

There are **2 forms required** to be completed and data entered for each patient consented in the PROTECT study regardless of the patient’s final eligibility status and study participation:

1. Informed Consent Tracking form (ICT) - documents the consent status for each recruited participant, and will document modification or changes in consent during the study.
2. Demographic Form (BDF) - provides the demographics needed for the study and for each site’s annual IRB renewal reporting, and NIDDK reports.

In addition, if a participant is deemed ineligible prior to initiating treatment on Day Zero, a Screen Failure Form (SFF) will be required. If a patient is determined to be ineligible after initiating treatment on Day Zero or later, a Study Withdrawal Form (SWF) will be required. These forms can be downloaded and printed individually on the Study Website, or they are included in PDF containing the set of forms necessary for Screening and Baseline on the website.

Refer to each form’s QxQ (Question by Question document) which includes general instructions for the form as well as specific instructions for each question. Refer to Chapter 10 ‘Data Management / Administrative Procedures’ regarding participant IDs, form ID labels, where to access forms for printing and data entry instructions.

Chapter 3: Screening and Baseline

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Chapter 3: Screening and Baseline

3.1 OVERVIEW

The primary objectives of the screening and baseline process are to confirm and document study eligibility and to collect baseline data and specimens as indicated in the study protocol to adequately describe the population in the trial.

The procedures and data collection requirements necessary for eligibility determination and baseline data collection are described below.

3.2 TIMING ISSUES

Eligibility determination is a process, rather than a calendar schedule of events and clinic visits. The process will vary depending on each clinical site's standard practices and procedures and the patient's clinical status.

Many of the screening procedures that provide the necessary clinical history and laboratory evaluation to suspect a diagnosis of UC may have already begun prior to study recruitment and study consenting. However study consenting is necessary for additional data collection specific to the study, collection of bio-specimens, use of study data collection forms, and subsequent per protocol treatment.

The actual timing of recruitment, screening, and baseline data collection may occur together over a very short period of time, or be done during separate clinic visits. Specifically, stool studies for routine culture should be done no more than 4 weeks prior to enrollment. Studies done for C diff should be done no more than 4 week prior to enrollment. Blood work from local laboratories should be done no more than 2 weeks prior to enrollment.

The most critical timing factors for PROTECT are the timing of the initial diagnostic studies, collection of bio-specimens, and treatment initiation following diagnosis. It is **critical that study treatment begin within 14 days of endoscopic evaluation and prior to any other disease treatment**. Treatment initiation occurs at the end of what we are calling the baseline period and is considered Day 0 (zero) for follow-up. Refer to MOP Chapter 5 "Day 0 (Zero)," regarding study treatment initiation and study data collection associated with treatment initiation. It is possible to have the Screening and Baseline visit be the same day as the Day Zero visit.

3.3 SCREENING AND BASELINE COMPONENTS

In brief, screening and baseline data collection provide the necessary information to determine if a recruited patient (consented) meets the PROTECT eligibility criteria. This will include:

1. Routine local blood/urine monitoring (standard of care)
2. Colonoscopy/flexible sigmoidoscopy results and biopsy specimen collection
3. Specimen collection for central laboratories (refer to Chapter 4 "Specimen Collection")
 - a. Blood for study central laboratories
 - b. Stool collection
 - c. Rectal mucosal biopsy (during colonoscopy/flexible sigmoidoscopy)
 - d. Histology slide (if not sending study biopsy in formalin which is preferred)
4. Medical Chart Review
5. Participant Clinical Exam

6. Case Ascertainment – Diagnosis of UC
7. Assessment of Inclusion and Exclusion Criteria

Pregnancy Testing: Pregnant or nursing mothers are not eligible to participate in our study. All female patients who are of child bearing age and/or menstruating must have a pregnancy test done at the start of the study as part of screening. This may be more easily accomplished as part of the pre-colonoscopy evaluation. Many centers will require pregnancy testing prior to endoscopic studies.

Table 3.1 below lists the study data collection forms needed to document the screening and baseline activities listed above. A general description of the forms and collection process is also described below.

Table 3.1 Screening and Baseline Visit Forms

Preparations		
Collect Participant Contact Information		
Obtain Medical Records and Reports		
Task / Procedure	Associated Data Collection Forms	Form Codes
Begin with...	Informed Consent Tracking Form	ICT
	Baseline Demographic Form	BDF*
	Eligibility and Recruitment Form (start form)	ERF
Important Forms for Screening	PUCAI	PUC
	Confirmation of Diagnosis	COD
Historical Information	Environment and Family History	EFH*
	Medical and EIM Baseline Summary Form	MES*
Imaging Assessment and Case Ascertainment	Disease Extent Data Form	DED
	Endoscopic Evaluation Form	EEF
	Site Biopsy Histology Score Form	SBH
Laboratory Collection	Local Lab Results Form	LLR
	Local Lab Normals Data Form (local lab)	LLN
	Specimen Collection Form	SCF

*Please complete these forms by week 4

3.4 ORDERING OF DATA COLLECTION DURING SCREENING BASELINE

Sites may organize and order the screening and baseline data collection to accommodate the patient’s condition and needs, as well as their own site’s standard-of-care procedures, staffing and organizational needs. Attention should be paid to those data that provide screening criteria in the interest of the patient and their family’s time. The Informed Consent Tracking Form (ICT) and Baseline Demographic Form (BDF) must be collected on all consented participants regardless of resulting eligibility.

Each data form will have an associated QxQ (Question by Question) document which includes more specific instructions on the form’s use and additional instructions or information associated with each form’s individual questions. These documents are located in the Study Reference Manual behind the copy

of the corresponding data collection form.

All current study forms and QxQs are also available for printing on the study website www.protectstudy.com. Forms associated with Consenting, Screening and Baseline Collection are available in a PDF titled 'Screening and Baseline Forms' containing the set of required forms with a "cheat sheet" cover page summarizing the procedures and forms required. In addition, all study data collection forms are provided individually for download listed in alphabetical order.

Participant ID labels for use on study data forms will have been provided to each site from the DCC. Refer to Chapter 10 "Data Management and Administrative Procedures" for information regarding participant IDs and participant form ID labels, site IDs and site ID labels, further information on accessing screening and baseline data collection forms for printing, and DMS instructions for data entry.

3.4.1 Screening/Baseline Contact Occasions

All screening and baseline forms listed above designated as baseline and screening forms are to be documented on the form as Contact Occasion 01 (CO:01). Some data forms such as lab results or the final results of the sigmoidoscopy may not be available during the official screening/baseline process, and may only be available just prior to treatment initiation (CO:02), however they should still be recorded as CO:01.

3.5 SCREENING AND BASELINE DATA COLLECTION FORMS

3.5.1 Study Inclusion/Exclusions

The **Eligibility and Registration form (ERF)** is a checklist of all protocol eligibility criteria (inclusion and exclusion) assessed throughout screening and baseline data collection. This form provides documentation of final eligibility for the study once screening has been completed, prior to initiation of study treatment.

3.5.2 UC Case Ascertainment

The **Confirmation of Diagnosis Form (COD)** presents the diagnosis requirements in a checklist to document and ascertain eligibility into the PROTECT study based on the colonoscopy results of clinical, histologic and endoscopic requirements for a UC diagnosis, as well as information for ruling out Crohn's Disease.

The **Endoscopic Evaluation Form (EEF)** documents the endoscopic assessment of the disease including the Mayo Severity Score. Refer to Appendix 3.1 at the end of this chapter for the photographic examples corresponding to each score. The Endoscopic Evaluation form should be completed after any endoscopic procedure is performed. A **jpg photo file** of the most involved area of rectosigmoid is also required and is to be electronically uploaded to the DCC's database through the DMS file upload feature. The jpg file is to be de-identified of patient information and named with Participant ID_Assessment Date. Example: PGA0016_12JUN2012, using the standard study date format. The DMS will only accept images with the file extension of ".jpg." The file name is also to be recorded on the EEF form (Question 4d, 5d).

The **Disease Extent Data Form (DED)** provides further supporting documentation of disease involvement, providing documentation of the imaging performed and the location of disease. This form should be completed at baseline and anytime there is imaging done. Results from imaging are recorded on the Clinical Data Day Zero (CDZ) and Clinical Data Follow-up Forms (CDF), respectively. The **Site Biopsy Histology Score Form (SBH)** is to be completed after the assessment of the colonoscopic biopsies by the site pathologist. Ideally this form is completed by the site pathologist directly but can be completed by either the Principal Investigator or Site Coordinator in conjunction with the pathologist.

Accuracy of this form is very important therefore the site PI should review this completed form for consistency with the Confirmation of Diagnosis form.

3.5.3 PUCAI

The Pediatric Ulcerative Colitis Activity Index (PUCAI) is initially assessed at two time points, onto the **PUCAI Form (PUC)**. The first is a pre-colonoscopy assessment which may have to be derived from chart review and interview (see note below). The second assessment is taken as a Day Zero measurement (refer to Chapter 4) at the time of treatment initiation.

The PUCAI assessments are critical to the study, including guiding treatment dosing and considerations, and providing outcome data to the study. The baseline PUCAI must be administered by the study physician based on clinical evaluation of the patient.

The data form (**PUC**) contains User's Guide information as does the PUC QxQ.

Note: The baseline PUCAI must be based on a pre-colonoscopy/flexible sigmoidoscopy time period, and **prior** to the clean-out preparation prior to the procedure. If a colonoscopy/flexible sigmoidoscopy has been completed, this information can be collected by the PROTECT study physician based on information they have directly obtained during clinical evaluation of the patient and with records review. If treatment is initiated on the day of the colonoscopy then the baseline PUCAI and Day 0 PUCAI are the same. If there is a delay between the colonoscopy and the initiation of treatment then the Day 0 PUCAI is determined by clinical activity over the one to two days prior to Day 0. The interval between the initial PUCAI and the Day Zero PUCAI should not be more than 2 days; any delay more than 3 days requires a new PUCAI, standard treatment is to evaluate PUCAI 24-48 hours prior to treatment initiation. Only obtain PUCAI at protocol specified visits or if there is a significant change obtained by PROTECT Staff.

3.5.4 Clinical and Medical History Data

Participant medical history and family history related to disease is documented in the **Medical and EIM Baseline Summary Form (MES)** and the **Environmental and Family History Form (EFH)**.

3.5.5 Laboratory Forms and Specimen Collection

3.5.5.1 Local Laboratory

Reporting of local laboratory results will most likely occur after the participant's clinic visit when results are received in the PROTECT clinic. Baseline laboratory data from the local lab reports are to be transcribed/entered into the **Local Lab Specimen Results Form (LLR)** at Contact Occasion 01 regardless of receipt date of the results.

Note: for female patients, a pregnancy test is required for study screening. Similarly, recording of baseline stool studies for enteric pathogens including Clostridium difficile toxin screening is noted on the ERF.

For quality control purposes, the coordinator should complete the **Local lab Normals Data Form (LLN)** which provides the reference ranges for analytes from the laboratory used. The LLN form is not a participant form, but a laboratory form associated with a clinic site. The form will be labeled/identified with the PROTECT Clinic ID Number and label provided by the DCC. It is entered as a "Site" form not a "Participant form". The LLN should be completed a maximum number of 4 times: once each for males and females below and above age 12 for each lab you use.

3.5.5.2 Biospecimen Collection for Central Laboratory

Additional study blood, stool, and rectal mucosal biopsy specimens (including a histology slide if a formalin specimen is not collected) will also be collected at diagnosis as part of translational science component of PROTECT and will be sent to the PROTECT Central Laboratory at Emory University. All specimens expected to be collected must be documented on the **Specimen Collection Form (SCF)**. This form is updated as specimens are requested, collected, and shipped with the appropriate information.

The **SCF** form is identified with the **Patient ID label containing the bar code** (received from the DCC).

The **SCF** form also serves as an inventory of specimens contained in a shipment. Every time a specimen is shipped a copy of the **SCF** form is to be included with the shipment. In the case of batched specimens (i.e. stools), there will be an **SCF** form included for each participants specimen included.

If the diagnosis is not clearly Ulcerative Colitis, please contact the Medical Monitor or hold shipments until diagnosis is confirmed. Specific instructions regarding specimens their collection, processing, and shipping, are detailed in MOP Chapter 7 “Specimen Collection” which contains a detailed User’s Guide for laboratory specimen collection, processing, and shipping.

At the time of shipment, an email notification link on the studies research staff website page <http://www.csc.unc.edu/protect/secure/> can be used to pre-address your email in your own system.

3.6 DATA ENTRY OF SCREENING/BASELINE FORMS

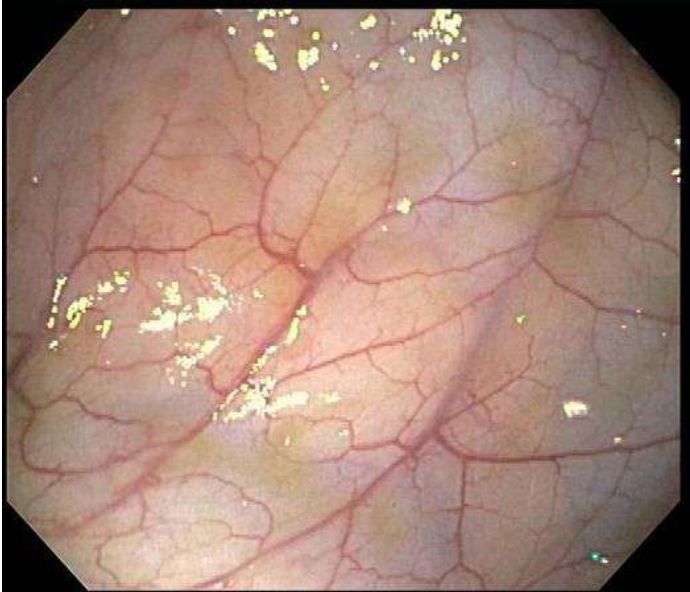
All PROTECT data forms are to be entered within 5 working days of data collection.

3.7 SCHEDULING NEXT CONTACT

If the patient is found ineligible, please complete the Screen Failure Form (SFF). If the patient is found eligible, treatment initiation is the next phase of data collection which begins at the end of the screening and baseline period described above. Clinics may find there is much overlap in the actual data collection process within these two periods. Treatment Initiation does include some clinical assessments prior to beginning treatment. This phase is referred to as Day Zero (or Contact Occasion 02) and must occur within 14 days of the diagnostic endoscopic evaluation. Refer to MOP Chapter 4 for information relating to Day Zero procedures and data forms

Appendix 3.1 Mayo Scoring Assessment – Sample Pictures

Mayo 0



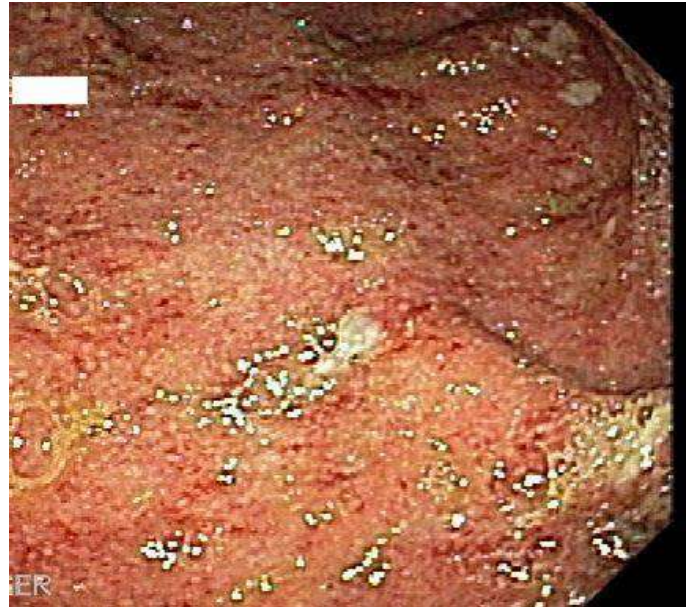
Mayo 1



Mayo 2



Mayo 3



Chapter 4: Day Zero, Treatment Initiation

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4.1 OVERVIEW

“Day Zero” is defined as the day study treatment is initiated. Prior to treatment, all screening data collection finalizing eligibility determination and all baseline data collection should be completed. In addition there are additional data collection associated with the day treatment is initiated that must also be collected. The procedures, data collection requirements, and data forms needed for “Day Zero” are described below.

4.2 DAY ZERO COMPONENTS

The following is a brief summary of the components of Day 0 procedures. Details of procedures and forms needed follow.

1. Review general screening and baseline data collection for completeness (refer to Chapter 2)
2. Day 0 baseline data collection (pre-treatment)
 - a. PUCAI assessment
 - b. Clinical data collection
 - c. Finalize Inclusion and Exclusion Criteria
3. Prescribe treatment/dosing
 - a. Pharmacy pick-up (if Pentasa)
4. Treatment Initiation
 - a. Documentation of study therapy
 - b. Documentation of ancillary treatments
5. Participant/Family instructions
 - a. Participant Website
 - b. Participant Passport
 - c. Self-Report Questionnaires
 - d. Scheduling Future Contacts

4.2.1 Ordering of Data Collection on Day Zero

Table 4.1 lists the data collection forms that need to be completed during the Day Zero activities. Baseline and screening data collection should be completed prior to beginning the Day Zero treatment initiation. Many of the forms contain questions whose response may trigger the need for another form. These are listed as “triggered” forms. If not triggered, then these forms are not required at this contact.

Forms to be used during the contact are available for downloading and printing on the study website (www.protectstudy.com) in the study area for Coordinators and Investigators. A form set, batched in the Follow_up_Forms PDF provides the required and commonly used forms for this contact; the first page of this document contains a “cheat sheet” summarizing the procedures and forms required. Less commonly used forms can be printed individually from the website.

Each data form will have an associated QxQ (Question by Question) document which includes definitions or instructions associated with the form questions. These are located in the PROTECT Study Reference Manual and are available on the study website.

Table 4.1 Day Zero Data Collection Forms

Task / Procedure	Associated Data Collection Forms	Form Codes
Begin and End with.	Enroll Data Form	EDZ
Prior to Treatment, Clinical Information	PUCAI Data Form	PUC
	Clinical Data on Day Zero	CDZ
	Ancillary Data at Day Zero	ATZ
Treatment Forms	Study Treatment Data at Day Zero	STZ
	Steroid Treatment Record	STR (triggered)
	Additional Medical Therapy Form	AMT (triggered)
Other Forms that Might be Triggered based on Responses to the Expected Forms	Additional Lab Results Form	ALF
	Serious Adverse Event Form	SAE
	Hospitalization Data Form	HDF
	Colectomy Data Form	CLF
	Screen Failure Form	SFF
Web-based Self-Administered Forms to be Completed at Home by 4 wk. FU.	Behavioral Assessment (participant and parent) Quality of Life (participant 9-17 yrs.)	Web access on Participant Study Website

4.3 DAY ZERO DATA COLLECTION FORMS

4.3.1 Completing Enrollment and Final Eligibility Determination

The **Enroll Data Form Day Zero (EDZ)** is a checklist that summarizes and documents the collection of all required screening and baseline data collection that assesses eligibility of the participant to continue to the treatment phase of the study. It guides the physician/coordinator to the appropriate forms to document therapy being initiated at this contact. This data form is designed to trigger additional data forms that will need to be collected under different circumstances.

Included in this data collection is the necessary clinical data collected prior to treatment initiation. The **Clinical Data Day Zero Form (CDZ)** is designed to capture basic anthropometric, physical development and routine urine monitoring, as well as the physician’s assessment of the disease activity. In addition, a repeat **PUCAI (PUC)** assessment is also required at this time just prior to treatment which will help guide treatment dosing and considerations (refer to Chapter 5).

Concomitant Medications are captured in the **Ancillary Treatment Day Zero (ATZ) form** using a simple checklist capturing information about current and pre-diagnosis use of specific daily supplements, antibiotics, and other specified medications of interest. Some of these are exclusion criteria for the study and are necessary as part of study screening.

4.3.2 Ineligible

In the event that a participant is deemed ineligible for the study prior to initiating treatment on Day Zero, the **Screen Failure Form (SFF)** will be completed. If a participant withdraws after initiating treatment on Day Zero, the **Study Withdrawal Form (SWF)** should be completed. This form will provide closure for data collection and document the disposition of specimens in the event that consent is withdrawn for specimen storage and analysis.

4.3.3 Treatment Initiation Data Collection

Refer to Chapter 5 ‘Treatment’ regarding procedures related to initiation of study treatment, type of treatment, initial dose selection, therapy worksheets, and concomitant therapy, etc.

If Mesalamine (Pentasa) is prescribed, please read Section 4.4 regarding adherence procedures.

All initiated treatment is to be documented on the **Study Treatment Day Zero Form (STZ)**. If steroids are indicated, their use is documented on the triggered **Steroid Treatment Record (STR)**. If any other additional medications (i.e. calcineurin inhibitors, biologics, or immunomodulators) are prescribed, the **Additional Medication Therapy Form (AMT)** is triggered. Use of these other medications will also trigger the need for additional local laboratory blood analysis as indicated on the **Additional Lab Results Form (ALF)**.

4.3.4 Other Triggered Forms

All clinic contacts will include a question asking if the participant underwent a colectomy. This will trigger the use of the **Colectomy Data Form (CLF)** capturing information regarding the procedure and any complications. Subsequently, the **Post-Colectomy Follow-up Form (PCF)** provides additional status of this participant.

A colectomy or any new or worsening hospitalization will require a **Serious Adverse Event Form (SAE)** and **Hospitalization Data Form (HDF)**. Serious adverse events must be collected on all consented participants regardless of their status in the study, including participant still completing the screening process. Refer to Chapter 8 Patient Safety and Adverse Events for adverse event reporting procedures.

4.4 MEDICATION ADHERENCE FOR PENTASA USERS ONLY

Adherence to medication use will be collected on all users of mesalamine (Pentasa), via standard pill counts at the clinic visits, and the MEMS cap system that goes home with the patients’ medication. The MEMS system will not be activated until the Week 4 visit, and is discussed in detail in Chapter 6 Follow-up.

4.4.1 Pill Count

Question #3 on the **Study Treatment Day Zero Form (STZ)** records the initial pill count dispensed for eventual adherence calculations done at the DCC based on follow-up clinic visit return counts.

4.5 SELF-ADMINISTERED FORMS

There are both participant and parent self-administered questionnaires that we ask families to complete as part of our study data collection. The forms scheduled for Day Zero can be completed via computer

though the “Study Participant” link on the PROTECT Study Website at the family’s convenience over the next 4 weeks. If a computer or web access is unavailable, the site should arrange for a computer to be available to them either at this visit, or at the week 4 clinic contact whichever is most convenient to the family. These 2 questionnaires should take approximately 15 minutes each to complete.

These questionnaires include:

- The Behavioral Assessment System for Children (BASC-2) standardized questionnaire, with age appropriate participant and parent versions.
- A standardize Quality of Life instrument (IMPACT-III) which is completed by participants aged 9-17.

Both questionnaires are available through a “Questionnaire” link in the Study Participant section of the PROTECT study website. Instructions will be provided on the site, however the family should be told that they will need to use the participant’s study ID number (label placed on the Participant Passport, refer to Section 4.6 below), as well as a username and password to access the website (label placed on the Passport). Younger participants will be completing this with the help of their parents. Let the participant and parents know that there are no right or wrong answers to these questions; they should just work through the questions, completing all questions as best they can.

Computer completion of the forms as close as possible to Day Zero is preferred. If it is not possible or convenient for the family to complete the forms via a computer, the site may provide the family with paper copies of the questionnaires which they can mail to the site as soon as they are completed. The site should scan these forms and email the scanned copy to PROTECTstudy@cchmc.org. As these forms contain important safety information, care should be taken to ensure the forms are completed, returned to the site, and emailed to CCHMC in a timely manner.

4.6 PARTICIPANT PASSPORT

Each participant or parent/guardian is to be given a participant handbook/diary (PROTECT Passport), and a PROTECT Follow-up Schedule, printed from a DMS report. The handbook provides an informational summary of procedures associated with the follow-up period and contacts. It also functions as a diary for recording illnesses, other medical care visits, and changes in concomitant medications that will need to be reported at subsequent follow-up contacts. Other important information and instructions for the participant and/or parent regarding the child’s participation in the study is also documented in the handbook, including proper use of the MEMS caps, the study’s public website, and important site contact information.

The Coordinator should add a participant ID label on the front page of the Passport labeled “Login ID”, and include a label with the username/password for the participant section of the study webpage. It is also recommended that the Coordinator review the handbook with the participant/family and instruct them on the use of the diary, the participant ID, and the access information to the study website. The website URL address is also listed on the front page of the Passport.

4.7 PARTICIPANT STUDY WEBSITE

The home page of the study website www.protectstudy.com has a link called ‘Study Participants’. This is a password protected space for the participant and family, where study information and updates, and the

link to the self-administered questionnaires are contained. Each site will have been provided with a site specific username and password access to this area to be given to the participant and families. There is a space located on the Participant Passport for a label with this information. Note: the site staff's username/password accesses this section of the website as well.

If possible, it is recommended that the participant/family be shown this website page during the clinic contact, especially showing the family the self-administered questionnaire link.

4.8 SCHEDULING FOLLOW-UP CONTACTS

Following Day 0 the next protocol scheduled contacts are a 2 week post treatment initiation telephone call and a clinic visit at 4 weeks. When scheduling the 4 week clinic, keep in mind the treatment supply provided to the participant. Week 4 is a very important event in the study, please make every effort to ensure the timeliness of the Week 4 visit.

All contacts have a window before and after each target date. Scheduling within the window is very important. The next two contacts after Day Zero should occur within 3 days before or after the target date of 2 and 4 weeks of Day Zero.

The DMS contains a PROTECT Participant Follow-up Schedule Report that lists all follow-up contact target dates, contact type (telephone or clinic visits), and the protocol allowed contact window. A copy of this report can be provided to the participant/family at this visit and the information can be included with the Patient Passport.

4.9 DATA ENTRY OF SCREENING/BASELINE FORMS

It is recommended that PROTECT data be recorded on paper data collection forms which are then entered into the PROTECT data management system (DMS). Alternatively, PROTECT data may be directly entered into the PROTECT DMS. The DCC requires all data collection forms to be entered within 5 working days of data collection.

Chapter 5: Treatment

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Chapter 5: Treatment

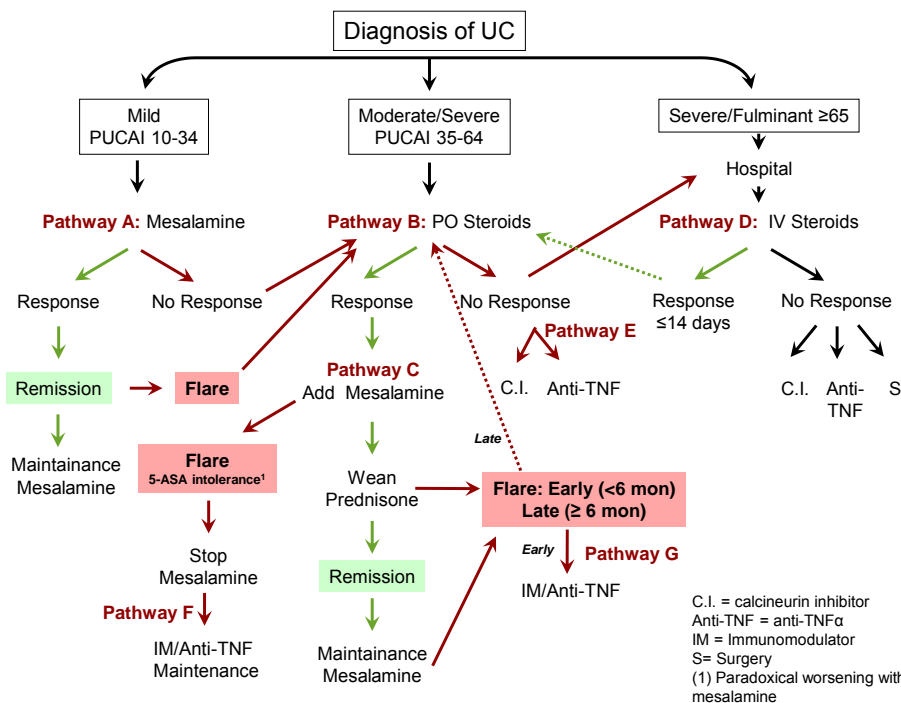
5.1 OVERVIEW

Basic induction therapy of UC usually includes aminosalicylates in subjects with mild to moderate disease, and CS and then aminosalicylates in those with moderate to severe disease; inadequate response often prompts the use of immunomodulators (IM), calcineurin inhibitors (CI; cyclosporine, tacrolimus), or infliximab. To date there has been no systematic examination of the response of pediatric patients with newly diagnosed UC to standardized regimens of either aminosalicylates or corticosteroids.

5.2 INITIAL PUCAI DETERMINATION

Prior to initiating therapy each patient will have a PUCAI score completed by the site clinical investigator. It is important that this PUCAI score represent the patient's overall condition at the time of therapy initiation and if therapy is started on the day of the diagnostic colonoscopy then the score should represent the patient's condition prior to the clean-out regimen for the colonoscopy. A treatment algorithm will be followed. The purpose of this treatment algorithm is to standardize treatment for patients at all centers in the PROTECT Study. Treatment algorithm deviations make interpretation of treatment response/remission as well as translational studies more difficult. Thus, every effort should be made to adhere to the algorithm shown in 5.3. That being said, it is anticipated that clinical situations will arise that will require physician discretion and should be discussed with the Study Medical Officer.

5.3 TREATMENT OVERVIEW ALGORITHM



5.3.1 Initiation of therapy

Choice of initial induction agent will be determined by the subject's PUCAI score and the PI/Medical Monitor's discretion.

- 1) Subjects with PUCAI < 10 are not eligible for this study
- 2) Subjects with PUCAI 10 to 34 will receive Pentasa (mesalamine)
 - a. In subjects unable/unwilling to swallow the capsule, it may be opened and the contents mixed with apple sauce or yogurt-like foods.
 - b. Therapy will be administered in two divided doses (doses do not have to be equal)
 - c. Subjects may escalate to the final dose over 4 days
 - d. All subjects will enter the standard treatment algorithm (Pathway A)
- 3) Subjects with PUCAI >35 will receive corticosteroids
 - a. Ambulatory subjects will receive oral corticosteroids (Prednisone/Prednisolone)
 - i. Both tablet and liquid preparations are acceptable
 - ii. All subjects will enter the standard treatment algorithm (Pathway B)
 - b. Hospitalized subjects receiving oral corticosteroids (Prednisone/Prednisolone)
 - i. Both tablet and liquid preparations are acceptable
 - ii. All subjects will enter the standard treatment algorithm (Pathway B)
 - c. Hospitalized subjects may receive intravenous corticosteroids (Pathway D)
 - i. If a subject is able to change from intravenous CS to oral administration within 7-10 days of commencing therapy then they will enter the standard treatment algorithm (Pathway B)
 - ii. If a subject is not able to transition to oral steroid administration within 7-10 days then they will continue to be followed and have data recorded, but they will not be required to enter the standard treatment algorithm

5.3.2 Initial Dose Selection

All initial Pentasa and Oral Steroid Doses should be based on the subject's weight according to the dose ranges in Table 5.3.2.

Table 5.3.2: Initial Weight-based Total Daily Dosage Recommendations for 5-ASA and Oral Steroids

<u>Weight Ranges</u>	<u>5-ASA Daily Dose*</u> ~70mg/kg/day	<u>Oral Steroid Daily Dose Range</u> 1 to 1.5mg/kg/day (Round UP to the nearest 5mg)	
		<u>Min</u>	<u>Max</u>
15 to 15.9 kg	1000 mg	15 mg	20 mg
16 to 19.9 kg	1000 mg	20 mg	30 mg
20 to 24.9 kg	1500 mg	25 mg	35 mg

25 to 26.4 kg	1500 mg	30 mg	40 mg
26.5 to 32.9 kg	2000 mg	30 mg	45 mg
33 to 39.9 kg	2500 mg	35 mg	60 mg
40 to 46.4 kg	3000 mg	40 mg	60 mg
46.5 to 52.9 kg	3500 mg	40 mg	60 mg
53 kg and above	4000 mg	40 mg	60 mg

*When initiating 5-ASA therapy, patients will be allowed to escalate to the final dose over 4 days to minimize side-effects such as headache.

The goal is to have the patient receive approximately 70 mg/kg of mesalamine daily, with a maximum dose of 75 mg/kg/day. For patients whose weight is well above 60 kg the mg/kg dose will be lower than that as the maximum dose per day is 4 grams.

5.3.3 Steroid tapering schedules

Participants who initiate treatment with steroid therapy should continue on their initial dose of steroids for a minimum of two weeks before adding Pentasa to their regimen. Once Pentasa is added, the participant should continue on their initial dose of steroids for one week while concurrently taking Pentasa.

All steroid doses will be tapered when clinically indicated by serial determination of PUCAI scores as shown in Table 5.3.3.

Table 5.3.3: Recommended Steroid Tapering Regimen Based on initial total daily starting dose

*All doses are in mg of Prednisone/Prednisolone per day

Start Dose	Step #1	Step #2	Step #3	Step #4	Step #5	Step #6	Step #7	Step #8
60	50	40	30	20	15	10	5	0
50	40	30	25	20	15	10	5	0
45	40	30	25	20	15	10	5	0
40	35	30	25	20	15	10	5	0
35	30	30	25	20	15	10	5	0
30	25	20	20	15	15	10	5	0
25	20	20	15	15	10	5	5	0
20	15	15	12.5	10	7.5	5	2.5	0
15	12.5	12.5	10	7.5	7.5	5	2.5	0

If a participant requires subsequent steroid courses during the study (following the initial course), the steroid tapering regimen is at the discretion of the provider.

5.3.4 Standardized Therapy Worksheets

The standardized therapy worksheets will guide the clinician in following the algorithm. There are multiple pathways designated by letters A through G. These pathways represent accepted clinical standards of care. Changes in PUCAI will drive changes in therapy.

Standardized Therapy Worksheet 1: Single Agent Therapy

**All tapering orders are dependent on the physician deeming tapering appropriate for the subject.*

***In the event that PUCAI is noted to be >65 during follow-up, the physician should be notified immediately, IV and/or rescue therapy should be considered, and the subject will leave the Standard Treatment Protocol if deemed necessary by site attending physician*

Initial Pathway A.

Subjects Receiving Pentasa Therapy Only At Initiation of Therapy

Timing	Level of response	Recommended Action****	Remain on Std Treatment Protocol
Weeks 1 and 2 from Baseline			
	Full / Partial / Non-Response (PUCAI has decreased from baseline)	Continue Pentasa	Yes
	Worsening Disease (PUCAI \geq 35)	Cease Pentasa (restart after 2 weeks if steroid responsive) Start Steroids (Table 1, Initial Dose) Move to Pathway B	Yes
Week 3 from Baseline			
	Full or Partial Response (PUCAI has decreased from baseline)	Continue Pentasa	Yes
	Unresponsive (PUCAI is unchanged OR PUCAI has increased BUT total score < 35)	Consider ceasing Pentasa and starting Steroids at the physician's discretion. Move to Pathway B (See Table 1 for Initial Daily Steroid Dose)	Yes
	Worsening Disease (PUCAI \geq 35)	Cease Pentasa (restart after 2 weeks if steroid responsive) Start Steroids (Table 1, Initial Dose) Move to Pathway B	Yes
Week 4 from Baseline			
	Remission/Response (PUCAI \leq 15)	Continue Pentasa	Yes
	Partial/ Non-response /Mild Worsening (PUCAI 16-34)	Consider ceasing Pentasa and starting Steroids at the physician's discretion. Move to Pathway B (See Table 1 for Initial Daily Steroid Dose)	Yes
	Substantial Worsening (PUCAI \geq 35)	Cease Pentasa (restart after 2 weeks if steroid responsive) Start Steroids (Table 1, Initial Dose) Move to Pathway B	Yes

Week 6 from Baseline and beyond			
	Remission (PUCAI <10)	Continue Pentasa	Yes
	Flare / Late Worsening (PUCAI 10 to 34 AND PUCAI increased by ≤ 20 points)	Consider ceasing Pentasa and starting Steroids or Rescue therapy at the discretion of the physician Move to Pathway B Consider addition of 2 nd line therapy (immunomodulator)	No
	Substantial Worsening (PUCAI increased by > 20 points and/or Total PUCAI ≥ 35)	Continue Pentasa Start Steroids or Rescue therapy (choice at the discretion of the physician) Move to Pathway B Consider addition of 2 nd line therapy (immunomodulator)	No

Initial Pathway B.

Subjects Receiving Steroid Therapy Only At Initiation of Therapy

Timing	Level of response	Recommended Action*, **	Remain on Std Treatment Protocol
1 week of steroid only therapy			
	Worsening Disease (Increase PUCAI ≥ 20)	Consider IV therapy and/or Rescue Therapy Move to Pathway D or E	No
2 to 3 weeks of steroid only therapy			
	Responsive (PUCAI reduced by ≥ 20 points AND total PUCAI is < 35)	Commence Pentasa (see Table 1 for dose recommendation) Move to Pathway C Continue Steroids at present dose	Yes
	Partially or Non-Responsive (PUCAI is unchanged OR has reduced but total remains ≥ 35)	Continue Steroids at present dose Do not commence Pentasa	Yes
	Worsening disease (PUCAI has increased)	Consider IV therapy and/or Rescue Therapy Ongoing treatment decisions are at the discretion of the physician Move to Pathway D or E	No
4 weeks of steroid only therapy			
	Responsive (PUCAI reduced by ≥ 20 points AND total PUCAI is < 35)	Commence Pentasa (see Table 1 for dose recommendation) Move to Pathway C Continue Steroids at present dose	Yes
	Partial/ Non-response (PUCAI ≥ 35 and/or PUCAI has not decreased by ≥ 20 points)	Consider IV therapy and/or Rescue Therapy Ongoing treatment decisions are at the discretion of the physician Move to Pathway D or E	No

Standardized Therapy Worksheet 2: Combined Agent Therapy

**All tapering orders are dependent on the physician deeming tapering appropriate for the subject.*

***In the event that PUCAI is noted to be >65 during follow-up, the physician should be notified immediately, IV and/or rescue therapy should be considered, the subject will leave the Standard Treatment Protocol if deemed necessary by the site attending physician.*

Pathway C.

Subjects Now Receiving Combined Steroid and Pentasa Therapy, Steroid Commenced or Tapered Last Week

Timing	Level of response	Recommended Action*,**	Remain on Std Treatment Protocol
1 week of combined therapy (minimum of 3 weeks of steroid therapy)			
	Steroid Responsive (PUCAI same or less than score last week)	Continue Pentasa Commence Steroid taper (Table 2, reduce dose to step #1, and then reduce by one step per week unless patient deteriorates)	Yes
	Potential Pentasa Intolerance (PUCAI increased but by < 15 points from last week)	Continue Pentasa Continue Steroids at present dose Review in one week	Yes
	Likely Pentasa Intolerance (Worsening Disease) (PUCAI increased by ≥ 15pts from previous week)	Consider Pentasa Intolerance Cease Pentasa. Move to Pathway F Ongoing steroid, rescue and second-line therapies are at the discretion of the physician	No
2 to 4 weeks of combined therapy, steroid taper occurred last week (minimum of 4 weeks of steroid therapy)			
	Remission (PUCAI <10)	Continue Pentasa Continue Steroid taper (Table 2, reduce dose by one step each week)	Yes
	Mild Worsening (PUCAI has increased by 0 to 19 points)	Continue Pentasa Do not taper Steroids	Yes
	Significant Worsening (PUCAI has increased by ≥ 20 points, but total PUCAI is < 65)	Increase steroid dose to the last dose at which the patient had <i>improvement</i> in symptoms Ongoing steroid, second-line and rescue therapy are at the discretion of the physician. Move to Pathway G	No
More than 4 weeks of combined therapy, steroid taper occurred last week (minimum of 6 weeks of steroid therapy)			
	Remission (PUCAI <10)	Continue Pentasa Continue Steroid taper (Table 2, reduce dose by one step each week)	Yes

	Mildly Active (PUCAI unchanged or reduced from last week but total remains between 10 to 34 points)	Continue Pentasa Do not taper Steroids Physician may consider rescue and/or second line therapy. Move to Pathway G	Yes (until rescue)
	Responsive but dependent Disease (PUCAI has increased from last week)	Increase steroid dose to the last dose at which the patient had <i>improvement</i> in symptoms - if the PUCAI decreases then recommence steroid taper, - if the PUCAI increases then consider rescue therapy. Introduction of second line therapy is at the discretion of the physician. Move to Pathway G	Yes (until rescue)

Pathway D.

Subjects Receiving Combined Steroid and Pentasa Therapy, Steroid Taper not yet Commenced or Currently on Hold

Timing	Level of response	Recommended Action*	Remain on Std Treatment Protocol
2+ weeks of combined therapy (minimum of 4 weeks of steroid therapy)			
	Improving, doing well (PUCAI now \leq PUCAI score at week 2)	Continue Pentasa Commence Steroid taper (Table 2, reduce dose to next step, and then reduce by one step per week)	Yes
	Deteriorating Disease (PUCAI now $>$ PUCAI score at week 2)	Ongoing steroid and second-line therapy are at the discretion of the physician. Move to Pathway G	No

5.3.4.1 Criteria to Institute Rescue Therapy

If the patient is corticosteroid refractory then rescue therapy should be instituted. The following criteria will establish the need to institute rescue therapy:

- The PUCAI continues to be ≥ 34 despite a minimum of 2-4 weeks of ≥ 1 mg/kg/day prednisone.
- Hospitalized patient with severe colitis (PUCAI ≥ 65) and failure to respond to intravenous CS within 7-10 days, or at the discretion of the attending physician rescue therapy with a calcineurin inhibitor or infliximab is warranted because of continued refractory/fulminant disease.

The choice of rescue therapy will be at the discretion of the attending physician. Section 5.3.4.3 details guidelines for use of such therapies to establish a standard-of-care amongst investigative centers.

5.3.4.2 Criteria to Institute Second Line Medical Therapy

If there is a lack of sustained response/remission with use of mesalamine as a maintenance agent, or if there is an adverse reaction to mesalamine preventing its use as a maintenance agent, then a second line medical therapy (either an immunomodulator or an anti-TNF agent) should be instituted. The following criteria will establish the need to institute second line medical therapy:

- Failure to wean prednisone below 0.5 mg/kg/day within 10 weeks of commencing corticosteroid therapy.
- Continued activity (PUCAI >10) and need for CS at weeks 12-24
- Clinical relapse within 6 months of initial successful weaning of prednisone
- Adverse reaction to mesalamine precluding further use

The choice of second line medical therapy will be at the discretion of the attending physician. Section 5.3.4.3 details guidelines for use of such therapies to establish a standard-of-care amongst investigative centers.

5.3.4.3 Guidelines when using Second Line or Rescue Medical Therapies

Immunomodulator (IM) therapy: Dosing of the thiopurines azathioprine (2.5-3 mg/kg/day) and 6-mercaptopurine (1-1.5 mg/kg/day) will be initiated assuming normal baseline thiopurine methyltransferase (TPMT) activity. If TPMT activity is intermediate the starting dose of azathioprine will be 1.25 mg/kg/day and the starting dose of 6-mercaptopurine will be 0.5 mg/kg/day. Subsequent measurement of 6-thioguanine metabolites will be at the discretion of the attending physician. Methotrexate dosage will be determined by the attending physician. All IM therapy administered will be recorded on the CRF. Patients who receive IM therapy will be considered treatment failures with respect to the study's primary outcome but will continue to be followed in the study for clinical outcomes as well as safety observations. Patients receiving IM will have regular monitoring of laboratory parameters (Table 5.3.4).

Biologic therapy (anti-TNF α agent): This therapy may be instituted if in the judgment of the attending physician immediate rescue therapy is warranted, or for non-fulminant disease in lieu of IM for CS-dependent/refractory disease. Prior to anti-TNF α therapy all patients will be screened for tuberculosis with either a PPD (5 units) or QuantiFERON-Tb test, and a chest radiograph. The dosage will be determined by the attending physician and recorded on the CRF. Patients who receive anti-TNF α therapy will be considered treatment failures with respect to the study's primary outcome but will continue to be followed in the study for clinical outcomes as well as safety observations. Patients receiving anti-TNF α therapy will have regular monitoring of laboratory parameters (Table 5.3.4).

Calcineurin Inhibitor (CI) therapy (cyclosporine, tacrolimus): This therapy may be instituted if in the judgment of the attending physician immediate rescue therapy is warranted. The dosage of these medications will be determined by the attending physician and recorded on the CRF. Patients who receive CI therapy will be considered treatment failures with respect to the study's primary outcome but will continue to be followed in the study for clinical outcomes

as well as safety observations. Patients receiving these medications will have regular monitoring of laboratory parameters (Table 5.3.4).

Table 5.3.4 Laboratory tests to be monitored following institution of Second-line or Rescue Therapy

Lab Test	Baseline (Week 0)	Week 1	Week 2	Week 4	Week 8	Every 8-12 weeks
TPMT activity*	For thiopurine treated patients only					
Amylase/Lipase*	X		X	X	X	X
CBC, differential	X	X	X	X	X	X
AST/ALT	X		X	X	X	X
BUN/CR†	X		X	X	X	X
Drug levels (cyclosporine, tacrolimus) †		X	X	X		X

* Only for those on immunomodulator therapy

† Only for those on CI therapy

5.3.5 Concomitant (Ancillary) therapy

Rectal therapy: Rectal therapy with either 5-ASA suppositories/enemas or hydrocortisone suppositories/enemas/foam will be allowed at the discretion of the physician for any patient and will be recorded on the CRF.

Probiotics/Fish oil: Probiotic therapy or fish oil will not be given per protocol. The use of these preparations will be discouraged. If a patient is reported to be receiving either probiotics or fish oil that will be noted on the CRF and the patient will continue to be followed.

Other medications: Anti-diarrheal medications (loperamide, diphenoxylate HCl) will not be allowed for 48 hours prior to each determination of a PUCAI score. Their use at other times will be recorded on the CRF. Patients will be prohibited from taking concomitant aspirin, non-steroidal anti-inflammatory agents (NSAIDs), as well as other products containing, or metabolized to mesalamine (e.g., sulfasalazine, olsalazine, balsalazide). Vitamin D supplementation can be given at the discretion of the site investigator based on locally determined serum Vitamin D levels and customary practice. The use of supplemental Vitamin D and dose will be recorded on CRFs. Other preparations such as iron, multivitamins, and calcium will be used at the discretion of the prescribing physician.. If a patient has been receiving an antibiotic for a presumed enteric infection and cultures are negative at the time of initiation of standardized therapy then the antibiotic will be discontinued at that time.

5.3.5.1 Record of Therapy

All exposure to 5-ASA (oral and rectal), corticosteroids (oral and rectal), IM, anti-TNF α and CI therapies that occurs during the study will be recorded on the CRF. Data will be collected at all encounters, both scheduled and ad-hoc, in person or via telephone. Exposure to listed

concomitant therapies will be recorded only at scheduled in-clinic study visits. Other therapies or drug exposures will not be recorded.

Table 5.3.5.1: CRFs required to record therapy

<u>Drug Name</u>	<u>Timing of Data Point</u>	<u>CRF</u>
5-ASA		
	Day 0 (treatment initiation)	STZ
	All Subsequent Encounters	SMF + AMT (AMT also required if after Week 52 and 5-ASA is not Pentasa)
Corticosteroids		
	Day 0 (treatment initiation)	STZ + STR
	All Subsequent Encounters	SMF + STR
IM		
	Not prescribed on Day 0	
	All Subsequent Encounters	AMT + SLR
Anti-TNF α / CI		
	Not prescribed on Day 0	
	All Subsequent Encounters	AMT + SLR
Additional Medical Therapy		
	Day 0 (treatment initiation)	AMT
	All Subsequent Encounters	AMT
Concomitant - Ancillary Meds (Supplements, antibiotics, Other, VitD)		
	Day 0 (treatment initiation)	ATZ
	Scheduled Follow-up Review Only	ATF

Note: These CRFs are further described in the Day Zero MOP Chapter 4 – and the Follow-up Chapter 6,

5.4 DRUG PROCUREMENT

Pentasa will be shipped from Shire Pharmaceuticals to the clinical coordinating site at Connecticut Children’s Medical Center. It will be stored in a secure, locked area under CCMC supervision and dispensed to the study sites by a CCMC pharmacist. Each site’s supply of Pentasa will be communicated to the clinical coordinating center and then the CCMC pharmacy to ensure adequate study drug is always available.

Pentasa will be provided to all eligible study patients taking Pentasa for up to 1 year from the initiation of therapy. It will be dispensed to the patient by the site pharmacy (if available) via the site research coordinator. At the time of initiation of therapy or if a patient started on prednisone is seen back at 2 weeks then an amount of drug for the initial 2-4 weeks will be dispensed. If the Investigator believes that there is a good chance that a participant could switch to Pentasa at the 2 week phone visit, it is okay to let the family take Pentasa home at the day zero visit with

instructions to wait until the 2 week call to start medication. At the week 4 visit drug will be dispensed for the next 8 weeks. At the week 12, 26, and 39 visits enough drug will be dispensed to last until the next scheduled visit. To ensure enough drug is dispensed it is advised that a few extra days worth of medication be included in case a scheduled visit is unexpectedly delayed.

5.4.1 Description of study drug

Pentasa controlled release 500 mg capsules are supplied in bottles of 120 capsules. Pentasa controlled release capsules are identified with a pentagonal starburst logo and Pentas 500mg or S429 500 mg on the capsules.

5.4.2 Storage

Pentasa should be stored at 25 degrees Celsius/77 degrees Fahrenheit with excursions to 15-30 degrees Celsius or 59-86 degrees Fahrenheit permitted.

5.4.3 Distribution to the clinical centers

Adequate study drug will be shipped from the Clinical Coordinating Center at Connecticut Children's Medical Center to each investigative site. Adequate drug will be sent to each site at the start of the study for approximately 6 patients. The site coordinator will work closely with the Clinical Coordinating Center to ensure adequate drug for current and new patients entered in the PROTECT study. Receipt of study drug will be acknowledged by the site study coordinator to the Clinical Coordinating Center.

5.4.4 Study drug storage

The study drug will be stored at the institutional pharmacy (if available) at each participating center. At sites with a pharmacy, the site coordinator will work with the pharmacy to acquire study drug for each patient.

5.5 MEDICATION ADHERENCE

Adherence will be measured on Pentasa use only. This will be done both by pill counts (pills dispensed and pills returned) at each appropriate contact, and by use of the Medication Event Monitoring System (MEMS Caps). The use of MEMS caps will not begin until the 4 week clinic visit. Refer to Appendix A Pharmacy and Coordinators Mesalamine (Pentasa) User's guide for subject specific product dispensing/return log and medical accountability record.

Please refer to the the MOP Follow-up Chapter 6 for further information on medication adherence and use of the MEMS caps.

Chapter 6: Follow-up

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Chapter 6: Follow-up

6.1 OVERVIEW

Follow-up data collection is conducted for a minimum of 1 year to a maximum of 5 years depending upon the actual time of enrollment. The first year of data collection follows a more frequent scheduling of telephone and clinic contacts, followed by biannual assessments as long as the patient is followed in the study.

Data is collected during both protocol specific clinic visits and telephone contacts. In addition, it is anticipated that there will be both unscheduled telephone and clinic visit contacts outside the protocol specified contacts. Data collection requirements for participant assessments during follow-up are detailed in this chapter.

Medication re-supply during the first year of follow-up will be important, and may not correspond to the follow-up assessment scheduling.

6.2 SCHEDULING FOLLOW-UP CONTACTS

Follow-up procedures will continue for each participant regardless of medication compliance, treatment failure (requiring rescue therapy) or study outcome. Follow-up procedures will cease only if a participant's diagnosis is changed to Crohn's disease or they are lost to follow up.

Upon completion of baseline data entry and diagnosis confirmation at Day 0 when treatment begins, the Coordinator should run the Scheduling Visit Report in the DMS. This report will include the target dates and windows for follow-up telephone calls and clinic visits. The report can be given to the participant and family for future scheduling/planning and generated for the Coordinator's files.

When scheduling clinic visits, the Coordinator should verify that the study clinic investigator or physician is available to perform any necessary examinations during scheduled contacts.

6.2.1 Target Dates and Contact Windows

The PROTECT Follow-up Schedule is presented in Table 6.1, along with target dates. The reference date that calculates a participant's target date for all follow-up contacts is the date that the study treatment was initiated (day 0) based on the Enroll Day Zero (EDZ) form's date.

Contact windows for the 2 through 4th week contacts are +/- 3 days around the target. Windows for the 12 week visits are +/- 7 days, windows for 26 and 29 week visits are +/- 14 days, and windows for the 52 week contacts are +/- 4 weeks. The window for annual visits after 52 weeks is +/- 4 weeks.

The Coordinator should make every attempt to schedule protocol contacts within the contact windows for the participant's target dates. However, there may be instances when this is not possible. Although not preferred, rather than miss a contact and the data collection, protocol contacts can be scheduled outside the target date window if necessary. , If a clinic visit cannot be scheduled within the target window, a phone contact should be made within the target window so that a phone PUCAI can be obtained. Care should be taken to not schedule two clinic contacts too close together. If needed consult the DCC regarding scheduling outside of the contact windows.

When a participant contact (clinic visit or telephone) cannot be scheduled before the next required contact, then it must be considered skipped (i.e. there will be no data collected for this contact occasion). If a contact is skipped, the Follow-up Data Form (FDF) for that expected visit must still be entered in the DMS as a permanently missing form (refer to Chapter 10 Data Management and Administrative Procedures) indicating that that contact occasion was missed.

Special care should be taken to schedule the first years contacts, as data and specimen collection at these time points are critical to the study’s main hypothesis.

6.2.2 Contact Occasion Numbers, Sequence Numbers, and FDF Numbers

Each protocol scheduled contact has an associated contact occasion number (CO#). Table 6.1 below shows the CO#s associated with patient scheduling. For unscheduled follow-up contacts made between protocol scheduled contacts, the rule for numbering is to use the previous CO# starting with CO:03.

All follow-up contacts begin with the Follow-up Data Form (FDF) form. However, all follow-up contacts will not always collect the same set of data forms. In order to track these forms collected together, we use the FDF#. The FDF# is incrementally sequenced within a CO# (beginning with 01). This FDF# should be recorded on all the other forms headers that are collected during this contact.

The Sequence Number (SEQ#), is independent of the FDF#, and is specific to each individual form. It provides a unique record in the DMS when more than one form is collected within a CO#. This is also incrementally sequenced within a CO# (beginning with 01).

For patients who undergo a colectomy, enter the contact where it would fall if they were a regular participant following the normal follow up schedule.

Please refer to Chapter 10 Data Management and Administrative Procedures, for detailed procedures on assigning CO#s and SEQ#s, and FDF#s. Do not hesitate to contact the DCC if you have any questions.

Table 6.1: Follow-up Contact Schedule

Follow-up Contact	Contact Number	Type of Contact	Target Date	Target Window
Day 0	02		Date entered i.e. June 15, 2012	
2 weeks	03	Telephone Call	Calculated i.e. June 29, 2012	+/- 3 days of target i.e. June 26 – July 2, 1012
4 weeks	04	Clinic Visit Specimen collection	calculated	+/- 3 days of target
12 weeks	05	Clinic Visit Specimen collection	calculated	+/- 7 days of target

26 weeks	06	Clinic Visit	calculated	+/- 14
39 weeks	07	Clinic Visit	calculated	+/- 14
52 weeks	08	Clinic Visit Specimen collection	calculated	+/- 4 weeks
78 weeks	09	Clinic Visit	calculated	+/- 4 weeks
2 yrs.	10	Clinic Visit	calculated	+/- 4 weeks
3 yrs.	11	Clinic Visit	calculated	+/- 4 weeks
4 yrs.	12	Clinic Visit	calculated	+/- 4 weeks
5 yrs.	13	Clinic Visit	calculated	+/- 4 weeks

6.2.3 Scheduling Reminders

Attempt to schedule protocol telephone contacts at the previous call or visit. Two to three days before the scheduled contact, the Coordinator should call or leave a message as a reminder of the upcoming call.

Clinic visit reminder calls are also necessary. Once a participant is at 12 weeks of follow-up, clinic contacts occur about every 3 months the first year, and then annually. Reminder calls should be made two to three weeks before the follow-up clinic visit. The Coordinator should remind the parent/guardian to bring in the Participant Passport (Handbook/Diary), stool sample if required, all study medication bottles (used and unused), MEMS caps, as well as any current medication the child is taking.

These reminder calls should be followed up with another call two to three days before each follow-up clinic visit. Again, the Coordinator should remind the parent/guardian to bring in the Participant Passport (handbook/diary), stool sample if required, all study medication bottles (used and unused), MEMS caps, as well as any current medication the child is taking.

6.3 GENERAL FOLLOW-UP PROCEDURES

6.3.1 Site Scheduling Report

The Coordinator will have a participant scheduling report that indicates a specific participant's follow-up schedule throughout the study. The DMS has two reports that can help with scheduling. The Participant Follow-up Contact Schedule lists all target windows by participant and the Clinic Contact Schedule lists all visits that should be scheduled within a given time frame.

6.3.2 Participant Missing Forms and Data Queries Report

The PROTECT DCC will generate a monthly report on missing forms, data, and general queries for all participants at each site.

6.3.3 Passport: Participant Handbook/Diary

At baseline, each participant's parent/guardian will be given a participant passport and a follow-up schedule. The passport provides a summary of procedures associated with the follow-up contacts, and also functions as a diary for recording illnesses, non-study medical care visits and changes in concomitant medications that need to be reported to the Coordinator at each follow-up contact. Other important contact information and instructions are also documented in the passport. (Please note, page #9 of the July 11, 2012 version of the passport contains an error regarding week 12 visits. The passport states that families should be completing questionnaires at week 12 but, questionnaires should only be completed at baseline (up to week 4) and again at weeks 52 and 104.)

6.3.4 Modification of Informed Consent

A participant/parent may modify their Informed Consent at any time during the follow-up period. If a participant/parent indicates a change in their consent to participate in the study, the Coordinator needs to complete an Informed Consent Tracking Form (ICT).

6.4 FOLLOW-UP ASSESSMENTS

6.4.1 Telephone Contacts

Telephone contacts occur early in the study during the CS tapering schedule. In addition unscheduled telephone contacts initiated by the participant/family during the follow-up period may be expected.

Study nurses or Coordinators will obtain a PUCAI score by patient report (PUC form), query for any adverse events, assess adherence monitoring, and help to monitor any treatment needs.

Mandatory telephone contacts for all enrolled participants are made by the Study Coordinator at follow-up week 2. Additional calls at weeks 6, 8, and 10 are required only for participants on steroids. These would all fall under CO:04.

Upon completion of one telephone follow-up contact, the date of the next follow-up (telephone or visit) contact should be confirmed.

6.4.2 Clinic Visits

The first protocol scheduled clinic visit occurs at 4 weeks.

All clinic visits require a PUCAI be administered by the study physician, this score will be used as the study outcome data.

Additional data required at clinic visits include collecting information regards ancillary treatments, clinical status, adherence, and standard of care laboratory monitoring. Depending on the visit (see visit scheduling table above), central laboratory specimen collection might be required. Use of the Follow-up Data Form (FDF) and the Clinical Data Follow-up Form (CDF) will guide the Coordinator on the data collection protocol for these visits.

6.4.3 Unscheduled Visits and Calls

In addition to protocol scheduled contacts, unscheduled calls and visits are likely. Use of the Follow-up Data Form (FDF) will guide the Coordinator on the data collection protocol for these visits.

6.4.4 Adherence

Adherence to Pentasa use is monitored 1) by pill counts from the Subject Specific Product Dispensing/Return Log and the Medication Accountability Record found in Appendix A (distributed and returned) that are recorded on the Standard Medical Therapy Follow-up Form (SMF) and 2) with the use of MEMS caps beginning by the week 4 follow-up.

MEMS data should be collected from the cap each time the participant brings in the medication bottle with MEMS cap. MEMS caps should be provided to participants with the first distribution of Investigational Product (Pentasa). PROTECT requests that all pills and MEMS caps are returned at each follow up clinic visit so that pills can be counted during the visit and MEMS data downloaded. Based on the adherence results provided from the MEMS cap download, adherence counseling may be necessary. Refer to the attached **MEMS Cap Instructions** guide for information on setting up the MEMS caps, dispensing and reading the MEMS caps during Year 1, and closing out a participant's MEMS cap at the end of Year 1. Refer to the MOP appendices regarding the software and reporting facilities using the medAmigo software for MEMS. Refer to the SMF QxQ and Appendix A - Mesalamine Guide for further information on accountability.

6.4.5 The Week 4 Follow-up Clinic Visit

Week 4 is a critical anniversary visit for PROTECT participants. It is important this clinic visit be conducted within +/- 3 days of the target date. If circumstances prevent this from happening then a phone based PUCAI should be obtained at the Week 4 target date. The week 4 PUCAI score is critical for the evaluation of several of the study's endpoints .

Scheduling PROTECT Week 4 Visits

The Coordinator should call the family a day or two before the week 4 visit to remind the parent/guardian to bring in the Participant Passport, stool sample, all study medication bottles (used and unused), MEMS cap(s) and any current medication the child is taking (if applicable). If the Coordinator has not yet dispensed the Pentasa and MEMS caps, they should do so at the week 4 visit if the participant is to take Pentasa.

Week 4 Specimen Collection

Week 4 is a critical specimen collection visit. All participants should have stool and blood (P100 orange top tube) collected at Week 4. **If circumstances prevent the participant from coming in for a clinic visit at week 4, the family should be notified to collect stool at home to keep it in their freezer until their next scheduled or unscheduled visit.** The participant should record the date the stool was passed from the patient's body on the specimen collection tube provided as this will be the "date collected" on section C question # 7b of the Specimen Collection Form (SCF). Copies of the SCF should be included with each shipment of specimens as an inventory of the contents of the shipment.

Please refer to Chapter 7 of the MOP for further details on specimen collection.

Week 4 Questionnaires

Baseline questionnaires should be complete by the week 4 visit. BASC and IMPACT questionnaires are required for ALL participants. If a participant has not yet completed their baseline questionnaires by the time of their week 4 clinic visit, the coordinator should have the participant complete the questionnaires during the week 4 visit either online or on paper. If participants complete the questionnaires on paper and/or get locked out of the online system, the coordinator should e-mail scanned PDFs of completed paper copies as soon as they are completed to CCHMC via the e-mail address: protectstudy@cchmc.org.

6.4.6 The 52nd Week Follow-up Clinic Visit

Week 52 represents the time of the primary clinical outcome of the PROTECT study. It is important that this visit be conducted within a 4 week window of the actual Week 52 date. If circumstances prevent this from happening then a phone based PUCAI should be obtained at the Week 52 date and a visit conducted as close as possible with collection of biospecimens. In addition to the standard data collection procedures, a flexible sigmoidoscopy will be offered to study participants at week 52 to assess for mucosal healing. Participants should be in clinical remission and receiving mesalamine only to be eligible. Parents or legal guardians of PROTECT participants should be invited to provide consent for this sigmoidoscopy at week 52 of follow-up (or a few weeks earlier if possible). Assent will also need to be obtained from the participant when appropriate based on age and institutional IRB requirements. The 52 week sigmoidoscopy should be done within a month of the 52 week follow-up data collection.

Participants who have undergone colectomy prior to the Week 52 visit are on a different follow-up schedule; please refer to section 6.4.8 entitled Post-Colectomy Monitoring for details. The following information refers to participants who have not had a colectomy and will have a Week 52 visit.

Scheduling PROTECT Week 52 Visits

When scheduling the week 52 visit, the Coordinator should verify that the study clinic investigator or physician is available to perform any necessary examinations. A reminder call should be made two to three weeks before the week 52 clinic visit and then again two to three days before the scheduled visit date. The Coordinator should remind the parent/guardian to bring in the Participant Passport (Handbook/Diary), stool sample, all study medication bottles (used and unused), MEMS cap(s) and any current medicines the child is taking.

Do not hesitate to contact the DCC, CCC or repository if you have specific questions on scheduling week 52 assessments, data or specimen collection.

Week 52 Specimen Collection

Week 52 Stool and Blood:

All participants should have stool and serum collected at Week 52 regardless of their therapy to date and regardless of clinical activity. Urinalysis should be completed on a yearly basis if the patient has been taking Pentasa. If at Week 52 the participant has an intercurrent infection (e.g., *Clostridium difficile*) or is sick with another illness please check with the Medical Monitor about timing of Week 52 biospecimens.

Week 52 Biopsies:

Participants may undergo endoscopic examination at Week 52 because it is the standard of care at that site, or because the participant has consented for a Week 52 optional flexible sigmoidoscopy. PROTECT will reimburse the site for a Week 52 optional flexible sigmoidoscopy. Standard of care colonoscopy will be billed to the participant's insurance carrier.

Participants who meet the following criteria are eligible for the Week 52 optional flexible sigmoidoscopy:

- Participant is taking Pentasa
- No rescue therapy has been received and participant has not undergone colectomy
- Participant is in clinical remission
- Participant has not taken steroids for at least the past two weeks

For any participant having a Week 52 endoscopic examination it is requested that following consent biopsy specimens be obtained from the rectosigmoid. Tubes for these biopsies can be obtained from the Kit Week 52 with biopsies. Collect 4 biopsies from the rectum. Put three biopsies in the orange-top cryogenic vial containing RNALater and put one biopsy in the 7mL vial containing formalin. Affix barcode labels on each tube/vial.

Cryogenic vials for RNALater may be shipped frozen. Formalin vials must be shipped at room temperature.

All specimen collection is documented on the Specimen Collection Form (SCF). Please use the Participant ID label with barcode on all SCF forms. Copies of this form are to be included with each shipment of corresponding specimens as an inventory of the contents of the shipment. Please refer to the lab manual and SCF QxQ for more detailed instructions.

One image of the most affected area of the rectosigmoid should be uploaded to the PROTECT website. If the mucosa is normal then a photo from any place in the rectum or sigmoid is acceptable.

Standard of Care (SOC) / Additional Clinically Indicated Colonoscopy

If a patient undergoes a colonoscopy during the study course that the attending clinician deems needed for clinical care decisions then consent to obtain 4 additional rectal mucosal biopsies for study purposes. Consent for this additional biopsy material may be separate from consent for the study. Assent will also need to be obtained from the participant when appropriate based on age and institutional IRB requirements.

Invoicing for Week 52 vs. Standard of Care biopsies

If the endoscopy procedure is done under the study then PROTECT will pay a stipend to your center. If the procedure is done as standard of care it should be billed through normal insurance. If the participant's insurance was billed for a standard of care colonoscopy at week 52 at the request of their doctor, the study cannot reimburse the \$1200 stipend as this is only billed if it is done for research purposes only. If it's standard of care, you should re-consent the participant with the Standard of Care consent form (from the version 4 protocol amendment dated March 11,

2013) to request standard of care biopsies (versus the week 52 consent) and invoice CT Children's Medical Center for the \$50 biopsy charge.

PROTECT will not be providing information from the biopsies collected. If your institution wants to independently send specimens to your pathology department, then it will be charged to insurance. PROTECT can only reimburse week 52 flexible sigmoidoscopies up to a maximum of \$1200 if the patient qualifies.

Week 52 Questionnaires

Questionnaires at week 52 are required for ALL participants, including colectomy participants. BASC measures should be completed within +/- 2 weeks of the 52 week visit date. If participants get locked out of the system, the coordinator should send completed paper copies to CCHMC (protectstudy@cchmc.org).

Week 52 Visit Data Forms

Coordinators should begin the week 52 contact with the Follow-up Data Form (FDF), this form has questions that trigger 'as needed' forms. The FDF and Clinical Data Follow-up Form (CDF) will guide the Coordinator on the data collection protocol for week 52 visits. A PUCAI will be administered by PROTECT study staff and used as the study outcome data.

Additional data required at the week 52 visit includes collecting information regarding ancillary treatments, clinical status, adherence, standard of care laboratory monitoring, urinalysis if the patient has been taking Pentasa, central laboratory specimen collection, and information about the flexible sigmoidoscopy, if applicable.

Table 6.2: Summary of Data Collection during Week 52 visits

Week 52 Data Collection Forms required:

FDF Follow-up Data Form
*CDF Clinical Data Follow-up Form (if clinic contact)
PUC PUCAI
SEF Side Effects / Adverse Events Form
SMF Standard Medical Therapy Form
SCF Specimen Collection Form

Forms that will be triggered for a flexible sigmoidoscopy:

EEF Endoscopic Evaluation Form
*DED Disease Extent Data Form
*SBH Site Biopsy Histology Form

** If your participant undergoes a week 52 flex sig but no results are obtained from the site pathologist because this was performed for research purposes only, CDF questions 3a, 3b, 4a, or 4b cannot be answered but this form must be completed in order to trigger the DED form.*

CDF question 2 –answer YES

CDF question 3 –answer YES; then answer 'Unknown' to questions 3a and 3b

CDF question 4 –answer YES; then answer ‘Unknown’ to questions 4a and 4b

For questions 3 and 4, add a notelog into the DMS explaining results were not sent to the site pathologist.

The DED must be completed for all flexible sigmoidoscopies. DED question #3, select ‘lower endoscopy (option 3b)’ then enter N/A for questions 4a-4j, please provide an assessment for 4k and 4l.

If no results were obtained from the site pathologist, enter the SBH as permanently missing in the DMS.

Additional Forms that might commonly be triggered:

AMT Additional Medical Therapy Form
ALF Additional Lab Results Form
ATF Ancillary Treatment Follow-up Form
MEF Medical and EIM Follow-up Summary Form
SEG Side Effects / General Form
STR Steroid Treatment Record

Forms less commonly used:

CLF Colectomy Data Form
ICT Informed Consent (if consent modification)
HDF Hospitalization Data Form
SAE Serious Adverse Events Form
SLR Second Line / Rescue Therapy
PCF Post-Colectomy Follow-up Form
SWF Study Withdrawal Form

Adherence, Medication and MEMS at Week 52

Pentasa adherence is monitored by pill counts (distributed and returned) that are recorded on the Standard Medical Therapy Follow-up Form (SMF) and with the use of MEMS caps. Pentasa is provided free of charge to each participant participating in this clinical protocol until the 52 week outcome assessment is completed or until it is discontinued prior to 52 weeks. After the week 52 assessment is completed, the treating physician should write a prescription to continue Pentasa and document on the SMF. If the physician decides to switch to another 5-ASA after 52 weeks then the new prescribed therapy should be recorded on the Additional Medical Therapy Form (AMT). A Standard Medical Therapy (SMF) form should also be completed.

MEMS data should be collected from the cap each time the participant brings in the medication bottle with MEMS cap. At the week 52 assessment the coordinator should read the last dosing history of MEMS data via MedAmigo. At week 52 the coordinator will close a participant out of the MedAmigo system by selecting the participant from the participant list and selecting “close patient” from the list on the left-hand side of the MedAmigo screen. For participants completing the week 52 assessment, the coordinator will select, “Patient ended the MedAmigo service definitely” and select the appropriate reason. For most instances the reason will be “others.” The

participant should return the MEMS cap to the coordinator after the week 52 assessment. MEMS caps will be collected and/or destroyed at the end of study.

6.4.7 Post 52 Weeks of Follow-Up.

Participants are followed for up to 5 years depending on their enrollment date. Participants will be seen at 78 and 104 weeks, then annually for 2-5 years of follow-up. The data collection differs for these visits. No specimens are obtained after week 52 unless there is a clinically indicated colonoscopy. Please refer to table 6.1 for the schedule of visits and assessments.

Although study-related specimens are no longer collected post-week 52, standard clinical care urinalysis is required per protocol at baseline, week 26, week 52, week 104 then annually thereafter up to 5 years for patients on Pentasa. As part of the study IND, the FDA mandates that patients on mesalamine have a yearly urinalysis as part of their routine clinical care. This can simply be performed in the clinic by dipstick--urine does not need to be sent to a lab. Results of urinalysis should be recorded on the CDZ and CDF to document blood and protein in the urine. Routine blood monitoring and questionnaires are required at 104 weeks. Routine blood monitoring should occur annually post week 52 per the investigator's routine practice.

Table 6.3: Post Week 52 Data Collection Forms

Form	Scheduled Study Visits (weeks 78, 104 and annual 3-5 years)	Unscheduled Visits Post Week 52
FDF Follow-up Data Form	Yes	Yes
CDF Clinical Data Follow-up Form (if clinic contact)	Yes	Yes
PUC PUCAI	Yes	Yes
LLR Local Lab Results	Yes (annual visits only)	No
	AS NEEDED	AS NEEDED
SMF Standard Medical Therapy Form	Yes	Yes
STR Steroid Treatment Record	Yes	Yes
SLR Second Line / Rescue Therapy	Yes	Yes
AMT Additional Medical Therapy Form	Yes	Yes
ALF Additional Lab Results Form	Yes	No

MEF	Medical and EIM Follow-up Summary Form	Yes	Yes
SCF	Specimen Collection Form	Only needed for SOC biopsies	Only needed for SOC biopsies
DED	Disease Extent Data Form	Yes	Yes
EEF	Endoscopic Evaluation Form	Yes	Yes
ICT	Informed Consent (if consent modification)	Yes	Yes
HDF	Hospitalization Data Form	Yes	Yes
CLF	Colectomy Data Form	Yes	Yes
PCF	Post-Colectomy Follow-up Form	Yes	Yes
ATF	Ancillary Treatment Follow-up Form	Yes	Yes
SAE	Serious Adverse Events Form	Yes	Yes
SWF	Study Withdrawal Form	Yes	Yes
BASC and IMPACT		Year 2 only	No
SEF	Side Effects / Adverse Events Form	No	No
SEG	Side Effects / General Form	No	No

Table 6.4: Follow-up Contact Schedule Post Week 52

Follow-up Contact	Contact Number	Type of Contact	Target Window
52 weeks	08	Clinic Visit Specimen collection	+/- 4 weeks
78 weeks	09	Clinic Visit	+/- 4 weeks
2 yrs.	10	Clinic Visit	+/- 4 weeks
3 yrs.	11	Clinic Visit	+/- 4 weeks
4 yrs.	12	Clinic Visit	+/- 4 weeks
5 yrs.	13	Clinic Visit	+/- 4 weeks

6.4.8 Post-Colectomy Monitoring

When a colectomy occurs, the participant is still followed for PROTECT but, the schedule will no longer follow the standard protocol anniversary visits (weeks 4, 12, 26, 39.), with the exception of the week 52 visit rather, PROTECT colectomy participants will have visits approximately every 6 months to document issues that arise from the procedure, to collect blood and stool specimens at anniversary visits and document questionnaires. All patients should have a week 52 visit.

When the colectomy initially takes place the Colectomy Data Form (CLF) should be completed (within 30 days of the procedure) along with an SAE. The CLF asks questions like: “Why did it happen?”, “What was the type of operation?”, “Were there complications in the first 30 days or after that?” etc. The CLF is a working form and can be updated as the participant has additional visits.

After the initial colectomy (within 6 months of the procedure), the Post-Colectomy Follow-up Form (PCF) and other applicable forms should be completed upon return visits as the participant has subsequent operations or other issues such as pouchitis. A new PCF should be completed throughout the study at six month intervals. Specimens and questionnaires should still be obtained from colectomy participants as close to the anniversary visit window as possible. For more specific details, please refer to the PCF QxQ.

Table 6.5: Colectomy Data Collection Forms required:

Initial colectomy:

- Colectomy Data Form (CLF)
- Serious Adverse Event Form (SAE)
- Hospitalization Data Form (HDF)

Post-colectomy:

- Post-Colectomy Follow-up form (PCF)
- Serious Adverse Event Form (SAE)
- Hospitalization Data Form (HDF)
- Specimen Collection Form (SCF)
- BASC Questionnaires (BASC)
- IMPACT-III (IMP)
- Ancillary Treatment Follow-up Form (ATF)
- Standard Medical Therapy Follow-up Form (SMF)
- Second Line/Rescue Therapy Form (SLR)

6.5 FOLLOW-UP PROCEDURES AND DATA COLLECTION

The tables below summarize the procedures and data collection forms used during participant follow-up in the PROTECT study. Some forms must be completed at specific telephone and/or

clinic contacts. Others are completed or updated on an “as needed” bases during follow-up. The Follow-up Data Form (FDF) is designed to be used at all participant contacts and will have questions that trigger ‘as needed’ forms.

Table 6.6 lists the forms used during follow-up. Specific attention is needed as the requirements are not the same for each follow-up contact. All follow-up contacts begin with the FDF form. Those with clinic visits include the Clinical Data Follow-up Form (CDF). The PROTECT study website contains a PDF of a form-set of those forms most used at a follow-up contact.

The table lists forms required at all contacts, forms commonly triggered for use, and forms less commonly used on an “as needed” basis throughout the study or for “unscheduled clinic visits”.

Triggered forms are those needed based on other data collection or responses given during the required data collection, and are based on the participant’s status in the study at a particular time. PDF documents of each of these forms are available on the PROTECT study website for printing as needed.

Refer to Chapter 9 “Data Management and Administrative Procedures” regarding participant IDs, ID labels, and additional information on completing the header information, and determining the appropriate contact occasion and sequencing number. This is particularly important for ad hoc forms.

All data collection during an assessment visit should be entered into the DMS within 5 days of the participant visit.

Table 6.6: Summary of Data Collection during Scheduled Follow-up Contacts

Follow-up Procedures required:

- PUCAI
- Assessment of current disease
- Record of medical therapy
- Documenting laboratory or specimen collections
- Clinical assessment (if clinic visit)
- Current diagnostic findings (if clinic visit)
- Physician assessment of disease activity (if clinic visit)

Data Collection Forms required:

FDF Follow-up Data Form
PUC PUCAI
SEF Side Effects / Adverse Events Form
SMF Standard Medical Therapy Form
LLR Local Lab Results

Additional Forms that might commonly be triggered for use at follow-up contacts:

AMT Additional Medical Therapy Form
ALF Additional Lab Results Form
ATF Ancillary Treatment Follow-up Form
CDF Clinical Data Follow-up Form (if clinic contact)
MEF Medical and EIM Follow-up Summary Form
SCF Specimen Collection Form (Wk4, Wk12, W52)

SEG Side Effects / General Form
STR Steroid Treatment Record

Forms less commonly used at follow-up contacts:

CLF Colectomy Data Form
DED Disease Extent Data Form
ICT Informed Consent (if consent modification)
HDF Hospitalization Data Form
SAE Serious Adverse Events Form
SLR Second Line / Rescue Therapy
PCF Post-Colectomy Follow-up Form SWF Study Withdrawal Form

6.6 FOLLOW-UP DATA FORMS

6.6.1 Follow-up Data Form (FDF)

The FDF is to be used for all protocol scheduled and unscheduled contacts, and triggers the need for other data reporting based on adverse events reported, and the status of study treatment, use of steroidal treatment, and rescue treatment.

6.6.2 PUCAI (PUC)

A PUCAI score is obtained by a study nurse or coordinator during telephone contacts, and by a study physician using the PUC form at each clinic visit. It is based on information they have directly obtained by patient interview or during clinical evaluation of the participant at that visit. All questions on this form are relevant, be sure to answer each question.

6.6.3 Clinical Data Forms

The Clinical Data Follow-up Form (CDF) is used at all clinic visit contacts and collects basic anthropometric data, the physician's assessment of the participant's disease state, continues to confirm the UC diagnosis, and documents whether the participant has undergone a colectomy.

The Medical and EIM Follow-up Summary Form (MEF) provides a continued medical history of the participant through the use of a simple checklist of EIMs and additional medical diagnosis.

6.6.4 Study Treatment Forms

Treatment forms are triggered by the Follow-up Data Form (FDF) and include data collection regarding study medication on the Standard Medical Therapy at Follow-up Form (SMF) and second line therapy on the Second Line/Rescue Therapy Form (SLR). The SMF form will trigger the Steroid Treatment Record Form (STR) if steroid use is reported.

Refer to Chapter 5: Treatment for all information on the treatment algorithm, Pentasa dosing, and steroid tapering. There are standardized therapy worksheets, and criteria and guidelines for using second line or rescue medical therapies, as well as concomitant ancillary therapy.

6.6.5 Ancillary Treatment

Concomitant Medications are captured in the Ancillary Treatment at Day Zero (ATZ) and Ancillary Treatment Follow-Up Form (ATF) using a simple checklist capturing information

about current and pre diagnosis use of specific daily supplements, antibiotics, and other specified medications of interest.

6.6.6 Adverse Event Forms

Data collection regarding adverse events and side effects, and serious adverse events are collected on the SEF, SEG, and SAE forms. These forms are triggered by the Follow-up Data Form (FDF). Please refer to and become familiar with Chapter 8: Participant Safety and Adverse Events for study definitions and reporting requirements.

6.6.7 Specimen Collection and Laboratory Forms

Table 6.7 provides the specimen collection schedule during follow-up.

Local laboratory ‘standard of care’ blood and urine monitoring is done at all clinic visits. Data from the local lab reports are to be transcribed/entered into the Local Lab Results Form (LLR) when results are received.

Additional study blood, stool, and rectal mucosal biopsy specimens will also be collected at specified follow-up contacts, and sent to the PROTECT Central Laboratory at Emory University. Specific instructions on their collection, processing, shipping, and inventory forms are detailed in MOP Chapter 7 “Specimen Collection.” The chapter contains a detailed User’s Guide for laboratory specimen collection, processing, and shipping.

All specimen collection is to be documented on the Specimen Collection Form (SCF). Specific to this form is the use of the Participant ID label with barcode to be placed in the form header, and the use of the specimen ID labels (provided by the lab in the lab kits) which also document the collection of specimens on this form. This form is copied and sent to the lab with all shipments of specimens documented on the form.

Table 6.7: Specimen Collection at Follow-up

Follow-Up CO Number	W4 04	W12 05	W26 06	W39 07	W52 08	W78 09	W104 10	1-3 yrs 11-13
Local Bloods	X	X	X	X	X		X	X
Urinalysis			X		X		X	X
Central Bloods	X	X			X			
Stool	X	X			X			
Rectal Biopsies					X			

6.6.8 SELF-ADMINISTERED QUESTIONNAIRES

The BASC Parent Rating and Child Self Report (BAS) and the Impact (IMP) Questionnaires are requested between baseline and 4 weeks follow-up, 1 year, and 2 years of follow-up. These questionnaires are completed by the participant/family in a web-based entry system done through the participant pages on the study website. Instructions must be provided to the participant and family on how to access the participant pages of the website and how to access the questionnaires. Participants should be provided with their Participant ID, the participant

username and password for entry into the participant website (this information should be added to the passport), and instructions or a quick demonstration of the website will be helpful. In addition, these forms are also available for printing by the Coordinator on the research staff website with other study forms. Scanned forms can be e-mailed to protectstudy@cchmc.org.

Younger participants will be completing this with the help of their parents. Instructions should include asking that respondents start with the first question, working down through the questions and completing all questions as best they can. Let the participant/parents know that there is no right or wrong answer to these questions.

If they get tired, they can stop the entry, and return back where they left off within 14 days.

6.6.9 Sigmoidoscopy/colonoscopy Forms

Following a sigmoidoscopy/colonoscopy, the Confirmation of Diagnosis (COD), Disease Extent Data at Follow-up form (DED), and the Endoscopic Evaluation at Follow-up Form (EEF) should be completed.

6.7 CHANGES IN CLINIC FOLLOW-UP PROCEDURES

6.7.1 Telephone Contact Replaces Clinic Visit

If a participant and their parent/guardian is unable to attend clinic visits due to severe health problems, geographical location, or another reason, and the clinic is unable to schedule a visit within the visit window outlined in Table 6.1, it is preferred to replace the contact with a telephone contact, so some data collection can occur. Some expected visit data may be able to be collected by medical records review. The FDF form will trigger all ad hoc forms.

6.7.2 Clinic Visit Replaces a Telephone Contact

Occasionally it may be appropriate to replace a telephone contact with a clinic visit. This might happen at week 2 as the family would like to return for in person discussion with the physician.

6.8 CHANGES IN PARTICIPANTS FOLLOW-UP STATUS

6.8.1 Participant Stops Taking Study Medication

If a participant refuses to continue taking the study medication, or the parent/guardian decides the child will stop taking the study medication as prescribed, they can and should continue to remain in the study unless they become ineligible and need to be withdrawn (see section 6.9). Study personnel should always try to convince the participant to continue taking appropriate medication, and to continue with the study's follow-up telephone calls and clinic visits.

6.8.2 Participant or Parent/Guardian Dropout

A participant is a dropout if the participant is living, but the child and family are not completing follow-up contacts. Examples of a dropout include a participant whose parents refuses telephone contacts as well as clinic visits, a participant who has moved and cannot be located, or a participant or parent/guardian with a long-term illness preventing their participation. Often this can be interpreted as a passive change in consent.

When this occurs, coordinators should determine the willingness of the parent/guardian to work on solutions to overcome barriers to participation. Negotiating follow-up through telephone contacts is one possibility. If the parent/guardian cannot be converted to continued telephone contact, the Coordinator needs to complete a modification/withdrawal of consent on the ICT form.

6.8.3 Participant is Moving Away

If a participant and family is moving to another PROTECT clinical site, it may be possible to keep the participant in the study for follow-up visits. The DCC should be contacted for instructions on how to transfer a participant from one center to another. If a participant is moving to a location that is not accessible to another PROTECT clinical site and the family agrees the enrolling site can continue telephone contact with that patient.

6.9 WITHDRAWAL FROM THE STUDY

Participants are expected to be followed throughout the study. Participants who require rescue or second line therapy are still followed the same way as patients who remain on the standard treatment paradigm with clinic visits and biospecimens. Participants who require colectomy will also continue to be followed (see Section 6.4.8 of this chapter for additional details). Study withdrawals do occur through death, dropout, lost to follow-up, change in diagnosis and by modifying/withdrawing consent.

6.9.1 Change in Diagnosis

It's possible that some initial diagnoses for UC may be changed to Crohn's disease during the follow-up period. These participants are no longer eligible to continue in the study. A Study Discontinuation Form (SWF) should be completed and follow-up assessments stopped.

6.9.2 Participant undergoes a Colectomy

Participants whose disease state requires they undergo a colectomy will continue to be followed and the appropriate post-colectomy forms will be completed at visits (CLF, PCF). See Section 6.4.8 of this chapter for additional details.

6.9.3 Investigator Decision to Withdraw

A participant can be withdrawn from the study if the clinical site PI determines that it is the best interest for the subject to stop participation in the study or that it is unsafe or unethical to continue in the study. PIs are encouraged to discuss this decision with the medical monitor.

6.9.4 Participant Request to Withdraw

Participation in PROTECT is voluntary. Participants or their parents may withdraw at any time for any reason. At the time of withdrawal participants can either 1) decline to provide any more data or specimens to the study but allow use of previously collected data and/or specimens, 2) withdraw all their data from study databases and request that any stored samples be destroyed, or 3) withdraw some portion of the data collected (i.e., participants may withdraw specimens but not examination data or vice versa). In this event, Coordinators and Investigators should attempt to discuss the reasons behind the parent decision, and try to negotiate levels of participation that

can continue. However, if consent is refused, there can be no continued study contact or data collection.

6.9.5 Procedures at Withdrawal

If a participant is withdrawing from the PROTECT study, regardless of the reason, the study coordinator should attempt a data closure on the participant, and complete the Study Withdrawal Form (SWF). The Coordinator should attempt to conduct an exit interview to determine the disposition of the participant's study data. The coordinator should review the query report in the event that these items can be completed. The participant may decline to participate in the exit interview, in which case the consent/assent in place at the time of study withdrawal will be used to determine the status of the participant's data.

MEMS Cap Instructions

Getting Started

1. Install WakeUp software on your computer (cd or <http://www.aardexgroup.com/helpdesk>)
2. Log into medAmigo site and familiarize yourself with it (<https://v2-app.aardexgroup.com/view/login.aspx>)
3. Do NOT give caps to pharmacy – coordinator should manage the caps themselves.
4. Do NOT wake up caps in advance due to the battery life. Leave them until 1-2 days before you need them.

Initial Dispensing of Cap (by 4-week follow-up)

1. Participants should receive a cap by their 4-week follow-up if they are receiving Pentasa
2. 1-2 days prior to visit, remove the closure protection from the cap and the asleep sticker from the top
3. Wake up the cap according to the software directions.
4. Log into medAmigo site (<https://v2-app.aardexgroup.com/view/login.aspx>)
5. Select “Initiate new patient” option at the top and follow the instructions on the screen.
6. Enter the patient number (participant ID) and the date FOR THE FIRST DAY THEY WILL TAKE THE MEDICATION.
7. Initiate the cap by putting it on the monitor when indicated by the website.
8. Enter the patient drug and dosing information.
9. Go back to the start menu (upper right on menu bar) and select “Visualize patients list”
10. Select the patient ID you just entered and double check that the summary information you entered is correct.

Cap Follow-up Procedures

1. Remind the participant to bring all drug bottles and the cap back to their follow-up visits
2. Try to meet the patient as soon as they arrive and get their cap so you can download the information first and the treating physician can look at the report to discuss adherence with the family.
3. Once you have the cap in hand, log into the medAmigo site (<https://v2-app.aardexgroup.com/view/login.aspx>)
4. Select “Read new dosing history data from MEMS monitor” option at the top and follow the instructions on the screen.
5. Once the data is uploaded from step 4, go back to the start menu (upper left on menu bar) and select “Visualize patients list”
6. Select the patient ID you just entered and note the adherence score at the top and the initial graphs provided.
7. You can print this initial page and other reports by selecting “Detailed views” from the menu on the left side of the page.
8. If you see any errors, you can select “Events history” to edit the dosing history or change the regimen.

9. You can now give the cap back to the patient to continue using.

How to close out a patient in medAmigo

March 4, 2014

Once a patient has had their 52-week visit or has been permanently discontinued from Pentasa then you will need to close out their MEMS cap in medAmigo. Take the cap and read it as normal in the system. View the patient's record.

Select "Close Patient" from the left hand menu.

Select Patient ended the medAmigo service definitely.

Under "When" choose the date the patient stopped drug.

For "Reason" select the most relevant. If it is 52-week visit then select "Other"

Then click save and the cap should be closed out.

Keep the used cap to be sent back to Krista at CCMC at the end of the study.

Start menu Patients list Configuration Help Ashley Britt: Logoff

Patient Monitor Last visit
311325 2/18/2014 Print report Options

Patient overview
Detailed views
Events history
Edit patient data
Close patient

Close patient

Patient continues with the medAmigo service
Next visit expected in 14 week(s) or on 5/21/2013

Patient ended the medAmigo service definitely

When 2/18/2014 Reason

Side effects
Side effects
Hospitalization / Surgery
Physician's change
Treatment's change
Cured
MEMS refusal
Others

Save Skip

Chapter 7: Specimen Collection

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7.1 OVERVIEW

Routine standard-of-care blood and urine monitoring is run at each site's local clinical laboratories. There are also additional local laboratory results requested as needed for participants who have been prescribed second line rescue therapy (immunomodulator therapies, calcineurin inhibitor therapies, biologic therapy).

Study specific blood, stool, and rectal mucosal biopsy specimens are collected for central laboratory analysis and for repository.

Table 7.1 below provides a summary of specimen collection during the study. All specimen types are collected at baseline and at the week 52 clinic visit, although Week 52 biopsies are only collected for participants who qualify for and agree to a week 52 flexible sigmoidoscopy, or who are having standard of care follow up colonoscopy per the site physician. Blood and stool specimens are also collected at week 4 and week 12. Standard of care blood monitoring is collected at all protocol scheduled clinic visits thru 52 weeks, then annually up to 5 years. Urinalysis is run at baseline, 26, and 52 weeks, then annually thereafter for 5 years of follow-up. There may be patients who have a standard of care colonoscopy at other than scheduled visits. These patients will be eligible to have biopsies obtained at that time as well.

This chapter provides instructions for the collection, processing, shipping and reporting of all laboratory specimens. The PROTECT Lab Manual is included at the end of this chapter; it contains the detailed instructions for all central laboratory specimen collection, handling, and shipment.

Table 7.1 Blood and Stool Sample Collection and Usage

Biospecimen	Baseline	Week 4 (Day 30)	Week 12	Week 26	Week 39	Week 52	Week 104	Annual Visits 3-5 yrs
Blood								
Standard of Care (local lab)	X	X	X	X	X	X	X	X
Study Specific	X	X	X			X		
Genomic DNA	X					X		
Urine								
Urinalysis (local lab)	X			X		X	X	X
Mucosal Biopsy								
Colon DNA	X					X		
Colon RNA	X					X		
Stool								
Study Specific	X	X	X			X		

7.2 LOCAL LABORATORY

Reporting of local laboratory results will most likely occur after a participant’s clinic visits when results are received at the PROTECT clinic. Once received, data from the lab reports are to be transcribed or direct data entered onto the appropriate data collection form described below. For quality control purposes, the coordinator should ask the local lab to complete the Laboratory Reference Range Form (LRR). **Note:** the LRR Form is not a participant form, but a site form and is labeled using the PROTECT Clinic ID Number provided to each site.

7.3 CENTRAL LABORATORY

Study specific specimen collection for translational studies“ will all be shipped to a central facility at Emory University School of Medicine. The central lab will either perform appropriate testing, or ship to other labs for additional testing or repository.

Refer to the attached PROTECT Lab Manual for instructions on specimen collection, processing, labeling, and shipping.

Results from central laboratory testing will be sent directly to the DCC on a regularly determined schedule. This data is not shared with the clinical sites.

The site should take particular care to only collect and ship study specific specimens on patients enrolled in PROTECT who have evidence of ulcerative colitis. If at the time of initial diagnostic colonoscopy the patient does not have evidence of ulcerative colitis then biospecimens should not be collected. If at the time of initial diagnostic colonoscopy it is not clear if the patient has ulcerative colitis or some other inflammatory disorder (e.g., Crohn’s disease) then the

biospecimens should be obtained and stored/processed locally until confirmation or exclusion by histologic examination of biopsy material. If at that point the patient is diagnosed with ulcerative colitis the biospecimens should be shipped. If the patient does not have ulcerative colitis, the biospecimens should be destroyed.

Stool collection will ideally take place before the clean out for the initial diagnostic colonoscopy. If that does not happen then stool should be collected 48 hours after diagnostic colonoscopy, and ideally before therapy is started. If that is not clinically possible then collect stool at 48 hours even if the patient has started therapy. It is important to note the date of collection of the stool on the SCF so we can ascertain when it was obtained vis-à-vis start of therapy. Stool should be promptly frozen and then kept on ice when transporting to the hospital for processing.

If the blood specimen for DNA testing was not collected at the baseline visit, obtain this specimen at the earliest possible post Baseline visit.

7.4 DATA COLLECTION FORMS

The required study data collection forms associated with specimen collection and shipping are listed and described below. Central laboratory results will be electronically transmitted to the PROTECT Study Database, and will not have corresponding data forms or laboratory results reported to the sites.

7.4.1 Clinical Data Day Zero Form (CDZ) and Clinical Data Follow-up Form (CDF)

This data form collects urinalysis (dip-stick results) and any stool microbial analysis.

7.4.2 Local Lab Results Form (LLR)

This data form reports on the local laboratory blood monitoring and is data entered at the sites upon receipt of results.

7.4.3 Local Lab Normals Data Form (LLN)

This form is completed for each local laboratory used for routine blood monitoring, to report on the laboratory standards by gender and age group (<12, ≥12). This information is collected by the site (the laboratory can be asked to complete the form), and is data entered at the site upon receipt of results.

7.4.4 Specimen Collection Form (SCF)

All specimen collection is documented on the SCF. Through this form, the DCC tracks the collection date, type of specimen collected, as well as date of shipment to the study central labs and repositories. Anticipated results are then monitored. Note: this form will need to be updated to record shipping dates for those specimens not shipped at the time of collection and initial recording of the SCF.

Please use the Participant ID **barcode label and all specimen specific barcode labels** on all SCF forms.

The original SCF forms are to be included with each shipment of corresponding specimens as an inventory of the contents of the shipment. Copies of the SCF forms are to be retained at the site.

Refer to the SCF QxQ for specific instructions.

Appendix A. PROTECT LAB MANUAL



PROTECT

LAB

MANUAL

Updated: 2/8/2013


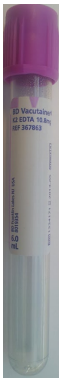
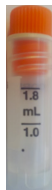


protectbiobank@emory.edu

(404) 727-4503

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Biospecimens will be collected at four visits.

Specimen Collection Calendar

Kit	Visit	Biospecimen				
		Whole Blood (for Plasma)	Whole Blood (for DNA)	Biopsy	Histology	Stool
Kit_Baseline	Baseline	✓	✓	✓	✓	✓
Kit_Week 4	Week 4	✓				✓
Kit_Week 12	Week 12	✓				✓
Kit_Week 52opt	Week 52*	✓	✓	✓	✓	✓
Kit_Week 52	Week 52*	✓	✓			✓
Std of Care opt	N/A			✓	✓	
	Collection Container	P100 (Orange top)	EDTA (Purple top)	Cryogenic Vial (Screw top)	15 mL vial with 10% Formalin	Para-Pak vial
						

* At week 52, only one kit will be used. If patients are on the biopsy sub-study, use Kit Week 52 Optional to collect samples. Otherwise, use Kit Week 52.

Kit_Baseline

Baseline

- **Blood** collection kit
 - 1 - 6 ml EDTA tube (purple top) for DNA
 - 1 - 8.5 ml P100 tube (orange top) for Plasma
 - Biohazard bag with absorbent pad
 - Blood collection directions insert
- **Mucosal biopsy** collection kit
 - 1 - 1.8 ml cryogenic vial (screw top) filled with RNALater
 - 1 – 7 ml vial filled with 10% Formalin
 - Biohazard bag with absorbent pad
 - Mucosal collection directions insert
- **Stool** collection kit
 - 1 Para-Pak vial for collection and transportation of stool
 - Collection bucket with lid and toilet frame
 - Specimen transfer spoon
 - Stool collection directions insert
- **Labeling** Stickers
 - **Protect Barcode labels** (DNA, PLASMA, STOOL, BIOPSY, HISTOLOGY) per patient kit

Kit Week_4

Week 4

- **Blood** collection kit (ORANGE TOP ONLY)
 - 1 - 8.5 ml P100 tube (orange top) for Plasma
 - Biohazard bag with absorbent pad
 - Blood collection directions insert
- **Stool** collection kit
 - 1 Para-Pak vial for collection and transportation of stool
 - Collection bucket with lid and toilet frame
 - Specimen transfer spoon
 - Stool collection directions insert
- **Labeling** Stickers
 - **Protect Barcode labels** (PLASMA, STOOL) per patient kit

Kit Week 12

Week 12

- **Blood** collection kit (ORANGE TOP ONLY)
 - 1 - 8.5 ml P100 tube (orange top) for Plasma
 - Biohazard bag with absorbent pad
 - Blood collection directions insert

- **Stool** collection kit
 - 1 Para-Pak vial for collection and transportation of stool
 - Collection bucket with lid and toilet frame
 - Specimen transfer spoon
 - Stool collection directions insert

- **Labeling** Stickers
- **Protect Barcode labels** (PLASMA, STOOL) per patient kit

Kit Week 52

Week 52

- **Blood** collection kit
 - 1 - 6 ml EDTA tube (purple top) for DNA
 - 1 - 8.5 ml P100 tube (orange top) for Plasma
 - Biohazard bag with absorbent pad
 - Blood collection directions insert

- **Stool** collection kit
 - 1 Para-Pak vial for collection and transportation of stool
 - Collection bucket with lid and toilet frame
 - Specimen transfer spoon
 - Stool collection directions insert

- **Labeling** Stickers
- **Protect Barcode labels** (DNA, PLASMA, STOOL) per patient kit

Week 52 Optional

- **Blood** collection kit
 - 1 - 6 ml EDTA tube (purple top) for DNA
 - 1 - 8.5 ml P100 tube (orange top) for Plasma
 - Biohazard bag with absorbent pad
 - Blood collection directions insert

- **Mucosal biopsy** collection kit
 - 1 - 1.8 ml cryogenic vial (screw top) filled with RNALater
 - 1 – 15 ml vial filled with 10% Formalin
 - Biohazard bag with absorbent pad
 - Mucosal collection directions insert

- **Stool** collection kit
 - 1 Para-Pak vial for collection and transportation of stool
 - Collection bucket with lid and toilet frame
 - Specimen transfer spoon
 - Stool collection directions insert

- **Labeling** Stickers
 - **Protect Barcode labels** (DNA, PLASMA, STOOL, BIOPSY, HISTOLOGY) per patient kit

Standard of Care Biopsy and Histology (optional)

- **Mucosal biopsy** collection kit
 - 1 - 1.8 ml cryogenic vial (screw top) filled with RNALater
 - 1 – 7 ml vial filled with 10% Formalin
 - Biohazard bag with absorbent pad
 - Mucosal collection directions insert

Shipping Materials will also be provided for each kit.

Shipping Materials

- **One crush proof boxes** with UN3373 sticker per kit
- One UN3373 **FedEx shipper bags** per kit
- Frozen Shipper Boxes (for Frozen shipments only)

Blood Collection

Note: Orange cap P100 tube should be LAST tube drawn

Contents: one 5 mL purple top EDTA & one 8.5 mL orange top P100 tube

*For Baseline and week 52, **both P100 and EDTA** tubes are collected*

*For weeks 4 and 12, **only P100** is collected*

- Use purple top EDTA tube to collect 5 mL blood.
- Use the orange top P100 tube to collect 8.5 mL of blood.
- Place barcode label on each tube/vial.
- Orange cap P100 tube should be LAST tube drawn. **Invert tube several times to mix contents with blood.**
- After blood draw, place purple top EDTA and orange top P100 tube from same patient into the 6 x 9 biohazard bag.

Biopsy Collection

Contents: one cryogenic vial (screw cap) containing RNA Later, one 15mL vial containing Formalin

- **Collect 4 biopsies from the Rectum.** Put **three (3) biopsies** in the cryogenic vial containing RNALater and put **one biopsy** in the 15mL vial containing Formalin.
- Give the tubes to research nurse or the research coordinator tasked to receive the tubes.
- Place all tubes in a 6 x 9 biohazard bag.

Stool







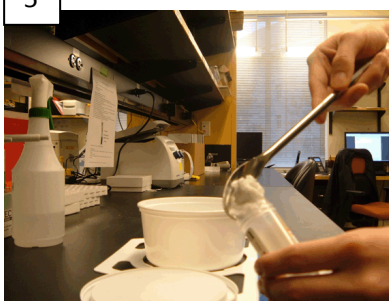





DO NOT collect stool during scope. Collect stool before clean-out for scope or before therapy starts (follow Diagrams/workflow below)

- Remove Para-Pak Clean Vial from zipper bag.
- Affix barcode label on each tube/vial.
- Collect 2 ml (1/2 teaspoon) of stool from the patient either in the clinic or at home.
- Place a check mark in the box on the vial to indicate stool consistency and insert vial into blue bag.

Please refer the patients and their families to the YouTube video for stool collection:

<http://www.youtube.com/watch?v=84aINcL3xkc>

Patient Stool Collection Instructions

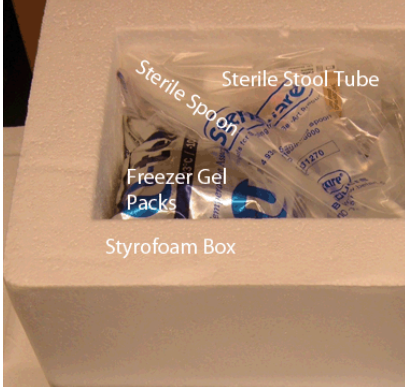






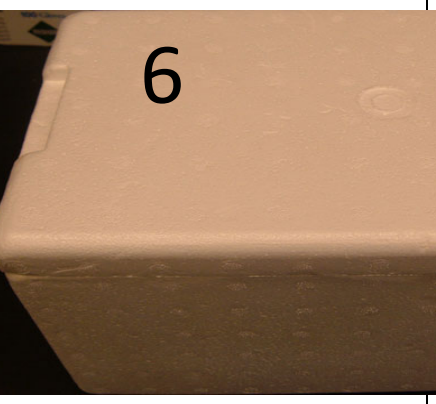
<p>Complete Patient Stool Collection Kit</p>  <p style="text-align: center;">Styrofoam Box</p>  <p style="text-align: center;">Stool Collection Bucket with frame and lid</p>	1		2	
	3		4	
	5		6	
	7		8	
	9			

Patient Collection Instructions:

- 1 – Upon receipt of the kit, immediately, place freezer gel packs into freezer and let freeze
- 2 – Place Stool Collection Frame on toilet bowl, lower seat, place Collection Tub in Frame
- 3 –Deposit sample inside the Tub (no urine should get into the tub)
- 4 – Using the Sterile Spoon, scoop sample

- 5 – Transfer the sample into the Sterile Collection Tube
- 6 – Seal the tube
- 7 – Place the sealed tube into a Ziploc bag
- 8 – Place the Ziploc bag inside a freezer until taken to the site
- 9 – When delivering to site, please use Freezer Gel Packs to keep the sample frozen during the trip

PATIENT TRANSPORT of Stool Back to Site

Stool Kit Going Home with Patients	Patients packaging stool sample for return from home to site			
 <p>Sterile Spoon</p> <p>Sterile Stool Tube</p> <p>Freezer Gel Packs</p> <p>Styrofoam Box</p>	 <p>1</p>	 <p>2</p>	 <p>3</p>	 <p>4</p>
 <p>Stool Collection Bucket with frame and lid</p>	 <p>5</p>	 <p>6</p>		

Shipping Guidelines **DO NOT SHIP ON FRIDAY**

Shipping Calendar

Tube Type	Specimen	Collection Day		
		Monday-Thursday	Friday	Before a three day holiday/weekend
P100 (orange top)	Whole Blood (Plasma)	Ship Overnight (Room Temperature)	Store (4°C); Ship Room Temperature on Monday	Spin, Aliquot and Freeze (-80°C); Batch Ship*
EDTA (purple top)	Whole Blood (DNA)	Ship Overnight (Room Temperature)	Store (4°C); Ship Room Temperature on Monday	Freeze (-80°C); Batch Ship
Cryogenic vial (small orange vials)	Biopsies	Ship Overnight (Room Temperature)	Store (4°C); Ship Room Temperature on Monday	Store (Room Temp) or Fridge Ship Room Temperature on Monday NEVER FREEZE
Vials (15mL) containing Formalin	Biopsies	Ship Overnight (Room Temperature)	Store (Room Temp) Ship Room Temperature on Monday	Store (Room Temp) or Fridge Ship Room Temperature on Monday NEVER FREEZE
ParaPak Tube	Stool	Freeze (-80°C); Batch Ship	Freeze (-80°C); Batch Ship	Freeze (-80°C); Batch Ship

* If blood samples must be stored for **more than 3 days** (more than a weekend), the blood in the purple cap tube (DNA) should be kept at -80°C. The blood in the orange top P100 tube (Plasma) must be centrifuged for 10 minutes at 2.5 rcf (relative centrifugal force) or 2500 g. The Plasma should be transferred into two vials or eppendorf tubes (not provided) and labeled with the exact same barcode number as the original P100 tube, and stored at -80C. **ALWAYS SHIP THE P100 TUBE BACK WITH THE SHIPMENT.**

Shipping Instructions

There are two types of shipments you will need to make: **Room Temperature** or **Frozen**.

Room Temperature:

- * Please make sure that all tubes are **correctly labeled**.
- * The correctly labeled tubes should be placed in the provided biohazard bag(s) containing an absorbent pad
- * The Biohazard bag(s) must be placed in the white crush-proof box labeled with a UN3373 sticker.
- * The white crush-proof box must be placed in a UN3373 FedEx shipper bag.
- * Print FedEx labels from www.fedex.com using the login and password provided by Emory.
- * Affixed (or place) the FedEx label to the UN3373 FedEx shipper bag.
- * Drop off the UN3373 FedEx shipper bag for pick up
- * Please notify Emory via email with patient enrollment number, visit and FedEx tracking number.

Frozen:

- * Store tubes between -20°C to -80°C until ready to send to Emory biorepository.
- * **BATCH** in lots of 6 samples in a large plastic bag.
- * Place large plastic bag inside the Frozen insulated UN3373 shipper box.
- * Place dry ice into box (2.2 kilos or 5 lbs) on top of the plastic bag. Avoid getting dry ice inside plastic bag with fecal sample vials.

- * Affixed **two labels** to the outside of an insulated shipper box: 1. Dry Ice label with marked amount of dry ice (paper) and 2. UN3373 label (indicates biological substance, category B).
- * When filling out the Fed Ex label, please mark "NO" under "does this shipment contain dangerous goods," then check "Dry Ice", and enter the amount in kilograms.
- * If done properly, the stool or other tubes should stay frozen for 3 days under the dry ice, inside the shipper. Please send FedEx next day to Emory on Monday through Thursday only, but **NEVER ship on Fridays or before holidays.**
- * The Frozen shipper box will be returned to the study site for future reuse in shipping additional fecal samples and pre-printed Federal Express air bills will enclosed.

FedEx.com instructions:

FedEx labels can be printed from www.fedex.com using the login ID and password provided by Emory.

Login ID: protectbiobank Password: 4EmoryLab

Label Instructions:

After logging in, use the "Ship" tab to "Create Shipment." Then under the "My shipment profiles" tab, click your site name and whether you are shipping Ambient or Frozen. After you make your selection your click "Ship" at the bottom. This will generate a FedEx label that can be printed from a standard office printer. Just print and affix the label to the shipper bag.

Ship **Priority Overnight** to:
 Kugathanan Lab
 Emory Children's Center
 2015 Uppergate Drive, Room 260
 Atlanta, GA 30322
 404-727-1456

If you have questions, please use email below:

Jarod Prince
protectbiobank@emory.edu or jjprinc@emory.edu
 (404) 727-4503

Shipment Notification

Required Information for Shipment Notifications:

Date Sample was shipped (if other than date of email)

Site Code

FedEx tracking #

Visit Number (Week #)

Patient Number and type of samples Sent (DNA, PLASMA, STOOL, BIOPSY or HISTOLOGY)

Biopsy Location and Number of Biopsies, if applicable

Comments (Please include a comment about any irregularities in shipments – For example, "Had to write on tube and use Avery label because I didn't have the PROTECT label."...)

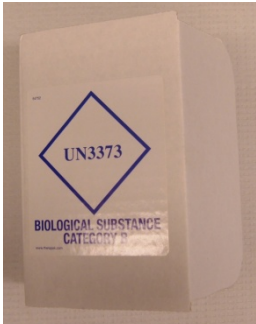
Please email the above information to:

TO: protectbiobank@emory.edu

CC: jjprinc@emory.edu

Assembling a Room Temperature Shipment

Crush-Proof Box with UN3373 sticker



Biohazard Bag with Absorbent Cloth



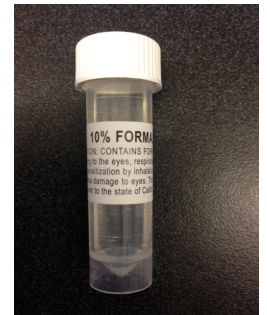
Labeled DNA and Plasma tubes



Labeled Biopsy Tubes (Cryogenic Vials)



Labeled Biopsy tube (15ml Formalin vial)



Samples inside biohazard bag placed in box (multiple sealed biohazard bags may be placed in the same box)

Also place Specimen Collection Form in Box



Box placed inside FedEx Pak. Each FedEx Pak can accommodate two boxes.



FedEx Pak with shipping label and ready for shipment



Anything added to the shipment beyond what is required (shown above) increases processing time and should be avoided.

Please refer to following YouTube video as a reference for preparing an ambient shipment:

<http://www.youtube.com/watch?v=UCATTca7tzA>

Assembling a Frozen/Dry Ice Shipment

Biohazard Bag with Absorbent Cloth



DNA and Plasma



Stool Tube



Blood/Biopsy tubes inside biohazard bag and stool tube inside zipper bag placed in box (multiple sealed bags may be placed in the same box). Add dry ice to the top (or top and bottom)

Place **Specimen Collection Form (SCF)** on top of closed styrofoam box.

Cardboard box sealed and FedEx shipping label affixed

Proper warning labels (UN3373 and UN 1845/Dry Ice) attached to one side and labeled. Write weight of dry ice and From/To addresses on Dry Ice Label



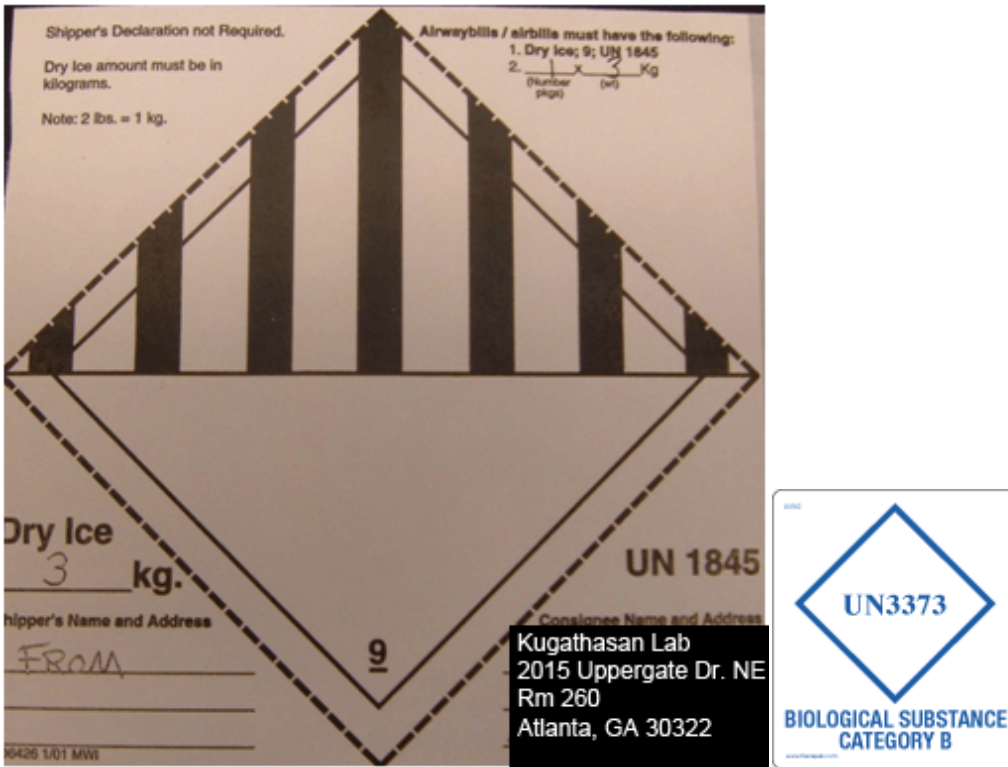
Ensure that patient labels are correctly affixed to each vial/tube.

Anything added to the shipment beyond what is required (shown above) increases processing time and should be avoided.

Please refer to following YouTube video as a reference for preparing a frozen shipment:


<http://www.youtube.com/watch?v=afxJrBvB7mY>

FROZEN/DRY ICE Shipment Labels for US and International Shipments



Dry Ice (UN1845) label filled out with proper information. **UN3373 Label.**
Please include the weight of dry ice along with the Name and Address of both the shipper and receiver (consignee).

Specimen Collection Form



Specimen Collection Form

Participant ID
Barcode Here

ID NUMBER:
 FORM CODE: SCF Contact Occasion:
 Seq #

Date of Contact:
 Staff Code:
 FDF #

A. Study Specific Blood Sample Collection

1. Orange Top: (check current status):

(1) Will not be collected → Q2
 (2) Requested → Q2
 (3) Collected → 1a. Date collected (dd/mmm/yyyy): ___/___/___
 (4) Shipped → 1b. Date Shipped (dd/mmm/yyyy): ___/___/___

1c. Orange Top Specimen ID: Stick CRF label here

2. Purple Top: (check current status):

(1) Will not be collected → Q3
 (2) Requested → Q3
 (3) Collected → 2a. Date collected (dd/mmm/yyyy): ___/___/___
 (4) Shipped → 2b. Date Shipped (dd/mmm/yyyy): ___/___/___

2c. Purple Top Specimen ID: Stick CRF label here

Comments: _____

B. Study Specific Mucosal Biopsy Sample Collection

3. Were any Rectal Biopsies Collected: No → Q7 Yes → 3a. Date Collected (dd/mmm/yyyy): ___/___/___

4. Biopsy for Histology

a. (1) Will not be collected → Q5a (2) Collected
 b. Collected as: (1) Formalin (2) Glass Slide

4c. Histology Specimen ID: Stick CRF label here

5. RNA Later (3 Bx for genetic analysis)

a. Biopsy #1: (1) Will not be collected (2) Collected (3) Shipped
 b. Biopsy #2: (1) Will not be collected (2) Collected (3) Shipped
 c. Biopsy #3: (1) Will not be collected (2) Collected (3) Shipped

5d. RNA Specimen ID: Stick CRF label here

6. Biopsy Ship Date (dd/mmm/yyyy): ___/___/___

Comments: _____

C. Study Specific Stool Sample Collection

7. Stool: (check current status):

(1) Will not be collected → END
 (2) Requested → END
 (3) Collected
 (4) Shipped → Q7c

7d. Stool Specimen ID: Stick CRF label here

a. Frozen/On ice when received from family: Yes No Unknown

b. Date collected (dd/mmm/yyyy): ___/___/___

c. Date Shipped (dd/mmm/yyyy): ___/___/___

Comments: _____

Specimen Collection Form (SCF) Page 1 of 1

SEND COMPLETED PHOTOCOPY WITH EVERY SHIPMENT

Place in the UN3373 Box or on top of the frozen shipper box (see page 12 and 13)
Send a photocopy and keep the original for your records

To Fill Out

Place the extra specimen labels that were sent in their proper place:

Orange Top = PLM12345
 Purple Top = DNA12345
 Histology = HIS12345
 RNA Specimen = BPY12345
 Stool = STL12345

ID NUMBER: Participant ID (PLB0000)

Also Place Barcoded Participant ID on Form

Predicting Response to Standardized Pediatric Colitis Therapy (PROTECT)

Chapter 8: Participant Safety and Adverse Events

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8.1 PARTICIPANT SAFETY

Participant safety always takes priority over all else. The International Conference on Harmonization's general principles of Good Clinical Practice will be followed. These principles dictate, first and foremost, that we have weighed and will continue throughout the study to weigh the anticipated benefits versus the foreseeable risks to all participants. Participants will be fully informed of these risks before they are enrolled. The study's leadership will continually review the medical literature to determine any new findings that might substantially affect the study's rationale or justification, and for new or previously unforeseen risks that must be conveyed to participants. Any significant new findings will be reported to the Data and Safety Monitoring Board (DSMB), study safety officer, and the NIDDK Project Officer in a timely manner.

A Data and Safety Monitoring Board (DSMB) has been established by the NIDDK to provide appropriate oversight and monitoring of the conduct of the trial and to ensure the safety of participants and the validity and integrity of the data. The DSMB's monitoring functions and oversight of such activities are distinct from the requirements for study review and approval by an Institutional Review Board (IRB).

Responsibility for monitoring patient safety during the study is shared by each clinical center's IRB, the study safety officer, the study's Data and Safety Monitoring Board (DSMB), and the FDA. In order to ensure appropriate monitoring can occur, clinics are responsible for following informed consent procedures, taking measures to ensure participant confidentiality, adhering to HIPAA regulations, and closely monitoring and reporting adverse events. Timely reporting of all untoward events occurring during the study is the only way to ensure that these groups can conduct appropriate monitoring of patient and study safety. Study procedures for monitoring and reporting of events are detailed below. Study monitoring of compliance to these procedures is described in the Quality Assurance and Quality Control Chapter 9 of the PROTECT MOP.

8.2 MONITORING EVENTS AT THE CLINICAL SITES

Data collection of adverse events/side effects and serious adverse events allows appropriate safety monitoring of subjects. Complete, accurate, and timely information is crucial. Detecting and reporting a serious adverse event is the responsibility of the Principal Investigator, although the actual data collection and reporting is often delegated to the site's Project Coordinator.

At each follow-up telephone and/or clinic visits, participants and parents will be asked to report on any hospital or other medical visits since their last study contact, and on any possible adverse reactions. Data collection on side effects and adverse events monitoring is triggered by questions on the Follow-up Data Form. Additional questions should be asked about any newly prescribed medications. A comprehensive approach will provide the mechanism for monitoring of side effects and adverse events.

For purposes of PROTECT, the study will collect information on all reported serious adverse events, and on any adverse events/side effects that the family or Investigator considers a potential medication side effect or related to UC.

8.3 DEFINITIONS RELATED TO ADVERSE EXPERIENCES

8.3.1 Adverse Event

An adverse experience or adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event can be any unfavorable unintended sign, symptom, or disease temporally associated with the use of a drug, without any judgment about causality.

Adverse events may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the patient or subject and/or observed by the physician or medical staff.
- Laboratory abnormalities of clinical significance.

Disease signs, symptoms and/or laboratory abnormalities already existing prior to the use of the product are not considered adverse events unless they recur after the patient has recovered from the pre-existing condition, or represent an exacerbation in intensity or frequency.

8.3.2 Adverse Reaction/ Side Effect

An adverse reaction/side effect means any adverse event caused by the drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

8.3.3 Serious Adverse Events

A **serious adverse experience or adverse event (SAE)** is any adverse event that results in any of the following outcomes:

- Death
- A life-threatening experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Requires intervention to prevent permanent impairment or damage
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All serious adverse events are reportable for PROTECT if they occur between the time the patient provides informed consent through 30 days after the participant completes or withdraws from the study.

The following hospitalizations are to be reported as SAEs in the PROTECT study:

- Any hospitalizations beginning on the day of consent that are the result of a complication of a study procedure or
- Any hospitalization beginning AFTER the date of consent.

The distinction between an adverse event and a serious adverse event is based on the definition for serious adverse events, and not on the severity of an event, i.e., serious vomiting is not considered a serious adverse event except if it requires hospitalization. Adverse events are reported regardless of the supposed relationship to study medication.

8.4 ADVERSE EVENT DATA COLLECTION FORMS

There are four study forms used for adverse event reporting from the clinical sites, the Side Effects/Adverse Events Form (SEF), the Side Effects/General Form (SEG), the Serious Adverse Events form (SAE) and the BASC Alert Form. In addition an SAE report might require an FDA Medwatch Form 3500A. These forms are all described below.

8.4.1 The Side Effects/Adverse Events Form (SEF)

The Side Effects/Adverse Events Form (SEF) was designed to capture known medication side effects taken from the Pentasa drug label; although collection of these effects is not limited to only those participants taking Pentasa. This form is designed as a checklist with item specific questions associated to the known medication adverse side effects. The SEF form is triggered by the Follow-up Data Form (FDF) which is administered during all telephone and clinic visits contacts. Completion of the SEF is optional after Week 52.

Each adverse side effect asks for a general rating of severity, the definitions for mild, moderate, and severe are as follows:

A mild adverse event is defined as: awareness of sign, symptom, or event, but easily tolerated.

A moderate adverse event is defined as: discomfort enough to cause interference with usual activity and may warrant intervention.

A severe adverse event is defined as: incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention. The *specific* definition for severe is given in parentheses at the end of each question (e.g., “severe = loss of consciousness).

In addition, some indication of whether the Investigator believes this side effect was caused by the study medication, and if medical care was sought for this event.

Reporting needs from the clinical site is completed by the prompt data entry of the SEF form into the study DMS. The DCC recommends data entry within 5 working days of data collection.

Tables reporting side effects/adverse events will be generated for all bi-annual DSMB reports which will be responsible for monitoring overall participant safety. In addition, the DCC will monitor these events regularly as part of standard quality assurance and quality control monitoring. If a question of safety arises, the DCC will consult with the study’s Safety Officer, and prepare additional reporting to the DSMB as necessary.

8.4.2 The Side Effects/General Form (SEG)

This form is similar to the SEF form described above, but allows the entry of additional events thought to be potential medication side effects or events related to UC that are not included on the SEF checklist. Its use is triggered at the end of the SEF with the question “Have you had any other health **problems since your last visit.**” Completion of the SEG is optional after Week 52.

8.4.3 Serious Adverse Event (SAE)

Serious adverse event reporting follows a much more critical timeline and process. Serious adverse events are reported using the Serious Adverse Events (SAE) form. This form requires a succinct diagnosis, a narrative of the event, and information about its expectedness and relationship to the study drug. Critical to the SAE report is a good narrative or detailed description of the event. It should provide rich, focused clinical detail regarding the signs, symptoms, and lab values supporting the initial diagnosis, a short history may be necessary to complete the narrative, and a list of medications the patient was taking or prescribed when the SAE occurred.

Follow-up information is added to the SAE form as it becomes available, providing information on the outcome of the event and resolution date.

The study Safety Officer is available for consultation with the site PIs regarding all serious events, their reporting, and any follow-up needs. Contact information for the study Safety Officer (Dr. Faubion) is located in the NEED STUDY HELP section of the home page for research staff on the PROTECT website (www.protectstudy.org).

8.4.4 Adverse Drug Reaction Report - FDA Medwatch Form 3500A

For serious adverse events that are both unexpected and related to study drug (Pentasa), the FDA required reporting form is the Medwatch 3500A. This form is available on the PROTECT study website under Study Documents -- Forms and QxQs. Detailed instructions written by the FDA on how to complete the Medwatch Form are included as embedded links within the form.. See instructions below in section 8.5.3 on this process.

8.4.5 BASC Participant Emails/BASC Alert Form

The BASC Alert Form (see Appendix A at the end of this chapter) is used to help guide site coordinators and PIs as they follow-up with families who have endorsed critical items on the BASC parent-report and child-report. Critical items include BASC questions that indicate the patients may wish to harm themselves or others. The form requires the site to record their initial response as well as how the issue was resolved (e.g., any follow-up actions the family may take such as, seeking further evaluation from a mental health professional).

Upon receiving a “participant alert” email indicating a critical item was endorsed by the parent or child on the BASC, each site should receive a BASC Alert Form via email from Cincinnati Children’s Hospital. Once the BASC Alert Form is received, follow-up should occur within 24 hours. The site coordinator or PI should take appropriate action as required by their IRB. After following up with the family and completion of the BASC Alert Form, the form should be sent back to Cincinnati Children’s Hospital (PROTECTstudy@cchmc.org) for documentation purposes.

8.5 SERIOUS ADVERSE EVENTS REPORTING PROCESSES

8.5.1 Timing of SAE Reporting

Serious adverse events falling under an FDA IND have reporting requirements for events that are considered “a suspected adverse reaction and is both serious and unexpected”. Medwatch Form 3500A is required for serious events that are unexpected and related (either possibly or definitely) to Pentasa . This definition is covered under questions 4 and 6 on the SAE form (unexpected and relationship of SAE to medication). An SAE is considered unexpected if: 1) it is not listed in the investigator brochure, literature protocol or informed consent; or 2) it is not listed at the specificity or severity that has been observed. A UC flare, or worsening of disease, is considered an expected event. Pancreatitis, rash, and headache are also examples of expected events. Unexpected events include broken limbs, testicular torsion or endocarditis. Note that unexpected serious adverse events that are possibly or definitely related to a non-Pentasa UC drug do not require Medwatch Form 3500A.

8.5.2 Reporting to the DCC

Notification of an SAE to the DCC begins with an email to the DCC with the subject heading “SAE – ID# Start Date”, where the ID# is the participant ID, and the Start Date indicates the date when the event began. . This provides a head-up to the DCC to be on the lookout for the fully documented event through the entry of the SAE form into the DMS. SAEs that are serious, unexpected and related to Pentasa (i.e. requiring FDA IND reporting) must be reported to the DCC as soon as possible by contacting the DCC (email), completing and entering the SAE form and completing a Medwatch Form 3500A which is then scanned and emailed to the DCC. It is understood that this is an initial report and that the site may still be collecting all the information describing this event. This reporting timeframe will allow us to meet any FDA report requirements. The DCC will send this report to the study Safety Officer and NIDDK within two days of receipt.

SAE forms not associated with an IND report are expected to be entered in the PROTECT DMS within 48 hours of the site’s initial report.

8.5.3 Reporting to the FDA

Based on the expectedness and association to study medication (Pentasa), the DCC will consult with the Study Officer (SO) regarding the need for FDA IND reporting (Medwatch Form 3500A). The code of federal regulations (21CFR312.32) offers the following definitions for IND safety reporting: Any adverse experience that is a suspected adverse reaction and is both serious and unexpected.

If IND reporting is indicated, the DCC and SO will consult with the study Investigator on completing the Medwatch form. This form must be completed and faxed to the DCC immediately.

Within 2 working days of receipt at the DCC of Medwatch Form 3500A, the DCC will submit reporting to the Project Officer at NIDDK, who will decide whether to forward the information on to the FDA, the PROTECT DSMB and all study Investigators.

8.5.4 Site IRB Reporting

Sites are responsible for reporting their own SAEs to their IRB. Some site IRBs may require IRB reporting of other adverse events or experiences that do not fit the study event descriptions above. This additional reporting would be the site's responsibility, and not part of study data collection.

Notification of SAEs reported by other sites falling under an IND **report** will be acted on by the IND Sponsor as required by NIDDK, or by the DCC based on a DSMB recommendation.

8.5.5 Reporting to Data and Safety Monitoring Board

In addition to the serious adverse event reporting based on a required IND report, the DCC will provide aggregate reporting of all safety data and adverse events to the independent Data Safety Monitoring Board (DSMB) according to the guidelines and schedule established by that group.

8.5.6 SAE Documentation

For each SAE, a printed copy of the data from the DMS should be signed by the investigator and added to the participant's binder.

Appendix A. PROTECT BASC Alert Form



BASC Alert Form

ID NUMBER:

Date of Alert: / /

9 Response to BASC Alert

Instructions: You are receiving a copy of this form because one of your PROTECT participants has indicated an alarm finding on one of the BASC questions. Please take whatever actions are required by your IRB and indicate your response below.

1. Record your site's initial response to the BASC alert you received

- (1) Patient/parent reported a data entry error in his/her response that generated the alert. →
- (2) Family contacted and patient brought to hospital/physician on immediate basis for further evaluation. →
- (3) Family contacted and patient scheduled for further evaluation. →
- (4) Family contacted and they did not feel further mental health evaluation was warranted. →
- (5) Other, please specify:

2. Was further evaluation done? Yes → No →

3. If further evaluation was done, record how the issue was resolved:

- (1) Patient is under the ongoing care of a mental health professional.
- (2) Patient was evaluated by a health professional who determined that no further action was required.

Note: In each patient's PROTECT file, please include documentation of the health professional that performed the evaluation, their phone number and date of visit.

4. Date of form completion: (dd/mmm/yyyy) ____ / ____ / ____

**Email completed form back to: PROTECTstudy@cchmc.org*

Chapter 9: Quality Assurance and Quality Control

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9.1 OVERVIEW

The integrity and ultimate credibility of the study depend on such factors as ensuring adherence to the protocol and study procedures, completion of follow-up information on all participants enrolled, and using quality control measures to establish and maintain high standards for data quality.

Procedures designed to enhance adherence to the protocol and study procedures begin with the training of clinic personnel before participants are enrolled. Once enrollment begins, these same measures will continue along with monitoring the clinical sites, operating suitable quality control systems and checking the quality of data collection and the timeliness with which data are received from the clinics and Central Laboratories.

9.1.1 Quality Assurance

Quality assurance is considered here as relating to activities to assure quality of data which take place prior to collection of data, while quality control relates more to efforts during the study to monitor the quality of data at identified points in the collection and processing stages.

Standardization provides for quality assurance within a study. This is the essence of the entire Manual of Procedures (MOP) and includes the following activities:

- Detailed procedures. A clear description of the study design, training, and the various data collection activities provides the blueprint for the study. The MOP is a written reference for study Investigators, Coordinators and other staff, and provides documentation of the standard procedures for the study. Procedures for handling the routine, as well as the unexpected, are given.
- Training and updating training. Training is the transfer of the study plans in the MOP to the study staff members. Training modules specific to the needs of the study Physicians, Coordinators, Pharmacies, Data Entry staff will be developed for PROTECT and will be the basis for initial training and continued education during the study. Arrangements will be made for Site staff unable to attend the various training and orientation sessions and for the addition of new staff throughout the study.
- Certification. Criteria to examine the adequacy of an individual's training may be established for some of the training modules provided. Individuals meeting these criteria will then be qualified to execute a procedure.
- Data forms: Data collection forms are designed to minimize subjectivity and maximize standardization by requiring specific information. Each form has a corresponding Question by Question (QxQ) document providing standardized definitions and instructions for administration.
- Standardization is also helped with the studies 'help line'. Clinic staff is encouraged to contact the DCC for an immediate answer to an operational question or for help in obtaining clarification of a particular situation to help assure study protocol and procedures are being adhered to. For questions of a clinical nature, and those the DCC is unable to answer, the DCC will consult the Chief Medical Officer of the study.

9.1.2 Quality Control

For quality control purposes, PROTECT data collection and transmission will be monitored by observation and by quantitative assessment using both specific quality control procedures and statistical analysis of study data. Onsite monitoring will be performed by the study's clinical monitors via periodic site visits. A summary of selected aspects of PROTECT quality control follows:

- **Protocol adherence:** Periodic clinic monitoring visits will be made to each site to review adherence to PROTECT recruitment and data collection procedures. Feedback and general recommendations for improvements will be provided. These visits also provide an opportunity for clinical staff to discuss questions, concerns, and suggestions.

Reports describing adherence to the study contact schedule as well as to the study medication, clinic-specific and overall, will be distributed to the Principal Investigators (PIs), Project Coordinators, Executive Committee, and the Data and Safety Monitoring Board.

Steps will be taken within the trial to assist a clinic with lagging performance. Reasons for missed visits and telephone calls should be noted and kept in the participant's chart. This information will be important in assessing adherence to protocol during clinic monitoring visits.

Each contact has a contact window around the target date for that contact, and all attempts should be made to complete a contact within the specified window. However, to avoid missing data altogether, a contact can be conducted outside of this window, and telephone contacts can be made, provided that it does not fall too close to next regularly scheduled contact. For a detailed discussion of visit scheduling, refer to MOP Chapter 6: Follow-up.

- **Quantitative monitoring, clinical sites:** A sample of data collected will be audited to assure that reported trial data are accurate, complete, and verifiable from source documents.
- **Quantitative monitoring, database:** The Data Entry System is designed with checks and balances to identify potentially incorrect data as it's entered. In addition both real-time and routine regular data queries of questionable or discrepant data will be part of data quality assurances for data collection/entry. At study end, the formal process of database closure and final documentation completes this QC process.
- **Quantitative monitoring, Treatment Adherence:** The Medication Event Monitoring System (MEMS[®]) will be used for treatment adherence measurement. This is a track cap monitoring system which includes a standard plastic vial and cap containing a microelectronic circuit that records each time the cap is removed. Adherence data parameters include number and percentage of doses removed, optimal daily dosing, estimation of therapeutic coverage, and mean and range of interdose intervals. Pill counts will also be obtained as a second measure.

Coordinators will document the number of pills dispensed and the number of pills returned at each visit.

The MEMS caps reporting system provides immediate feedback to the site and participant regarding adherence since the last reading. Reports generated by the DCC to the PROTECT Executive Board and DSMB will include overall adherence by site. Steps will be taken to work with a site to help with their participants' medication adherence. This will include discussions on providing regular feedback and encouragement to the participant and family, and continued discussions with participant/family regards benefit.

- **Reporting results:** Two aspects of reporting quality control monitoring should be emphasized. First, the results must be timely. When remedial action is required, reporting must be prompt so that a return to an acceptable level of performance is not delayed. Second, the reporting format must be easily understood. Routine reporting that present both QA and QC status will include Monthly Management Reports, Data and Safety Monitoring Reports, Clinic Monitoring Visit Reports.
- **Action on results:** With conscientious and trained staff, quality control reports provide an opportunity to praise a job well done. On the other hand, a poor performance is the basis for remedial action. Depending upon past performance, the amount of error, and, taking due account of personal circumstance, the appropriate action may be a simple discussion to encourage a better performance. Re-training may also be appropriate at times.

9.2 TRAINING OF CLINICAL CENTER STAFF

Training of study personnel is an essential aspect of effective quality assurance in PROTECT. Each Principal Investigator and Study Coordinator must attend a central training hosted by both the CCC and DCC to cover all study procedures and data collection activities. This training will occur soon after the start of the PROTECT study. Additional clinic staff at each site can be trained using the PROTECT Coordinator Training Checklist (see Training section of the PROTECT website).

Attendance at the central training generally completes any certification requirements. After attending a central training or being trained at the local clinic by another centrally-trained coordinator, and meeting any specific certification requirements, a study coordinator is considered certified. Areas of training essential for certification include, drug handling and accountability, specimen collection and processing, adverse event reporting, the studies schedule of events, data collection forms review, and learning the data management system.

A continued investment in quality data during the study will be made by periodic refresher training sessions via web-based conference calls which will review the protocol and update personnel on any changes which may have occurred.

In order to maintain proper collection of data despite potential for personnel changes over the long term follow-up period, the DCC and CCC is responsible for establishing and providing the requisite minimum criteria and training and ensuring continued adherence to standards.

9.3 CONFIDENTIALITY, SECURITY, AND INTEGRITY OF DATA

The safety, and confidentiality of participants and study data, is protected by multiple layers of security.

- The first layer is physical security (lock and key), which limits access to paper files and to computers where study information is kept to authorized staff. Each clinical site, as well as the CCC and DCC, will maintain secure paper records in locked drawers and file cabinets, and in locked offices.
- The second layer is logical security (network firewalls) and is designed to allow access to hospital/university networks and to specific computers to authorized users only, and to deny access to all others. All electronic study records are stored in password protected computers, and through password protected systems.
- The third layer is control access to the DCC's data management system and study database, as well as to the study website with archives study documents. Access is regulated and monitored by the DCC, which requires regular updates of usernames and passwords for access. All internet communicated data developed as part of the DCC data management system is transmitted through secure portals and encrypted for security when necessary. Site PIs and Coordinators are limited to access data only at their site. The DCC maintains appropriate certifications and documentation of security, data confidentiality, and backup.
- The fourth layer consists of controlling staff capabilities within the sites, the CCC, and the DCC for appropriate access to study documents, electronic data, and the data management system and database. Each user must be included on the list of key staff, with roles and responsibilities identified. Appropriate access and permissions are granted based on roles and responsibilities. Study participant confidentiality is maintained by the use of participant IDs and independent numerically coded specimen samples. Access to confidential information such as names and addresses, or other identifying information (i.e. Medical records numbers) is kept at the clinical site, and restricted to the research team member charged with the responsibility of following a particular participant.

Numerous precautions have been instituted to protect the confidentiality of the research participants and the data we obtain. Study research data is de-identified and separated from each participant's identifying information. The confidential data linking the participant to their ID is stored by the site coordinator or PI in a paper log kept under lock and key or electronically on a computer that is password-protected, but cannot link directly to the study data.

The DCC will work closely with the study investigators to ensure that the online transmission of forms and laboratory data protects participants' confidentiality, meets IRB requirements and satisfies HIPAA regulations requiring the proper de-identification of participants.

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Chapter 10: Data Management and Administrative Procedures

10.1 OVERVIEW

This chapter contains general guidelines for data collection and processing that will be used throughout the study. It covers topics such as

- Identification of participants
- Correct usage of contact occasion, FDF #, and sequence numbers
- Instructions for recording and correcting data collection forms
- General data entry guidelines, adding revisions to the Manual of Procedures and to the forms, and
- General data management guidelines to ensure participant confidentiality, data security accuracy and accessibility.

10.2 PATIENT CONFIDENTIALITY

Violating participant confidentiality is regarded as a serious problem. Each Clinical Center's Investigator is responsible for confidentiality of study documents, although this responsibility may be delegated to the Center's Study Coordinator. All study personnel are expected to maintain participant confidentiality.

All study documents should be treated as confidential. Of particular concern is any document that contains both the Study ID Number and the participant's name or other personal identification. Clinical data is especially sensitive.

All research data forms and/or paper records or participant binders should be kept stored in locked cabinets or offices. Records in use must be kept under the supervision of study staff that has been appropriately trained in HIPPA and site-specific confidentiality procedures.

Data management procedures for PROTECT were designed with participant confidentiality in mind. All data collection forms are entered and stored at each Clinical Site. Participant name or any other personal identifier will not be entered in the data management system. Participants are identified only by study ID number on all data files at the Data Coordinating Center (DCC).

No data containing participant personal information should be sent to the DCC. If certain participant data are required to be sent to the DCC, such as records containing details regarding an adverse event or endpoint, personal identifiers must be removed at the clinical center prior to sending to the DCC.

10.3 PARTICIPANT ID NUMBERS

ID numbers for participants screened and enrolled into PROTECT are generated at the Data Coordinating Center (DCC). Each participant is assigned a unique PROTECT ID number. This ID number is what is used in the studies database to discern participants, with no participant names or other identifying information. The clinical site is the only location that maintains the link to any identifying information of the participant.

Each site will be given an Excel Spreadsheet of valid Participant IDs for its own data management purposes, and sheets of ID labels for use on data collection forms will be provided.

Only one ID is assigned to a participant over the course of the study. The IDs are assigned at the time the participant signs the study consent. PROTECT ID's follow the following format:

7 fields:

- Field1 P (for PROTECT)
- Field2-3 Site Identifier
- Field 4-6 Participant ID number
- Field 7 Check Digit (based on arithmetic algorithm for QC)

The following site identifiers are used:

Site Code	Site Name
BO	Harvard - Children's Hospital Boston
BU	Women & Children's Hospital of Buffalo WCHOB
CH	Ann & Robert H. Lurie Children's Hospital of Chicago
CN	Cincinnati Children's Hospital Medical Center
CT	Connecticut Children's Medical Center
CU	Morgan Stanley Children's Hospital at Columbia University
FL	Nemours Children's Clinic
GA	Emory Children's Center
HP	Cohen Children's Medical Center
IN	Riley Children's Hospital Indiana University School of Medicine
LA	UCLA Medical Center
MD	Johns Hopkins Children's Center
MN	University of Minnesota Medical Center
NC	University of North Carolina at Chapel Hill
NJ	Goryeb Children's Hospital/Atlantic Health
NS	IWK Health Centre
NY	Mt. Sinai Hospital
OH	Nationwide Children's Hospital
ON	Children's - East Ontario
PH	Children's Hospital of Philadelphia CHOP
PT	Children's Hospital of Pittsburgh of UPMC
RI	Hasbro Children's Hospital
SF	University of California at San Francisco
TN	Monroe Carell Jr. Children's Hospital of Vanderbilt
TO	Toronto Sickkids Hospital for Sick Children
TX	UT Southwestern
UP	SUNY Upstate Medical University - Golian Children's Hospital
UT	Primary Children's Medical Center University of Utah
WI	Medical College of Wisconsin

10.3.1 Participant ID Labels

Each site will be provided participant ID Labels. These are ½” x 1 ¾”, with 80 labels per page, all of the same ID to be used for the general data collection forms. In addition, a sheet of ID labels with associated bar codes will be included. These are to be used in the header on the Specimen Data Collection form.

We ask that you use these labels rather than writing the participant ID number on data collection forms to prevent transcription errors.

Initial shipments of labels will be sent to each activated site. The DCC will monitor each participant’s status in the study and provide additional labels as needed for each ID, or for additional participants. The site can request additional labels at any time.

10.3.2 Laboratory Specimen IDs and Labels

Specimen labels are provided along with the necessary laboratory kits from the PROTECT central laboratories. Refer to Chapter 4 for descriptions of laboratory kits. See Chapter 1 for more information regarding ordering additional laboratory kits, specimen labels.

10.3.3 Linking Participant IDs to Central Lab Specimen IDs

The linkage to Participant ID and Central Lab Specimens is done through the Specimen Collection form, whose header contains the Participant ID number with bar code. The Specimens IDs are contained on the lab labels provided with the specimen kits. All IDs are entered into the database, providing the data linkage.

10.4 PAPER FORMS

In PROTECT, the DMS screens are designed for entry from paper forms, where data are collected. Forms are available on the study website as a PDF form set, and individually for downloading and printing as needed.

10.4.1 Recording Responses

Most of the questions in the PROTECT forms have pre-coded responses. There are a few questions, however, that you must write in a response to the question. Some questions have pre-coded responses as well as an “other” category. If the participant’s answer does not fit into a pre-coded answer, you must specify the response. The recording practices below must be followed at all times to assure that the response recorded accurately reflects the participant’s answers and to assure the questionnaire data can be converted to machine-readable form.

- You must listen to what the participant says and record/key the appropriate answer if the response satisfies the objective of the question.
- In recording answers to open-ended questions or “other” categories, print/key the response verbatim.

- Use a blue or black ballpoint pen when recording on paper form.
- Record in the white space below the questions any responses “that don’t quite fit” in one of the response categories. Your notes will help the analysts in understanding points of confusion, difficulty, etc. When using direct data entry, these notes can be entered as note logs in the DMS.
- Always print or write legibly when using paper forms.
- If a participant refuses to answer a question, write “refused” in the left margin beside the question, in the DMS this field is left blank but coded as missing using the DMS feature available for each data field, click on the >> next to the field, and select from the drop down window at the bottom of the pop-up box, to avoid future queries.
- If an answer is unobtainable for any reason, or is validly missing, write ‘missing’ in the left hand margin beside the question and in the DMS leave the field blank but code as missing using the DMS feature available for each data field, click on the >> next to the field, and select from the drop down window at the bottom of the pop-up box, to avoid future queries.
- A single answer choice code must be checked or circled for each question to represent the participant’s answer, unless the item states you can answer all that apply.

Some of the questions in the PROTECT study ask about recall of events over time. You may assist the participant by working with him/her on math or pinpointing dates or events. Another way to help pinpoint more accurate information is to ask the participant to think about time of year or season when an event occurred.

10.5 MANAGING OFFICIAL STUDY DOCUMENTS

Current versions of all study documents, protocol, data collection forms, chapters of the MOP, user’s guides, and other important documents are available on the study website at <http://www.protectstudy.com>. These require the appropriate username and password for entry into the documents section. Each document exists as a PDF file in order to retain any necessary formatting.

IMPORTANT: Versions of these documents that are designated as usable in the field will be sent to each study site in the official PROTECT Study Reference Manual (SRM) notebook. One notebook is provided to each Project Coordinator, and is considered an official study document. Note: all contents of this notebook are also available on the study website. Section 9.5.1 below describes the process of communicating and verifying receipt of communication on modifications and updates of documents.

10.5.1 Numbered Memos

The DCC will routinely send various emails or memos that are numbered and identified as “Numbered Memos”. These memos are considered official documents and are to be stored at the back of the SRM notebook. Updated information regarding the protocol, forms, SRM chapters, QxQ’s, and other documents being used in the field will be sent to the centers as Numbered Memos. Numbered Memos will be sent to all PROTECT Project Coordinators and Principal

Investigators. It is each site's Project Coordinator's responsibility to make sure this notification goes to all PROTECT staff at their site. Each Project Coordinator must send email confirmation of receipt of every Numbered Memo and binder update as described in the memo.

10.5.2 Adding Revisions to the Study Reference Manual

The Numbered Memo will instruct the recipient to print updated documents (contained in the accompanying email or available at the PROTECT Study Website) and place the updated versions into the Site's Study Reference Manual (Project Coordinator's notebook), replacing the older version. Numbered memos should be stored at the back of each binder, with the most recent memo on top. Each site should provide archival storage of previous versions of documents according to their Institutional requirements. The DCC will also keep all versions of official documents archived. Only memos that say "DCC Memo #" should be filed in the Numbered Memos section. The status of this notebook is monitored during site monitoring visits.

Outdated pages of the SRM, forms and/or QXQ's should be attached to a copy of the appropriate numbered memo and placed in a permanent, chronological "Archive Manual" binder or file folder.

In the event that study forms are revised, you will be instructed on how to update patient binders with copies of the newly revised forms which will be emailed to you by the DCC.

10.6 SOURCE DOCUMENTS

Source Documentation - A source document is a document that contains the original recording of study data. Source documents are needed to validate information recorded in data collection forms and in the Data Management System. GCP guidelines require that investigators maintain source documents, separate and apart from the study data forms, for all study patients.

The following are examples of source documentation for the study:

- Patient medical records and chart
- Patient progress notes during the study
- PROTECT paper forms from interview
- Documentation of all contacts with the DCC or CCC regarding study patient issues

Data recorded in the Data Management System are subject to verification and will be monitored for legibility, completeness, accuracy and verification with respect to the source records.

All necessary data collection forms will be provided by the DCC in the study SRM for all assessments in the study upon site activation. In addition, electronic copies of these documents are kept on the study website for site printing.

10.7 DATA COLLECTION FORMS

All data collection in PROTECT is documented on case report forms (CRF). Each specific PROTECT case report form has an associated QxQ (question by question) instruction document

to aid in the data collection process. A listing of all forms and copies of each form and QxQ are contained in the SRM.

In addition to each case report form being stored in PDF format on the study website, PDFs of form sets (required forms for each contact type) will be stored, labeled with an instruction sheet providing information on procedures, forms, the follow-up timeframe and contact occasions for easy identification. Sites should print these for use during their contact calls and visits.

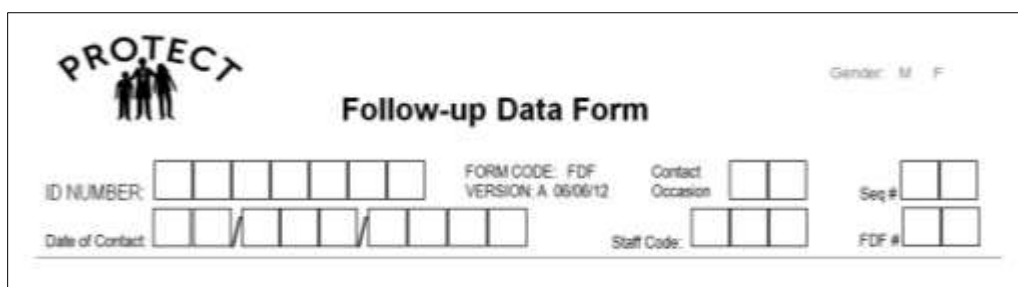
10.7.1 Form Headers

Data is to be collected on paper forms. The computer screens used for data entry are designed to correspond for data entry from paper data collection forms. All forms begin with one of the following “headers”.

Example header of a form used only at Screening, Baseline, and Day 0 (not used during follow-up)



Some forms are used at Screening, Baseline, Day0 and Follow-up, or only at Follow-up. These forms have a slightly different header with the addition of the FDF# on the lower right. See Section 10.7.1.5 regard the FDF#.



10.7.1.1 Form Title

Identifies the data form by name, and is often referred to by the 3-letter form code mnemonic.

10.7.1.2 Participant's ID Number

Preprinted participant ID labels (supplied by the DCC) should be used in the header whenever possible. If the 7-digit ID number is handwritten, care must be taken to make sure the number is very legible for data entry.

10.7.1.3 Form Code and Version

Form code is the 3-letter abbreviated form mnemonic made up from the forms title, and is unique for each data collection form in the PROTECT study. Form versions begin with the letter ‘A’, then increment as revisions are made to the data collection forms. Form codes and versions are preprinted on all forms.

Form codes and versions are part of the unique identifier of a data record along with ID, visit and sequence number, and are used as part of each data items identifier. For example, question #2 on the Demographic Form, version A, would be referred to as DEMA2. All data queries and communication from the DCC regarding data items will use this terminology.

10.7.1.4 Contact Occasion Number and Sequence Number

Contact numbers are used to differentiate a participant’s protocol contact visit or call. Each protocol contact is associated with a Contact Occasion Number (CO#).

Some data collection forms are collected multiple times over the course of the study, and can even be used multiple times within a contact occasion. The general rule of thumb is:

Forms designated as Screening/Baseline are recorded as CO:01

Forms designated as Day 0 (zero) are recorded as CO:02

Follow-up contacts are all designated beginning with CO:03 and for forms collected during follow-up that are collected between protocol scheduled contacts, the visit number recorded should correspond to the last expected visit number (beginning with CO:03).

Forms that are collected more than once within a protocol scheduled contact number are differentiated by incrementing the sequence number. An example of this might be SAEs occurring, or even additional clinic visits at the request of the family. The Sequence Number is 2-digits and begins with 01. Sequence number can be assigned when completing the form, but should be verified when entering the form into the DMS. Sequence number is the DMS count of the multiple forms entered within form code and contact occasion.

10.7.1.5 FDF Number

The Follow-up Data Form (FDF) is required at every patient contact; this form triggers the appropriate data collection for that contact. In order to tie together all the data forms collected for a contact associated to the FDF, we use the FDF#. The FDF number is independent of the DMS and the Sequence Number, though will often be the same number. FDF# is a 2-digit number beginning with 01. This number is incremented within the FDF and contact occasion the same way the Sequence Number is, for multiple FDF forms within a specific contact occasion to accommodate unscheduled contacts. All other data forms collected during that contact associated with the FDF are to have the FDF # that is recorded on that FDF form onto their form header. In this way, the DCC can create form sets of each contact.

Follow-up example:

- Family calls at wk 1
- Site calls at wk 2 (protocol)
- Family comes to clinic at wk 3
- Family comes to Clinic at wk 4 (protocol)

FDF Form header is completed:

CLF Form header at these contacts is completed

	CO#	Seq#	FDF#		CO#	Seq#	FDF#
wk 1	03	01	01	wk 1	no CLF form, telephone contact		
wk 2	03	02	02	wk 2	no CLF form, telephone contact		
wk 3	03	03	03	wk 3	03	01	03
wk 4	04	01	01	wk 4	04	01	01

10.8 DATA MANAGEMENT

10.8.1 Web Based Data Management

The PROTECT Data Management System [DMS] is a set of programs which the DCC uses to manage data collected in the PROTECT Clinical Centers. This DMS has been designed for flexibility using World Wide Web systems. The system can be used from any computer with a high speed Internet connection. An interactive tutorial is available on the study website for training. The URL is <https://cdart.csc.unc.edu/PROTECT>, the username and passwords to use the system will be provided to each site's Project Coordinator from the DCC in a secure and confidential manner.

The DMS provides several major functions:

- Data Entry: Allows data collection forms to be keyed, edited and updated, locally through the PROTECT internet DMS.
- Reports: Provides reporting based on study needs.

10.8.2 Clinical Center Data Management

The DMS will have numerous reporting programs designed as a tool to help facilitate data management at the sites. The PROTECT DMS reporting systems will generate participant lists, form inventories, scheduling reports, recruitment reports, missing fields check, etc. to help the clinical centers with any data management tasks.

Actual scheduling and other managing of participant flow, data collection, and filing of paper source data are the responsibilities of the clinical site.

A DMS User's Guide will contain documentation of the reporting functions. Information on updates and changes to these reports will be provided through the Numbered Memo communication. Additional training will occur via emails or Project Coordinator conference calls.

10.8.3 Central Laboratory Data Management

The Specimen Collection Form (SCF) documents the collection and shipment of specimens. It is both data entered at the site, and a copy is to be included with the specimen shipment.

Specimens are analyzed either in batch or upon receipt at the Core Lab. Laboratory results will be electronically transferred to the DCC from the labs. Investigators and clinic staff will be blinded to all non-standard testing done at the central laboratories.

10.8.4 DMS Training and Certification

DMS training will be provided at the central training scheduled at the beginning of the study, and additional training is available online on the PROTECT website. Project Coordinators at each site are required to attend the training. Clinic staff who are unable to attend central training can

be trained using the PROTECT Coordinator Training Checklist (see Training section of the PROTECT website). There will also be site monitoring visits throughout the study and some DMS training can occur during these visits as well (depending on site needs, available time and resources).

10.9 GENERAL INSTRUCTIONS FOR COMPLETING PAPER FORMS

The following provides instruction on how to appropriately complete and make corrections on the study's paper forms. Data recording should be done with a black or blue ball point pen. Responses should be printed legibly; please do not use cursive writing.

10.9.1 Recording and/or Correcting Data Items

All items fall into one of three main categories:

- Fill ins
- Multiple choice,
- Qualitative information (comments/short-answer questions).

Techniques for completing each of these types of items, as well as making corrections, are described below. A general rule is to record information only in the spaces provided (except for some error corrections).

Corrections should be made in the following manner:

- ◆ Cross out the original response in such a way that it is still legible.
- ◆ Write the correct response above or to the side of the original response.
- ◆ Date and initial the correct response.
- ◆ In cases where numerous corrections were made to the same response, the final corrected response should be circled.
- ◆ Major changes should be documented with a brief explanation in the margin.

Do not attempt to correct errors by using correction fluid or erasers at any time.

When a response is outside normal limits or seems contradictory based on other data, confirm the data and then write 'CONFIRMED' in the margin. This will decrease time-consuming queries.

Carefully proofread each page of data for legibility, accuracy, and completeness prior to transferring the form to the data entry staff.

10.9.2 Recording and correcting "fill-in" responses

For questions requiring a text response, an acceptable amount of space will be provided.

Example:

~~0~~ ~~7~~ BAB (date)
 . 4 ~~7~~ ~~0~~

10.9.3 Recording or correcting multiple choice responses

In this type of question several alternatives are given for the answer, each having a corresponding alpha code (wherever indicated) and word description. Circle or check (if boxed) the correct response.

Example: Has the patient used oral or IV corticosteroids for any non-GI indication in the past four weeks?

Y N U

If a response is marked incorrectly, mark through the incorrectly coded response with an "X" and check the correct response, initialize and date correction.

Example: The actual response is Unknown. The correction looks like:

BAB (date) U
 N

10.9.4 Recording Qualitative Responses

Some forms contain a substantial amount of qualitative data. These short answer and comment questions will be handled differently than the "fill in" type data. Since these types of questions will almost certainly be filled out by hand any unreadable answers/comments should be answered to the best of the data enterers' ability with a note describing what was illegible.

10.10 SKIP PATTERNS

Skip patterns occur in some multiple choice type items. Here, if a certain response is selected, it is necessary to skip over one or more items to the next applicable item. This may be indicated on the form with a "skip to question #" statement usually italicized and in parentheses. If that response is selected, the next item to be asked is the one indicated in the skip to statement. If the other response is selected, always proceed to the next item unless otherwise directed.

Example:

Has the dose been stable for 1 month?.....Yes No→**Go to Item 15**

In this case, if the response is "No", skip to item 15. If the response is "Yes", proceed to the next question.

Occasionally, a skip pattern will occur in a fill-in type item. In those instances, specific instructions are provided on the form. Again, if the skip criteria are not satisfied, continue with the next item.

10.11 COMMENTS AND NOTELOGS

Comments The Specimen Collection form is the only form that has allocated spaces for comments. However there may be times where you may want to add a comment on specifics of the data. Comments should only be recorded if they are related to the overall collection of the data on the form. Comments should be brief and concise. A comment we might expect to see would be, for example, on the CDZ, ‘Patient had a cast on right leg’ (since that may impact the measurement of both height and weight). Comments can be entered in the DMS as notelogs.

Notelogs: A notelog is a feature in the DMS that allows for comments that relate to a specific Item on the form. See Data Management Users Guide (Appendix A of MOP chapter 10) under “Adding a Notelog” for the notelog feature. ,.

10.12 PERMANENTLY MISSING FORMS AND UNRESOLVABLE FIELDS

The DMS training, and the ‘Data Management User’s Guide provides specific instruction on what to do in the system if an entire form is permanently missing. A permanently missing form is when a form is required at a contact but data is unable to be obtained. Under each visit, the DMS lists all forms that could be used at that visit, but not all of these forms are required since many forms are only used in specific circumstances. For instance, the SAE form is listed at each visit, but is only required when an SAE has occurred. Forms that are not required do not need to be marked as permanently missing.

If a field on a form is missing, and that data cannot be obtained do not skip over the question. For unresolvable fields click on the >> to the right of the field a window will open for you to select a reason the field is missing. See Data Management Users Guide for Setting Data Fields to Permanently Missing. To verify all fields of a form have been completed save the form then enter the form again. At the end of the form is a button called missing fields. This will run a quick report identifying which fields need to be completed)

10.13 UNSCHEDULED VISIT FORMS

In the event that assessments or biological specimens are collected during an unscheduled visit, the visit number on the form is recorded as the previous scheduled visit the patient attended. The SEQ on a form from an unscheduled visit is always 02 for the first unscheduled visit (and is 03 if there is a second unscheduled visit between visits, and so on).




DMS Users Guide

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Legend of Icons:

The information icon  is located in the upper left corner above the forms menu and just to the left of the Subject ID. Clicking on the icon brings up the Legend (show below)



Clicking on the icon brings up the Legend (below) providing a legend of all the icons on the form entry screens



Note: The lock function has been disabled for PROTECT

Running Reports:

On the main menu on the left of the screen:

Click on Data Extraction

Click on Reports, 1st row under Data Extraction



Click on the icon  to the right of the report you want to run.

Report Selection

Report Title	
clinic_scheduling	
generic_followup_contact_schedule	
participant_followup_contact_schedule	
participant_followup_status	

Once the report comes up, you can choose to print it (or save to file) by clicking on the 2nd to last icon on the right (looks like a printer), in the upper left tool bar (just below the URL address). The other icons are not features useful in our study.



Adding a Notelog:

A notelog is a feature in the DMS that allows the site to include comments related to a specific item on the form. Occasionally a notelog may automatically pop-up during entry of certain fields that may require additional comments. Notelogs should be very short and specific.

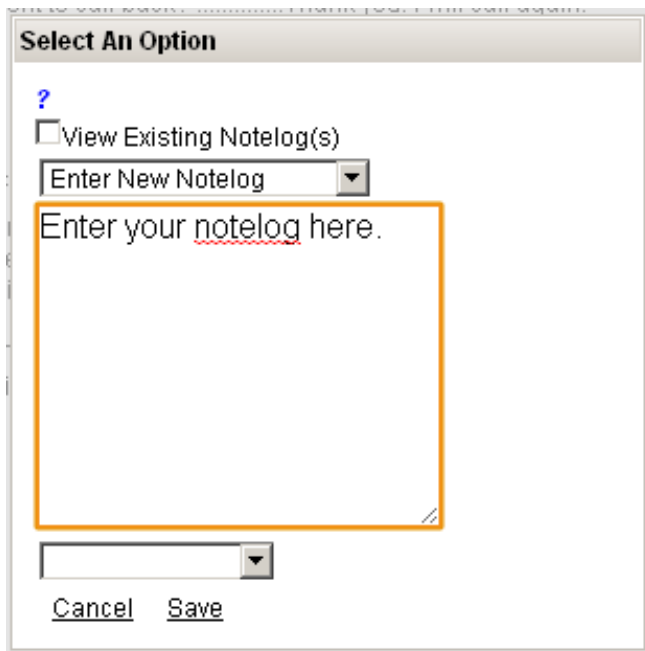
Click on the >> icon to the right of the data field.



A box will open on the screen “select an option”.

The 1st drop down menu will say “Enter a Notelog”

Use the space provided to enter the Notelog and then click ‘Save’.



The screenshot shows a dialog box titled "Select An Option". At the top left is a question mark icon. Below it is a checkbox labeled "View Existing Notelog(s)". Underneath is a dropdown menu with the text "Enter New Notelog". Below that is a large text area with the prompt "Enter your notelog here." and a red dashed underline under the word "notelog". At the bottom of the text area is a small icon. Below the text area is another dropdown menu. At the very bottom are two buttons: "Cancel" and "Save".

Setting Data Fields to Permanently Missing:

All data fields (except valid skipped fields) are required. The 'data field permanently missing' option is used to let the DMS know that this field is unobtainable, thus eliminating further queries for the data.

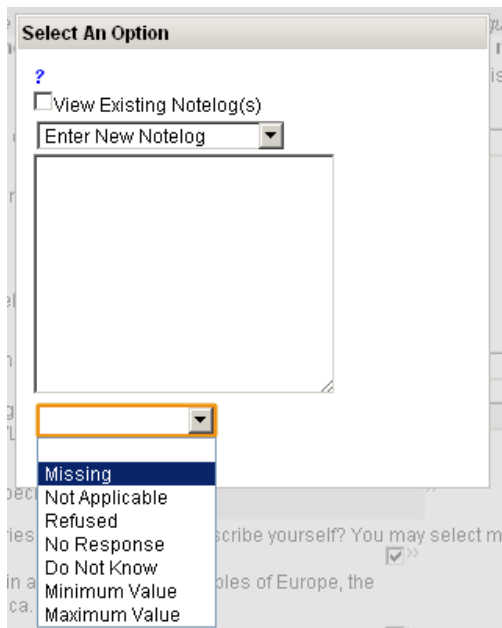
Click on the >> icon to the right of the data field.



A box will open on the screen "select an option".

The 1st drop down menu will say "enter a notelog"

At the bottom of the box is another drop down menu—one selection is "missing (or) permanently missing". Select this option and then click on the "save".




The >> icon will convert to a ✓.



Setting Form to Permanently Missing:

Occasionally there may be an expected or required data form (or a full contact) that is unobtainable.

From the form grid click on the check box associated with a form in the last column, then click on the last icon in the header .

The status column will state “permanently missing”.



Contact Name	Form Name	Seq#	Status						
CO 01 Screening/Baseline	*								
CO 02 Day Zero	*								
	ADT - Additional Med	1							
	ATZ - Another TRT Day0	1	Entry Complete						
	CDZ - Clinical Data Day Zero	1	Entry Complete						
	CLF - Conductivity								
	EDZ - Erial Day0	1	Entry Complete						
	HDF - Hospitalization								
	IT - Informed Consent Tracking	1	Entry Complete						
	LLR - Local Lab Results	1							
	PVC - PUGAI	1	Entry Complete						
	SAC - Service AE								
	STR - Stored TRT	1	Entry Complete						
	STZ - Study TRT Day0	1	Entry Complete						
	SWP - Study Withdrawal								
CO 03 2wk FU	*								
CO 04 4wk FU	*								
CO 05 8wk FU	*								
CO 06 8wk FU	*								
CO 07 10wk FU	*								
CO 08 12wk FU	*								
CO 09 20wk FU	*								
CO 10 28wk FU	*								



DMS Reports for Sites

16April 2014

Clinic Scheduling:

This report presents a sites upcoming protocol scheduled contacts (target data and windows) among active participants, for a time period specified by the users.

Colectomy Expected Dates:

This report lists expected dates for follow up visits on participants who have had a colectomy at each site

Data_Inventory_byID:

Listing of all data forms entered into the DM for a specified ID, sorted by Contact Occasion, FDF#, Seq#, and FormCode.

Data Inventory_bysite:

Listing of all data forms entered for all participants in the DM for a specified site, sorted by ParticipantID, Contact Occasion, FDF#, Seq#, and FormCode.

Enrollment Report:

This report generates a list of participants that were enrolled at a site for a specific time period.

Generic_Followup_Contact_Schedule:

This report generates a participant contact follow-up schedule. Site enters a participant ID and enrollment date (DayZero from EDZ), target follow-up contact dates and windows are presented.

Participant_Followup_Contact_Schedule:

Similar report above, site enters participant ID, database is searched for enrollment date (from entered EDZ form), target follow-up contact dates and windows are presented.

Participant_followup_status:

Table reports on numbers of participants completing protocol scheduled follow-up contacts up through 52 weeks, including withdrawals, by site. Based on data entry of EDZ, FDF, and SWF.

Recruitment_report:

Simple report of numbers of participants consented, enrolled, and screen failures, based on data available in data base (ICT, EDZ, SWF).

SAE Listing:

This listing lists all SAEs for all participants at a site and is especially helpful when reporting to site IRBs

Chapter 11: Regulatory Documentation

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11.1 REGULATORY REQUIREMENTS

Each site will maintain a regulatory binder on paper, or other secured data storage. The regulatory binder should contain at a minimum the documents listed below. The Clinical Coordinating Center (CCC) at the Connecticut Children's Medical Center must have the following documents on file prior to site approval and initiation of the study and as they are updated:

1. Original signed Protocol Signature Page
2. Copy of IRB approval documentation for current protocol
3. Copy of the most current IRB approved informed consent form and participant recruitment materials
4. Original FDA 1572 (or most current copy)
5. CV for the Principal Investigator and co-investigators (first page signed and dated)
6. Medical License for the Principal investigator and co-investigators
7. Site personnel Conflict Of Interest (COI)
8. GCP/HIPPA training for ALL study personnel

9. Delegation of duties/signature page

The study's Data Coordinating Center (DCC) at the University of North Carolina at Chapel Hill must have the following documents on file prior to the start of the study and as they are updated:

1. Copy of IRB approval documentation for current protocol
2. Copy of the most current IRB approved consent form

3. Delegation of duties/signature page
-

11.1.1 Initial IRB Approval Letter and subsequent amendment letters

The approval letter must:

- include complete correct protocol title and current version date
- state the study material reviewed is specifically indicated (i.e. protocol, amendments, informed consent, etc.)
- signed/initialed by IRB Chairperson or authorized representative
- IRB's project number

11.1.2 Informed Consent (IC)

A. DRAFT ICF –

A template Informed Consent Form was created for your use. We require that you E-mail your IC to the CCC **prior to submission** to the IRB. This will keep repeat submissions to the IRB to a minimum.

The IC must contain the following:

- Affiliation with Section 1 and/or 3 of the 1572 must be present on the ICF
- All information is listed correctly (i.e., PI name, any sub-I's names, site info etc.)
- A **new Version date** must be used each time the ICF is revised to distinguish between consent versions
- NIDDK repository language same as the template

B. APPROVED ICF

Send a copy of the IRB approved Informed Consent Form to the CCC and DCC. Please provide a stamped ICF if your IRB customarily stamps approved consents. If your IRB does not stamp the ICF, the IRB approval letter must reference the version date of the ICF approved.

C. Participant recruitment materials created beyond the provided study brochure should be submitted to the CCC as well.

11.1.3 Form FDA 1572

The form needs to be typed. The original signed and dated Form FDA 1572 is to be retained at the site and a copy sent to CCC (this applies to all future revised 1572s also).

Section 1: Type the PI's name and mailing/UPS address. The PI's name should be spelled correctly and correspond with the CV. Be sure to list suffixes such as Jr. Sr. II, III. If the test article should be shipped to an address other than that listed in Section #1, the address must be listed in Section #3.

Section 2: The PI's curriculum vitae (CV) or other statement of qualifications must accompany the Form FDA 1572. We have placed an "X" in this box for you.

Section 3: List the name(s) and address(es) of any facility(ies) where subjects will be examined, test article dispensed/stored, study documents will be stored, and key study-specific procedures will be performed on subjects. If the study is conducted at the address that is entered in Section #1, the name and address must also be entered in Section #3. "Same as above" or "See Section #1" cannot be used. The pharmacy where drug will be shipped should also be listed here.

Section 4: List the names and addresses of laboratories being utilized in study as they appear on their lab certificates. The central Laboratories have been listed for you.

Section 5: The full name and address of the IRB/ with jurisdiction over the location(s) listed in sections 1 and 3 should be entered. This needs to correspond to the name and address on the approval letter, membership roster, and patient informed consent.

Section 6: List all Sub-investigators the PI has authorized to participate in this study. Their names should be spelled correctly and correspond with the CV. Enter "none" when appropriate. **Do not leave this section blank.**

Section 7: The complete protocol title and number are listed in this section.

Section 8: This is a phase 4 study. This section has been completed appropriately.

Section 9: This section lists the commitments/responsibilities that the PI agrees to. The PI needs to read these before signing and dating the form. This section will be reviewed during the Pre-Study/Study Initiation process.

Sections 10 & 11: The PI (listed in Section #1) must sign and date the form in the spaces provided (must be the PI's handwritten date). Please use black ink. Stamped signatures will not be accepted. **Ensure the date is legible.**

The 1572 form serves as a direct communication with the FDA. Please remember that the information on this form is utilized by the FDA to determine where and by whom the clinical trial is being conducted. A new 1572 is required whenever changes in any of the information listed has occurred. **Additionally, your IRB should be notified of changes made to study site(s) and or personnel.**

11.1.4 CV for Principal Investigator

- Copy of a current CV (signed and dated) for the PI who is listed in Section #1 of the 1572 (the CV should be no more than two years old at any given time)
- Ensure that the PI's name is spelled correctly and corresponds with the name listed in Section #1 of the 1572
- CV indicates affiliation to a location/institution where the study will be conducted (an address listed in Section 3 of the 1572)
- Relevant education, experience and training is documented that qualifies the PI for the study

11.1.5 Current Medical Licensure for the Principal Investigator

- Photocopy of current license from the state/provincial licensing board is required for the principal investigator to be provided to the CCC via email

11.1.6 Proof of Human Subjects Training for all Study Staff

All principal investigators and key personnel are required to undergo training in the protection of human subjects in research. Please complete the training required by your institution and keep records of completing such training on file for all study personnel. If your institution does not offer training in human subjects' research, you may complete the training offered by the NIH at <https://www.citiprogram.org/Default.asp>

11.1.7 Delegation of duties/signature page

Sites must maintain a Delegation Log of Study Personnel. This will contain contact information (email address) and study role (see Appendix C).

- All study personnel must sign the signature log regardless of role.
- If someone leaves the study team, a stop date should be provided noting the date of termination. The staff member should not be lined through or deleted from the signature log.
- Any added study personnel should sign as they join the project.
- For sites utilizing a pharmacy to distribute study medication to patients, it is suggested that the name of the pharmacy director or the name of the lead pharmacist for the study be included on the Delegation Log for the site.

- A copy of this log must be forwarded to the CCC and DCC via email each time someone joins or leaves the study team.

11.2 ONGOING REGULATORY DOCUMENTS

All sites must retain a regulatory binder that must be updated as new revisions of study documents are available and approvals are renewed. A copy of each subsequent report to the IRB to support continuation of the study, modification of the study (amendments), and final report to the IRB should be kept on file.

Study documents include:

- All IRB approvals for the protocol and informed consent
- All IRB correspondence
- Copies of all revisions of the protocol
- Copies of all revisions of the informed consent forms
- Updated FDA 1572
- Licenses and CVs for New Principal Investigators and Co-Investigators listed on the FDA 1572
- Monitor site visit Reports
- Site signature and delegation log
- IRB Communication
- Notification of SAE and related reports and necessary safety information (to sponsor , IRB and others are required)

11.3 AFTER STUDY COMPLETION OR TERMINATION OF THE TRIAL

After completion or termination of the trial, all of the documents identified in section 11.1 and 11.2 should be in the file together with the following:

- Investigational drug accountability
- Documentation of investigational product destruction
- Completed subject identification code list
- Final trial close-out checklist

11.4 OTHER DOCUMENTS REQUIRED AT STUDY-START UP BUT NOT FOR SITE APPROVAL

1. CV for all study personnel listed of the FDA1572 (signed and dated)
2. Current medical licensure for all personnel listed of the FDA1572

11.4.1 CV for all study personnel listed of the FDA1572

- Copy of a current CV (signed and dated) for each personnel listed in Section #6 of the 1572.
- Ensure each study personnel's name is spelled correctly and corresponds with the name listed in Section #6 of the 1572.
- CV indicates affiliation to a location/institution where the study will be conducted (an address listed in Section 3 of the 1572).
- Relevant education, experience and training is present that qualifies the study personnel for the study.

11.4.2 Current Medical Licensure for all for all study personnel listed of the FDA1572:

- Photocopy of current license from the state/provincial licensing board is required for all study personnel (if applicable)
- The name on the license corresponds to the name in Section 1 or 6 of the 1572 for each study personnel (if applicable)

11.5 REGULATORY DOCUMENT STORAGE

1. Archiving Regulatory Documents

Study documentation must be kept so that the data is accessible after the trial is completed. This is because future studies may suggest further period of follow-up, allegations could be made of fraudulent behavior, or concerns arise about side effects and participants need to be contacted

2. When documents should be archived

Regulatory documents should be archived as soon as practicable after the completion of the study.

3. How should documents be archived

All archived material should be stored in archival boxes that are clearly labeled with the name and reference number of the study, Sponsor, Investigator and date documents will be archived to. (See example in Appendix A.)

Details of the archiving location should be recorded in a location register stored in the site office. (See example in Appendix B.) This register should record the name and reference number of the study, Sponsor, Investigator and date until which documents will be archived. Storage conditions should ensure that regulatory records are maintained in a legible condition and can be retrieved upon request of a regulatory authority. Any change in the location of the stored documentation should be recorded in order to allow tracking.

Adequate and suitable space should be provided for the secure storage of all regulatory records from completed studies. The facilities should be secure, with appropriate environmental controls and adequate protection from physical damage.

The investigator should inform the CCC of the storage arrangements for their regulatory documents.

The ultimate responsibility for the documents to be retained by the investigator/institution resides with the investigator/institution. If the investigator becomes unable to be responsible for their regulatory documents (e.g. relocation, retirement etc.) the CCC should be notified in writing of this change and informed as to whom the responsibility has been transferred.

The documents to be retained by the investigator may be stored in commercial archives. This may also be an option for source data, when the hospital/institution is unable to retain patients' trial records, relating to clinical trials, for a sufficient length of time.

4. **How long documents should be archived**

The site investigator must retain investigational product disposition records, copies of CRFs and source documents for a minimum of four years after the trial is complete or for the maximum period required by Institutional policies, whichever is longer.

11.6 INVESTIGATORS RESPONSIBILITIES (GOOD CLINICAL PRACTICE)

Good Clinical Practice (GCP) guidelines are not regulations or legal requirements but represent a standard of practice acceptable to the FDA. Adherence to GCP guidelines assures sponsors that no adverse action will be taken by the FDA.

- ✓ Conduct the study in strict adherence to the protocol.
- ✓ Obtain Institutional Review Board (IRB) approval to conduct the clinical trial.
- ✓ Provide the CCC and DCC with written documentation that the study protocol, any protocol changes, and the informed consent form have received approval from your IRB.
- ✓ Report to the IRB as required. The IRB must assume continued responsibility for the study and review the research on at least an annual basis (renewal schedule provided by your IRB).
- ✓ Adhere to Regulatory Document Requirements presented in this manual.
- ✓ Store the study medication in a secure and locked area with limited access. The storage and custody of the study medication are the responsibility of the investigator.
- ✓ Supervise the use of study medication as outlined in the protocol. The study medication may only be dispensed by staff working under the supervision of the investigator or hospital pharmacist for use in the study.
- ✓ Maintain adequate records of the receipt and disposition of all study medication, to include dates, quantities and use by study patients.
- ✓ Inform each patient of the risks and benefits of participating in the study and obtain a properly signed and dated informed consent form previously approved by your IRB.
- ✓ Ensure there are procedures for contacting study patients who do not return for scheduled visits. If a patient is lost to follow-up, the site should document two phone calls made to the patient and should send the patient a certified letter requesting a follow-up appointment.

- ✓ Document all Adverse Events in the DMS and source documents; report all Serious Adverse Events immediately to UNC via the Data Management System (DMS) and document thoroughly.
- ✓ Report all Serious Adverse Events to the IRB as required by your IRB guidelines.
- ✓ Document and maintain accurate source documents and enter the data in the DMS for all study patients.
- ✓ Storage and custody of all study-related records are the responsibility of the investigator.

11.7 REGULATORY BINDER ORGANIZATION

Each site should create a 3 ring regulatory binder at the beginning of the study.

- All files shall be updated throughout the study.
- All documents and correspondence shall be filed in chronological order with the most recent item at the front of the section and under the correct tab. See table below.

Make sure to file the necessary regulatory documents at your site and send the required documents to the CCC.

Tabs Title	Document to be filed	Located in file of	
		Site	CCC
Study Protocol	All versions of the approved protocol: the original version and all revisions	X	X
IRB Approved Informed Consent	All versions of the approved consent: the original version and all revisions	X	X
IRB Correspondence	<p>Copies of all materials submitted to the IRB with dated proof of submission and IRB approval (when appropriate) for the following:</p> <ul style="list-style-type: none"> • Advertisements • All versions of consent forms • All protocols and amendments • Annual reports to the IRB • IND safety reports/Adverse Event Report • Initial protocol submission • Investigational safety package inserts • Protocol specific education material • Subject compensation • Any other documents receiving IRB approval or their favorable opinion • Any other written information to be provided to subjects will be given • Any other pertinent communications with the IRB 	X	X
Conflict of Interest	The original, signed COI is to be filed with the CCC prior to study initiation and a copy will be placed in the regulatory files at the site	X copy	X original

Tabs Title	Document to be filed	Located in file of	
		Site	CCC
FDA 1572	<ul style="list-style-type: none"> The original version a form is be filed with the CCC prior to study initiation and a copy will be kept at the site regulatory binder If changes or additions are made, a new 1572 must be completed, resubmitted to the CCC and a copy is stored in the Study Regulatory File with previous versions 	X copy	X original
Protocol signature page	Filed a copy and return the original to the CCC	X copy	X original
CV-LIC and training Cert	<ul style="list-style-type: none"> Curriculum Vitae (CV) for all study personnel listed on the 1572 Medical Licenses for all study personnel listed on the 1572 Training Certificates for all study personnel (including copies of the Research Coordinator Training Checklist for all coordinators who did not attend central training; see Appendix D) 	X	X
Delegation Log	File Original at the site regulatory binder and a copy of this log must be forwarded to the CCC and DCC each time someone joins or leaves the study team	X original	X copy
Monitoring/Visit log	<ul style="list-style-type: none"> The following report will be filed under this section <ul style="list-style-type: none"> Monitoring Reports Close-Out Checklist To document that trial procedures were reviewed with the investigator and the investigators trial staff To document site visits by, and findings of, the monitor 	X	X

Tabs Title	Document to be filed	Located in file of	
		Site	CCC
Communications	Any communications other than site visits, for example: <ul style="list-style-type: none"> • Letters • Meeting Notes • Notes of Telephone Calls • E-Mail Messages <p>Electronic or paper copies are sufficient.</p>	X	
Communication cont	<ul style="list-style-type: none"> • Copies of correspondence with the CCC concerning consent form content • All correspondence (including electronic) between the sites and the CCC and the DCC should be filed in the regulatory binder or an electronic copy may be archived 	X	
SAE Reporting	Notification to the IRB for any reportable adverse event, as per institution guideline.	X	
Subject Identification Code List	The investigator must keep a confidential list of names of all subjects allocated to trial numbers upon enrolling in a trial. Allows investigator/institution to permit identification of all subjects enrolled in the trial in case follow-up is required	X	

APPENDIX A Example of Archive Label

Sponsor Name, Protocol Number, Ethics Number _ _ _ / _ _ _

Protocol Title:

Principal Investigator Name & Contact Info

(Brief description of content)

Archive from [insert date] until [insert data]

APPENDIX B Example of Archiving Log

Please indicate the number of archiving boxes, specific contents per box and exact storage location

Sponsor Name	
Protocol Number	
Protocol Title	
Investigator	
Site Name	

Box #	Contents of Box	Storage Location
Box 1		
Box 2		
Box 3		
Box 4		

<p>Principal Investigator Declaration</p> <ul style="list-style-type: none"> • All essential documents are filed within the Investigator File as per the requirements of ICH-GCP <input type="checkbox"/> • All consent forms are in the Investigator file <input type="checkbox"/> • The archive boxes will be stored as per requirements to conform to ICH-GCP <input type="checkbox"/>
<p>Principal Investigator Signature: _____</p> <p>Date _____</p>

APPENDIX D Research Coordinator Training Checklist

ACTIVITY	Trained by: (Trainer initials & date)	Confirmation of understanding (CRC initials & date)	Unable to complete (Reason)
PROTECT Site Organizational Documents			
Read most recent version of PROTECT Protocol	N/A		
Read consent(s) and assent(s) (including SOC and 52 week sub study)	N/A		
Review IRB approval letter and when renewal is needed	N/A		
Review IRB procedures for consent, protocol violations, and SAE reporting	N/A		
Review PROTECT budget and invoicing process with coordinator or clinical coordinating center			
Review scheduling and medical records systems with coordinator/PI			
Review pharmacy logs and medication labeling requirements with Pharmacist or coordinator			
Review regulatory binder and update appropriate documents (FDA1572, Signature log, etc)	N/A		
PROTECT Study Reference Manual Materials			
Read main MOP chapters	N/A		
DMS report lists	N/A		
Pharmacy User's Guide	N/A		
Review MEMS procedures and materials (including training slides)	N/A		
Review participant brochure and passport	N/A		
Review MOP cheat sheets (inclusion/exclusion card, Mayo scoring, Treatment Overview, Therapy worksheets)	N/A		
ACTIVITY	Trained by: (Trainer initials & date)	Confirmation of understanding (CRC initials & date)	Unable to complete (Reason)

PROTECT Website Materials to Review			
Review forms, QxQs and form packet cheat sheets (Screening/Baseline, Day Zero, Follow-up)	N/A		
CDART Training	N/A		
Photo Image Upload training with DCC	N/A		
PROTECT Cameo Training 02 Recruitment	N/A		
Review training from 4/26/2013	N/A		
Phone Training			
Central lab training call if requested			
DCC Training call if requested			
On site Training			
Shadow a consent and enrollment visit by a trained coordinator			
Shadow an in person and phone follow up visit by a trained coordinator			
Shadow shipping procedures for ambient and frozen shipments by a trained coordinator			
Have a trained coordinator follow your first visit with a patient			
Meet with pharmacy regarding study drug and if not using pharmacy then determine what disposal options you have via investigational drug pharmacy			
Ongoing Training			
Attend monthly PI & Coordinator Webinars	N/A		

Chapter 12: PROTECT Publication and Presentation Policy

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12.1 PUBLICATION POLICY OBJECTIVES

The Predicting Response to Standardized Pediatric Colitis Therapy (PROTECT) Publication Committee (PC) objectives are as follows:

- a. To assure timely development and submission of publications and presentations from the studies conducted by the group
- b. To avoid inappropriate publication of results including results that might compromise (1) ongoing studies (such as publication of trends before they become statistically convincing) or (2) future publication in a more appropriate format or journal
- c. To maintain high quality of material published
- d. To prevent duplicate publication of results, by screening all projects and informing the PROTECT members of pending publications, and by coordinating efforts with other PROTECT committees
- e. To assure equitable and appropriate attribution of credit to the PROTECT participating members and provide all investigators with equitable opportunity to participate in and author publications and presentations

12.2 GUIDING PRINCIPLES

- a. The data collected by PROTECT are the joint property of the Principal Investigators and NIDDK
- b. No data collected as part of PROTECT will be presented, published or otherwise disseminated, except as provided for under these guidelines.
- c. Ultimately, PROTECT data, with appropriate provisions for protection of participant privacy and confidentiality will be made publically available as specified in the NIDDK policy on data sharing. Use of that version of the database is not controlled by this policy.

12.3 SCOPE OF POLICY

All material to be presented orally or submitted for publication or dissemination that includes any PROTECT data or any aspect of the PROTECT scientific plan will be subject to the PROTECT publication policy.

12.4 SOURCE OF SUGGESTIONS FOR PUBLICATIONS

The PROTECT Publications Committee (PC) may suggest topics for abstracts, original peer reviewed papers, or reviews. In addition, any PROTECT Investigator is invited to suggest topics to the PC, who shall review the request, to assure that the project is scientifically meaningful and valid, and that there is no overlap with existing writing assignments. Topics should be suggested in writing, dated, and should include a brief outline of the proposal not to exceed one page.

Overlapping proposals will be granted based on submission date and focus of proposal. The final decision will be made by the PC.

The PC will maintain a list of suggested topics that should be prepared for publication and to assure that all completed aspects of the work of the PRO-KIIDS are reported to the scientific community in a timely fashion. This list will be circulated yearly to members of PROTECT.

The scientific society or journal to which an abstract or manuscript will be submitted will be a joint decision of the authors and the PC.

12.5 ORGANIZATION

12.5.1 Publications Committee

- a. The Publications Committee will be responsible for reviewing suggestions and proposals for manuscripts and presentations, for managing the development of manuscripts, and for reviewing and approving manuscripts, abstracts and presentations prior to submission. The Committee will be responsible for adjudicating any conflicts that may arise between writing groups.
- b. The Publications Committee will be chaired by the Chair of the Executive Committee and will include one member each from the Data Coordinating Center, the NIDDK Project Office, and 3 representatives from Clinical Investigators who will each serve for 2 year terms.
- c. The Executive Committee will monitor the progress of data collection and database closure and will consult with the PC about the timing for proposals for baseline and outcome manuscripts.
- d. The PC will review each manuscript proposal for overlap with existing proposals. In such cases, the overlap will be communicated by the PC Chair to the proposer and to the lead of the relevant Writing Group. The proposer will then be responsible for contacting the lead of the existing writing group to adjudicate the overlap.
- e. The PC will prepare/maintain a listing of potential publications and presentations and delegates the responsibility for a particular project to the appropriate individual(s).

12.5.2 Writing Groups

- a. Topics suggested for presentation or publication will be discussed by the PC and be circulated to the PROTECT site principal investigators. These investigators are requested to volunteer to participate in the writing committee or to suggest (and justify) names for other authors, subject to review by the PC.
- b. If a topic is suggested by a participating investigator in the PROTECT trial, the writing group will be formed as just described except that the person making the suggestion may be considered as the lead author.
- c. The PI of an ancillary study would be the lead author of material derived from that study. Disputes regarding authorship will be settled by the PC Chair after consultation with the members of the PC.

- d. In general writing groups should include no more than 8 individuals. Where practical, members should be included from a variety of PROTECT sites (i.e., clinical treatment centers, clinical coordinating center, DCC, central laboratory, and the NIH). All writing groups that require analysis of PROTECT data will be assigned a member from the DCC, regardless of whether the DCC is conducting the statistical analysis.
- e. The Chair of the writing group (lead author) is responsible for communicating with the members to develop the manuscript. This ordinarily will involve a series of conference calls, e-mail communications, and perhaps, in-person meetings. The analysis plan provided in the manuscript proposal should be elaborated to a more detailed statistical analysis plan. If the DCC is conducting the statistical analysis, the DCC will create one or more statistical computing requests to document and guide the derivation of analysis variables and statistical testing. The DCC representative will provide the group with statistical reports, including tables, figures, and text with results of those analyses. With approval of the DCC, the writing group may provide its own statistical analysis, in which case the member of the writing group completing the statistical analysis is responsible for appropriate documentation of derived analysis variables and statistical testing, with review by the member from the DCC, if requested by the DCC.
- f. The Chair of the writing group in consultation with the PC determines the order of authorship. A major criterion for the order of authorship is the level of effort or contribution made by the members of the writing group.
- g. By the determination of the writing group chair, if some members of a writing group have shown little or no interest in participating in the work of the group or have failed to contribute to the task of preparing the manuscript, their names may be left off the list of authors, pending review by the PC. If a problem emerges, the PC will resolve it.
- h. The Chair of each writing group is to update the PC on manuscript process every 2 months after the writing group is formed. If the PC has not received a report from a lead author, or if satisfactory progress has not been made:
 - 1. The PC may replace the lead author with another member of the writing group.
 - 2. If no writing group members are interested in assuming the lead position, other PROTECT Investigators outside the writing group may be solicited to be lead author.
- i. All members of the writing group should review the final manuscript before their submissions to the PC for approval, and after revisions suggested by the journal are made.
- j. All members of the writing group must submit current disclosure of potential conflicts of interest in a form acceptable to potential journals and professional societies as well as to the PC.

12.6 AUTHORSHIP POLICY

Each primary publication will have a primary author, senior author, and contributing authors.

Authorship rules will be governed by guidelines established by the International Committee of Medical Journal Editors (ICMJE), http://www.icmje.org/ethical_1author.html

“Authorship credit should be based on 1) substantial contribution to the conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3. Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship. All persons designated as authors should qualify for authorship and all those who qualify should be listed. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.”

Consistent with these ICMJE guidelines, those who participated in conception and design, analysis and interpretation of data, drafting of the manuscript or abstract, critical revision relating to important intellectual content, and final approval should be included as authors. Biostatistical expertise that relates directly to the conduct of the study is an additional criterion for authorship. Provision of study material or patients; collection and assembly of data; provision of administrative, technical, or logistic support; and obtaining funding do not necessarily merit authorship but should be considered on a case-by-case basis, especially when other contributions are included.

It is expected that the primary author will have performed the majority of work on the project including conception of the idea, data retrieval and analysis, and writing. The senior author will have also contributed significantly to these aspects of the work. When appropriate the PC will consider co-primary and co-senior authorship.

It is anticipated that different types of manuscripts will be written. Some, which contain outcomes largely driven by the entire study population, will likely consider for authorship all center Principal Investigators who contributed any patients toward PROTECT. There will also be other more focused manuscripts that will examine sub-sets of patients or sub-sets of data. It is our intention to follow the PRO-KIIDS (Pediatric Resource Organization for Kids with Intestinal Inflammatory Disorders) policy and consider for authorship those site Principal Investigators whose centers were in the top 50% of recruiters. Significant contribution to analysis and writing of the abstract/manuscript will also be considered for authorship designation. The order of the contributing authors will be determined jointly by the primary author, senior author, and PC.

It will be the responsibility of all potential authors to provide relevant disclosure forms to the appropriate societies or publishers. Failure to do so can result in the loss of authorship rights.

12.6.1 Priority / Primary Papers

The Publications Committee (PC) and Executive Committee (EC) will develop a list of priority papers. The process for authorship of the priority papers will be established by the PC, with approval by the Executive Committee (EC).

12.6.2 Group Authored and “Unauthored” Publications and Presentations

The PC may recommend to the EC, and the EC may decide that one or more publications be written on behalf of the PROTECT group. For example, a design paper might be un-authored or group authored. An appropriate list of participating investigators will be identified in an appendix to such publications, and members of the actual writing group will either remain anonymous or, as appropriate per journal policy, be acknowledged in the publication.

12.6.3 Data to be obtained from PROTECT

Most analysis throughout the study will have data analysis done by the DCC. Some papers will have analysis done by the writing group under the supervision of the lead author. For those analyses done by the writing group, the following rules apply:

- a. PROTECT data required for analysis of a paper will be provided by the DCC after approval of manuscript proposals that specify the dataset required.
- b. NIDDK rules for data distribution will apply, implemented through signed data distribution agreements.

12.6.4 Abstracts

Abstracts should be derived from approved manuscript proposals, and are to be submitted to the PC for review and approval (see Section 12.9.1 for schedule of review). All abstracts accepted for presentation and publication should be submitted to the DCC for archival. It is permissible to submit previously cleared abstracts to other meetings; copies should be sent to the DCC for inclusion in the inventory listing of PROTECT Publications and Presentations. The first version of any abstract must be submitted to the PC a minimum of 3 weeks prior to submission deadline. The final version must be approved by the PC before submission.

12.6.5 Invited Talks

- a. An Investigator receiving an invitation for a national talk on behalf of PROTECT should send an abstract of the talk to the PC and must obtain PC and EC approval. No approval is necessary for local talks or grand round.
- b. When an invitation is directed to the Chair of the Executive Committee or Chair of the PC, in the case where these two positions are filled by separate individuals, the respective chairs will decide who is to represent PROTECT. Invitations directed at NIDDK will be reviewed and approved by the NIDDK Project Office.
- c. When a PROTECT Investigator or NIDDK scientist receives a personal invitation to make a presentation, they should notify the Chair of the PC to ensure listing of the presentation on behalf of the PROTECT Group.
- d. All presentation in response to such invitations should be based on published PROTECT reports unless prior approval is granted by the PC.
- e. Requests received by PIs or their staff to present or discuss at Investigators institution meetings any previously published PROTECT data need no prior clearance by the PC and acceptance of such invitations is encouraged.

12.6.6 Ancillary Studies

Ancillary studies follow the same publication process as the main PROTECT papers, and must submit proposals to the PC, but an ancillary study may select and recommend its own working group. In most instances this should include representation from clinical center PIs, the DCC, Project Office and relevant Laboratories.

12.6.7 Reports of PROTECT

Any written communication to scientific meetings, journals, or lay organizations that detail specific works performed by PROTECT will fall under auspices of the PC. All work coming from PROTECT will list PROTECT as the directing body of the work.

12.7 ACKNOWLEDGEMENTS

- a. Study Identification: All manuscripts produced from PROTECT data must have the study acronym (“PROTECT”) listed in either the title or the list of authors.
- b. Support: All manuscripts that report PROTECT data must include the following statement: Research reported in this publication was supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under Award Number U01DK095745. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.
- c. Staff and Participants: Writing groups are strongly urged to acknowledge the PROTECT participants and staff.
- d. PROTECT (for ancillary studies): In addition to acknowledging their funding source, manuscripts arising from PROTECT ancillary studies should follow the PROTECT publication policy guidelines.

12.8 STUDY TIMING OF MANUSCRIPTS AND PRESENTATIONS

- a. Background papers: Manuscripts that describe the justification for the PROTECT study.
- b. Methodological papers: Manuscripts describing the design and/or scientific methods used in the PROTECT trial.
- c. Baseline papers: Manuscripts that report only data collected at the time of or prior to treatment and follow-up.
- d. Outcome papers: Manuscripts including data collected following enrollment of participants.

Development of baseline papers will be encouraged as soon as enrollment is complete and the baseline database is closed (i.e., while follow-up is on-going). The first baseline paper of the overall PROTECT study population will include a description of the general characteristics of the study population.

Development of outcome manuscripts can begin once collection of follow-up data is complete and the corresponding database is closed. The first outcome paper submitted will be the primary results manuscript. Other outcome manuscripts cannot be submitted until the primary results paper has been accepted.

Methodological papers which do not require PROTECT data may be developed at any time. Those methodological papers that include substantial data, particularly outcome data (e.g., results of a quality control program) will follow the timeline required for the data included.

In general, PROTECT manuscripts are expected to include data from all of the relevant participants. Papers including only a subset of the participants is discouraged, unless part of an official ancillary study.

12.9 MANUSCRIPT/ABSTRACT/PRESENTATION PROPOSAL AND REVIEW

All proposals must be submitted using the PROTECT Manuscript Proposal form and Abstract Proposal form. These forms will be accessed and submitted through the Publications Hub of the PROTECT study website. See Figure 1 for a list of items needed for a complete manuscript proposal. The writing group is encouraged to seek input from the DCC in writing the statistical analysis plan section of the proposal.

At the time a writing group is constituted, the PC will establish a timetable for the completion of the writing assignment that takes into account deadlines for publication, the time required for data analysis, other commitments of the DCC, and priority of the publication.

The Chair of the writing group should provide the Chair of the PC a general outline of the proposed publication within a month of receiving its assignment, to permit the PC to identify any overlap with assignments of other writing groups. The Chair of the PC will report at each meeting of the Executive Committee on the progress of the various writing groups. If the timetable is not met, the chair of the PC can name a new chair for the writing group or reconstitute the membership of the writing group.

For proposals that will be analyzed by the DCC, in the event there are more proposals approved than the DCC has resources to actively work on, the PC will set priorities for the order in which analyses will be conducted by the DCC. With approval of the DCC, the writing group may provide its own statistical analysis.

In general, Investigators are discouraged from leading more than a few manuscript proposals at any one time. In the case of an Investigator with multiple approved proposals, the PC may identify which proposal(s) will receive active attention from the DCC at a particular point in time.

12.9.1 Abstracts and Presentations Expedited Proposal Review

The following procedure will be used to expedite reviews of abstracts and presentations:

- a. The writing group wanting to submit an abstract or other material for which there is an explicit submission deadline shall 1) submit an online Abstract proposal through the PROTECT study website, indicating the submission dates, 2) contact the Chair of the PC, and 3) contact the DCC (if data analysis will be required). In the event that the Chair is unavailable, the Alternate Chair may be contacted. The Chair (or Alternate Chair) will name a subcommittee of two to three members of the PC to review the submitted material. The submitted material should be provided to the reviewers no fewer than seven (7) days prior to the deadline for submission.
- b. The members of the subcommittee shall review the material and notify the Chair of their approval or disapproval. The PC Chair (or Alternate Chair) shall inform both the submitter of the decision of the PC, and the DCC.

- c. All materials submitted for approval in this fashion will be distributed, together with notice of the disposition, to all members of the PC and to the Chair of the Executive Committee. Approved materials will be forwarded to the NIDDK Project Coordinator, and for record purposed to the Principal Investigator of the DCC, and will be distributed to the entire membership of the Executive Committee at the next meeting of that Committee.

All presentations will be developed in coordination with the DCC. Completed presentations and abstracts will be simultaneously reviewed by the PC Chair, EC Chair, DCC Statistician, and NIDDK Project Officer. Full committee reviews will not be required. Proposed abstracts and presentations must be received by the DCC a minimum of 21 days prior to the deadline for submission in order to be reviewed.

12.10 REVIEW OF PAPERS BY THE PC

All materials and all papers that may result in a citable scientific reference, whether or not there is a deadline for submission, must be submitted to the PC for formal review by the entire Committee. If there is a deadline for submission, it is the responsibility of the submitter to be certain that it is submitted to the PC at least thirty (30) days prior to the submission deadline. The review will be conducted as follows:

- a. The PC shall appoint two to three primary reviewers, including at least one PC member. The PC will circulate the submitted material to the entire PC committee and to the primary reviewers. The primary reviewers will each send to the PC a written critique of the submitted material for distribution to the entire PC. The primary reviewers will be given a deadline by which their critique must be received by the PC.
- b. The PC shall schedule a meeting of the PC (generally by conference call), including review of papers as Agenda items. The primary reviews will be distributed to the committee with the agenda. The discussion of the submitted papers and other materials will be led by the primary reviewers.
- c. Three dispositions may be made: a) approval of the material as submitted (possibly with minor recommendations for revision that do not require re-review), b) non-acceptance of the material as submitted but with recommendations to the authors for revisions and resubmission, or c) to discontinue the project.
- d. The PC will communicate the decision of the Committee to the authors, together with a summary of suggestions for revision, if any.
- e. If a scientific journal to which an approved manuscript is submitted requires revisions to the manuscript, the PC will determine whether the revised manuscript should again be reviewed by the PC prior to resubmission. If the PC determines that a review of the revised manuscript is necessary, the PC will attempt to appoint the same reviewers that first read the paper to review the revision, and will make every effort to expedite repeat reviews.

12.10.1 Criteria for Review of Materials by the PC

Materials submitted to the PC will be reviewed for acceptability on two grounds:

- a. Materials shall be evaluated for scientific accuracy, quality, importance, and style.
- b. Material shall be reviewed to assure that it conforms to the assignment to the writing committee, does not encroach on assignments to other writing groups, and does not divulge prematurely the findings of PROTECT or compromise the eventual publication of PROTECT in high quality peer reviewed journals.

12.11 MAINTENANCE OF RECORDS OF PROPOSALS, PUBLICATIONS, AND PRESENTATIONS

The DCC, working with the PC Chair, will maintain a current online listing and database of all official publications and presentations of PROTECT, including PDF copies of all papers, chapters, or abstracts accepted for publication.

Figure 1.
Key Items Included in a PROTECT Manuscript Proposal

The Manuscript Proposal Form is obtained from the Publications Hub of the PROTECT study website, and is submitted through this website.

1. **Title**
2. **Proposed Writing Group Members (First listed member is the lead author)**
3. **Rationale**
4. **Hypotheses/Objectives**
5. **Research Methods (study design, inclusion/exclusion criteria**
6. **Will any non-PROTECT data be analyzed (e.g., ancillary study)? If so, please document approval or explain data access**
7. **Will any outcome (post-enrollment) data be utilized?**
8. **Where will the data analyses be performed? (Data coordinating center; other, specify)**
8. **Data (variables to be used in the analysis)**
9. **Statistical analysis plan**
10. **Manuscript Timeline (in months from approval of proposal)**
11. **Target Journal**

Chapter 13: PROTECT Ancillary Studies Policy

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13.1. INTRODUCTION

To enhance the value of the PROTECT Clinical Trial (PROTECT), the PROTECT Executive Committee and the CCFA PROKIIDS Pediatric Network welcome proposals from individual investigators to carry out PROTECT ancillary studies. However, to protect the integrity of PROTECT, ancillary studies must be reviewed and approved by the PROTECT Ancillary Studies Committee (ASC) and approved by the PROTECT Executive Committee (EC) before the inception or submission of an ancillary study proposal for external funding consideration.

13.2. OVERALL GOALS AND OBJECTIVES

The ultimate goals of the PROTECT study are to:

- 1) Evaluate the safety and efficacy of standardized initial therapy using either mesalamine or corticosteroids then mesalamine for the treatment of children and adolescents newly diagnosed with ulcerative colitis.
- 2) Identify clinical, genomic, and immune predictors of treatment response

Ancillary studies which: 1) make use of clinical, genetic, and immune data collected during the PROTECT study and/or 2) Generate new clinical data from surveys or 3) new genetic or immune or other data from biospecimens, are encouraged. These may be studies which test hypotheses related to the overall goals of the PROTECT study, or studies which test new hypotheses unrelated to the goals of the PROTECT study.

13.3. WHO CAN SUBMIT AND PARTICIPATE

Applications for ancillary studies are encouraged from any CCFA PROKIIDS Pediatric Network investigator and institution with the capability to perform the proposed studies, without restrictions. Three types of investigators will be considered, with priority given to Type 1 and 2 investigators:

1. PI with proven track record of independent investigation related to IBD basic, translational, or clinical research, as evidenced by first or last author publications and/or independent funding.
2. PI at the career development stage of IBD research, with a mentor who meets the criteria in 1 above.
3. PI with a proven track record of independent investigation in a non-IBD area, as evidenced by first or last author publications and/or independent funding, who now seeks to apply those skills to answer an IBD question.

13.4. WHAT RESOURCES CAN BE REQUESTED?

In general, three types of resources may be requested. Projects which will utilize biospecimens, which represent a finite resource, will in general need to receive an outstanding impact score (see Section X Review Criteria), to receive approval by the ancillary studies committee. Projects which will only utilize existing data may be approved with an overall impact score in the very good to excellent range, and may be more exploratory. **Careful attention will be paid to the amount of the biospecimen requested; in general it should be less than 5% of the original amount in the tissue bank. To summarize ancillary studies should be clearly classified in the request to indicate that they will:**

1. Only utilize existing clinical, genetic, or immune data.

2. Generate new clinical data, e.g. with surveys to subjects or providers.
3. **Generate new human or microbial genetic or gene expression data, or new immune or serologic data, using banked sera, human genomic DNA, mucosal or fecal DNA, or mucosal RNA.**

13.5 TIMING OF SUBMISSIONS

Proposals that will be submitted to the PROTECT Ancillary Studies Committee should begin with a one-page concept proposal (see Section IX Instructions for Preparation of Ancillary Proposals). The ASC will determine if there are any special barriers to this application going forward. The ASC provides concept approval and notifies the applicant within 4 weeks whether he or she should proceed with developing the full proposal.

Full proposals should be submitted to the ASC no less than 3 months prior to the planned date of submission to a funding sponsor to assure that ASC review, input, and approval can be provided in ample time to meet sponsor deadlines. PROTECT will make every effort to complete review of such proposals by its ASC and Executive Committee within 4-6 weeks, allowing successful applicants 6-8 weeks to prepare and submit applications for funding. Note that additional detailed scientific reviews of such proposed ancillary studies that are submitted to NIH for funding will be conducted by the NIH Study Sections that review the associated applications.

For proposals that will not undergo future rigorous, scientific peer-review, the deadline for receipt of the completed full proposal will be modified to include 8 weeks for the ASC to conduct its own scientific review (see Scientific Review section).

Proposals for ancillary studies to PROTECT for which funding has already been secured or for which application will be made to some other potential funding source should be submitted to PROTECT for its approval at least three months prior to the intended project starting date, allowing PROTECT to conduct its own scientific review.

13.6. EXECUTIVE COMMITTEE REVIEW

During ASC review, all ancillary studies proposals will be circulated to the PROTECT Executive Committee for comment. Interested PROTECT investigators may contact the PI of the proposed ancillary study and request to participate as collaborators in the study. In addition, as appropriate, the ASC may recommend that the ancillary PI consider adding additional sites to provide added power, a more diverse population, or to contribute specific scientific expertise.

13.7. FUNDING

There is no direct cost to the ancillary study for biospecimens but there will be a charge for aliquoting and shipping. All additional costs for the ancillary study will be borne by the investigators conducting the ancillary study. DCC costs for collecting and cleaning additional data, data transfers, and data archival should be included in the ancillary study budget. Before applying for external grant funding using biospecimens from PROTECT, investigators must receive an approval letter for their ancillary study proposal. The level of funding requested must be sufficient to support the additional data collection, management, and analysis required by the ancillary study. Investigators planning an ancillary study are encouraged to consult with the ASC during development of the proposal to ensure consensus on the resources required for the project. Funding of a grant proposal for an ancillary study at a reduced level from that proposed will likely require corresponding modifications to the work scope of the ancillary study. The ASC

will review the proposed modifications before submitting it to the Executive Committee for final approval, as outlined in the instructions below.

ASC approval of a study is valid for eight months and if, within 8 months of initial approval by the ASC, an investigator is unsuccessful in obtaining the necessary resources, including funding, the initial approval of the project will be withdrawn.

13.8. INSTRUCTIONS FOR PREPARING ANCILLARY STUDY PROPOSALS

1. The development of an AS involves a good deal of work on the part of the applicant. It is suggested that a one-page concept proposal using the Word form “Proposal Submission Memo of Intent” (stored on the PROTECT website under Ancillary Studies) be submitted to the ASC who will determine if there are any special barriers to this application going forward. The ACS provides concept approval and notifies the applicant within 4 weeks whether he or she should proceed with developing the full proposal.
2. The PROTECT website also contains a Word Form for the “Full Ancillary Proposal Submission Memo”. Ancillary study proposals should not be longer than 7 pages and should include the following elements:
 - Cover page with Project Title, Investigator Names and brief Abstract (<500 words). (1 page)
 - Research Plans including Specific Aims/Hypotheses, Background and Significance, Research Design and Methods, sample size justification, and Statistical Analysis including:
 - a. Sample size justification
 - b. Participant selection criteria and consideration
 - c. Advantages to using PROTECT cohort to answer research questions
 - d. Recruitment and data collection methods
 - e. Time burden, burden on participant, burden on clinic staff
 - f. Proposed compensation
 - g. Results/alert reporting
 - h. Potential benefits of participation (if any)
 - Description of specimen or data request (1 page)
 - a. Specific types(s) of samples
 - b. Volume of each sample
 - c. Time of sample collection (baseline vs. post-baseline)
 - d. Number of participants
 - e. Proposed laboratory that will perform the assays
 - f. DNA specimens – special needs should be delineated.
 - g. Other required study data (e.g. baseline and/or follow-up data)
 - Time table with key dates (grant submission, target date for receipt of specimens, and completion of study)
 - Agreement to return any unused biological specimens and data sets
 - Budgetary issues
 - a. Source(s) of funding
 - b. Draft budget – should describe costs related to:
 - i. Space, personnel, equipment, and IRB approval
 - ii. Statistical analysis and data management
 - iii. Visits or examinations outside of the primary study protocol.

PI should consult with DCC in preparing budget if their data management and analysis services are requested.

- NIH-style Biosketches for all Key Personnel. (No page limits).

All proposed ancillary studies must be reviewed and approved by the PROTECT ASC and the PROTECT EC before submission to a funding agency. See Section VI regards timing of submissions.

13.8.1. Review Process

Requests will initially be reviewed by the ASC, and assigned an overall impact score (below good, good, very good, excellent, outstanding) using the Ancillary Study Review Sheet, stored on the PROTECT website under Ancillary Studies, and recommendation of Approve, Disapprove, or Defer to the PROTECT Executive Committee. To ensure thorough scientific review, the Chair of the ASC may elect to seek outside expert opinion. The ASC will recommend approval or rejection to the Executive Committee, or will request modification. The ASC will make every effort to complete review of proposal within 4 weeks.

A proposal, which receives an affirmative majority from the ASC, will be forwarded to the Executive Committee. The Executive Committee will have 4 weeks to authorize proposals approved by the ASC. A failure of the EC to provide an opinion back to the ASC will be considered an affirmative vote. Approval or disapproval in both the ASC and Executive Committee is based on majority opinion.

Projects which are disapproved will be returned to the PI, without an option to re-submit. Projects which are deferred will be returned to the PI, with an option to revise and re-submit, one time. This process is modeled on the current NIH Study Section and Council system.

The investigator may only proceed with the ancillary study after he/she has received a formal approval letter from the PROTECT ASC. Any changes that occur in the structure or concept of an ancillary study that has been approved must be submitted to and reviewed by the ASC and Executive Committee according to the policies outlined for initial submissions.

Principal investigators of all ancillary studies will provide a written annual report to the ASC and Executive Committee on study progress.

13.8.2 Material Transfer Agreement

In all cases, PIs whose projects are approved by the ASC and Executive Committee for support of ancillary studies will abide by the MTA for the CCFA PROKIIDS pediatric network. A site conducting an approved ancillary study may share biospecimens with another laboratory if that sharing was part of the original proposal approved by the ancillary studies committee. If sharing with another laboratory was not part of the original ancillary study proposal then the ancillary study site Principal Investigator must obtain clearance from the ancillary study committee prior to sharing specimens. Specifically, materials can be transferred to other PROKIIDS Pediatric Network Members, CCFA and other third parties for teaching and academic research purposes pursuant to the terms and conditions of the MTA.

13.8.3 Human Subjects / Data Confidentiality

Confidentiality of PROTECT enrolled patients must be guaranteed. Individually identifiable data may not be released. If the data requested for an ancillary study is not covered in the original informed consent process for the main PROTECT, then a signed consent must be obtained from

every participant in the ancillary study. Any investigator or personnel having access to PROTECT data must receive an orientation on the Trial's confidentiality policy. Key personnel of the ancillary study must be certified in the NIH OHSR or equivalent training course.

A copy of the IRB letter for the ancillary study should be sent to the Clinical Coordinating Center and Data Coordinating Center. If a separate consent form is required for the ancillary study, a copy of the signed ancillary study consent form for each study participant must be included in the PROTECT record. A data file tracking all signed ancillary consent forms must be maintained by the ancillary study and an electronic copy of that file must be delivered to the PROTECT DCC.

The principal investigator of an ancillary study will be responsible for monitoring the study to assure continuing compatibility with confidentiality and consent policies of PROTECT and providing written progress reports on the ancillary study.

13.9. ANALYSIS AND PUBLICATION OF RESULTS OF ANCILLARY STUDIES

The site responsible for performing the statistical analysis of the ancillary study must be specified in the Ancillary Study application. Applicants are encouraged to contract data analyses with the DCC. Ancillary studies funded as career or training awards as well as studies taking place in a subset of clinical sites will be situations in which data analysis might occur outside the DCC. These situations will require approval by the ASC and Executive Committee and the investigator of the ancillary study to provide interim reports on analyses to the DCC to ensure (1) consistency with data in the PROTECT database and (2) the quality of the analytic approach.

Since ancillary projects must involve at least one PROTECT investigator in a collaborative relationship, each abstract, presentation, and manuscript should also include PROTECT investigators as co-authors to recognize their participation. The ancillary project lead should work with the Publications Committee to determine investigators who are eligible for authorship. This condition should be met unless extenuating circumstances exist that should be stated and justified as part of the *original submission to the ASC*. All publications, presentations, and abstracts derived from an approved ancillary study must acknowledge support from the PROTECT grant as well as the specific support for the ancillary study. All manuscripts that report PROTECT data must include the following statement: Research reported in this publication was supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under Award Number U01DK095745. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Proposals for manuscripts resulting from all ancillary studies must be submitted for review to the Publications Committee and will require approval by the EC prior to submission for publication or presentation. Publications reporting baseline data from an ancillary study will only be approved following the publication of the main study baseline manuscript. Publications based on outcome data will follow the primary study outcome manuscript. The phrase "PROTECT Clinical Trial" should be included in the title in all scientific presentations and manuscripts and listed as a key word whenever possible. Manuscripts should also contain an appendix listing PROTECT investigators when appropriate.

13.9.1. Sharing of Results with Participants

Results of ancillary studies based on laboratory testing of biological samples can be reported to enrolled patients and/or their physicians if the results are published in a peer-reviewed scientific manuscript and are deemed sufficiently medically useful, and if data was generated in a CLIA-certified lab. Patients will not be informed of results generated by a research laboratory not CLIA-certified. Such reporting should follow standard PROTECT protocol for notification of participants, including a layperson summary of the conclusions and limitations on the PROTECT web site, with instructions to contact their site PI for further details.

13.10. HANDLING OF PROTECT CLINICAL TRIAL DATA AND SPECIMENS

At the time of distribution of PROTECT specimens and/or information, the PROTECT ASC, in coordination with the DCC, will make explicit arrangements with the ancillary study PI for the security of these study materials, and for their final disposition at the conclusion of the ancillary study. The safety and confidentiality of the PROTECT data at the collaborating institution is the responsibility of the ancillary study PI, as is the appropriate disposition of biological materials after the ancillary study has been completed.

13.11. ANCILLARY STUDY DATA

An archival copy of the newly collected data and/or laboratory results not already held at the DCC will be sent to the PROTECT DCC at the conclusion of the data analysis and publication of ancillary studies. The ancillary study must also provide appropriate documentation for the data to make it useful for outside investigators. Once transferred back to the PROTECT DCC, these ancillary data will become part of the aggregate PROTECT data and included in the NIDDK's limited access data program. Limited access data is made available to the public in accordance with the NIDDK Policy for Distribution of Data.

13.12 ANCILLARY STUDIES COMMITTEE MEMBERSHIP

The Chair of the ASC will come from the EC. Each ASC member will serve a 3-year term starting January 1 of their appointed year. Members may be considered for a second consecutive term by the PROTECT Executive Committee.

In addition, when needed, we will establish a panel of ad hoc reviewers in specific areas of expertise who are not PROTECT site investigators.

Appendix A: Pharmacy and Coordinators Mesalamine (Pentasa) Guide

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GENERAL DESCRIPTION = MESALAMINE

Mesalamine (Pentasa®) has been chosen as the aminosalicylate for this study because of ease of administration to children of all ages in clinical practice over the past 10-15 years, ease of standardization of dosage, and lack of oral staining that is associated with balsalazide. Additionally, it can be administered to children unable to swallow the capsule by opening up and mixing with apple sauce or yogurt-like foods. The investigators have obtained an IND (111863) for this study. Mesalamine will be provided by Shire Pharmaceuticals in 500 mg capsules that will be distributed to study sites. The package insert describing properties of the drug as well as potential toxicity is attached at the end of this document. This medication will be provided free of charge to each patient participating in this clinical protocol until the 52 week outcome assessment or until it is discontinued prior to 52 weeks.

A.1 DRUG PROCUREMENT

A.1.1 Connecticut Children's Medical Center (CCMC) Department of pharmacy

Drug will be shipped to sites from CCMC. The primary tasks of the CCMC department of pharmacy with respect to drug distribution are to monitor the storage, shipping, ordering, and disposal of medications. Refer to Section (A.2) in regards to medication distribution.

A.1.2 Bottling and Labeling

The study medication will be bottled in 500 mg white bottles (120 capsules) with a child resistant cap. Each bottle of Mesalamine (Pentasa®) will have a lot number and expiration date which will be recorded on the bottle.

Figure 1 below shows an example of the label that should be affixed to the front of the medication bottle. This example is partially completed for the Connecticut site; your site will need to modify the contact information (name, address, telephone number) and switch out your Investigator's name.

All labels must indicate the IND number and the instructions, and include the cautionary note as worded on the bottom of the example, "New Drug--Limited by Federal law to investigational use and IND #111863". Each site is allowed to come up with its own labels, if it has better outpatient prescription software (i.e: QS1) and outpatient prescription handling procedures, or they can use the example label as a template for the necessary wording.

Fig 1. Sample Template of Pentasa Bottle Labeling

CCMC Department of Pharmacy

Tel: 860-545-9935

282 Washington St. Hartford, CT 06106

Pt: _____

RX: Mesalamine (Pentasa®) 500mg Capsules

Take ___ capsule(s) by mouth in the morning and ___ capsules by mouth in the evening. Take capsules with meals or food, at approximately the same time each day.

For investigational use, IND #111863

Dr. Jeffrey Hyams Disp: ___ capsules R.Ph. _____

Caution: New Drug--Limited by Federal law to

investigational use and IND #111863

A.1.3 Shelf Life, and Temperature Limitations

A.1.4 The expiration date of each batch of medication will be determined by the drug manufacturer. The study medication from a particular batch will not be distributed 7 months prior to the expiry date of a batch. The shelf life of a particular batch will depend upon usage and/or expiry date. Connecticut Children's Medical Center (CCMC) Department of Pharmacy closely monitors the inventory of the study medication. Study medication should remain in a climate-controlled area in the temperature range between 59-86°F (15-30°C). The temperature of the storage area should be recorded daily, or an alarm system maintained so research personnel will be notified if the temperature deviates from the parameters specified. Access to the storage area should be limited to essential research personnel. Temperature logs may be reviewed during monitoring visits.

Distribution to Clinical Centers

A.1.4.1 Packaging and shipment of Study Medication to the Clinical Sites

CCMC Department of pharmacy will serve as the storage facility and distribution center for study medication. CCMC Department of pharmacy will ship bottled study medication to each center via ground delivery in accordance with a schedule provided by each site research coordinator.

A.1.4.2 Initial Shipment

The PROTECT sites will receive an initial shipment of study medication from CCMC Department of pharmacy that will be expected to last for the first 6 months after recruitment has begun (max dose for 6 patients). The number of bottles of medication to be sent in the initial shipment will be approximately 72 bottles.

A.1.4.3 Subsequent Shipments

Subsequent batches of study medication will be packaged by CCMC Department of pharmacy as needed, based on recruitment patterns, and the relative closeness of the study medication's expiration date. For more medication, research coordinators or pharmacy personnel should complete an inventory request via the RedCap ordering website: <https://redcap.emory.edu/surveys/?s=TvPcJbP3Qp> (see MOP chapter 1 on supply ordering) PROTECT medication is distributed by the project manager Krista Spada (kspada@connecticutchildrens.org) or designated research pharmacy technician..

A.1.4.4 Clinic Medication Distributor (CMD)

The site's Principal Investigator is responsible and accountable for the distribution, storage, and inventory of the investigational drug. The PI may delegate responsibility for the investigational drug to another qualified researcher involved in the study, known as the Clinic Medication Distributor (CMD). Medication shipments will be addressed to each site's Clinic Medication Distributor (CMD). This should be a pharmacist, Project Coordinator, or a responsible person with knowledge of receiving, dispensing and inventory of drugs. For some sites the CMD is the Project or Study Coordinator, and for others, the CMD is the site's research pharmacist. The Clinic Medication Distributor should be listed on the PROTECT delegation of duties log.

A.1.4.5 Receipt of Shipment at the Clinic

The CMD is responsible for receiving the medication shipment, verifying the contents of the shipment against the packing list, storing the medications, and monitoring the distribution of the study medication. The CMD will be notified via email that a drug shipment will be arriving.

Upon receiving the study medication, the CMD will inventory the contents of the shipment for accuracy.

Project Coordinators are responsible for providing contact information of the CMD. The Project Coordinator should notify Krista Spada (kspada@connecticutchildrens.org) of any changes to the Clinic Medication Distributor (personnel, address, phone, etc.), or to medication storage, distribution, recordkeeping, or disposal procedures.

A.1.4.6 Medication Storage at the Clinic

The study medication should be stored in a secure and climate-controlled location (59-86°F; 15-30°C). The storage location will vary depending on the policies of the institution. In some clinics the study medication will be maintained in the hospital pharmacy and requisitioned by study personnel as needed. In other clinics the study medication may be stored in a secure locked cabinet within the research facility.

A.2 CLINIC PROCEDURES

The Investigator is to follow protocol procedures (also outlined in Chapter 5 Treatment of the MOP) regards the appropriate study medication and the medication dosing to complete the appropriate prescription for study medication.

A.2.1 Medication Management Logs

Drug accountability documentation should be completed upon arrival of supplies, each time drugs are distributed, and when drugs are destroyed. PROTECT has a ‘Subject Specific Product Dispensing/Return Log’ (attachment 2) to document medication distribution. This form should be completed by the Study Coordinator when medication is dispensed.

In addition there is the ‘Medication Accountability Record’ which can be used by the Pharmacy if they choose to. Clinic pharmacies that are dispensing PROTECT medication, must maintain their own inventories that address their center’s IRB and other regulatory requirements documenting medication distribution.

These logs are not data entered, and will be monitored by the studies clinical monitor during site monitoring visits.

When all participants have completed the study medication, the records should be checked for accuracy and should be signed and dated.

A.2.2 Distributing Bottles to Participant

After filling a participant prescription, the Coordinator will log the medication bottles assigned to each participant onto the Subject Specific Product Dispensing/Return Log. Prior to dispensing, all medication bottles must have a participant ID label, or the participant ID added to the bottle label, and medication dose must be recorded on the bottle.

Careful identification of the proper bottle codes and checking of the bottle expiration dates before distribution will be essential in avoiding errors related to this procedure. The expiration date must be at least 7 months after the date of distribution to a participant. In addition, the CCMC Department of pharmacy will notify the clinics when remaining medications in a batch must be discarded due to impending expiration. (See section A.2.3 for information on medication disposal.)

All bottles of medication dispensed are documented on the Subject Specific Product Dispensing/Return Log. This tracks the quantity dispensed and returned based on pill counts (this is also recorded on each participant's STZ and SMF data collection form by the Study Coordinator). This log also tracks the MEMS cap serial number provided to each participant on Pentasa.

Pentasa is provided free of charge to each participant participating in this clinical protocol until the 52 week outcome assessment is completed or until it is discontinued prior to 52 weeks. Enough medication should be provided to the participant to last through week 52. If the patient has pills remaining after the week 52 visit, you do not have to destroy the unused medication. After the week 52 assessment is completed, the treating physician should write a prescription to continue Pentasa and document on the Standard Medical Therapy (SMF) case report form. If the physician decides to switch to another 5-ASA after 52 weeks then the new prescribed therapy should be recorded on the Additional Medical Therapy Form (AMT) as well as the SMF.

If an institution has satellite centers, it is acceptable for practitioners to bring study drug with them when seeing patients to dispense. It is acceptable to pre-order the Pentasa from pharmacy so that medication can be distributed accordingly. It is also acceptable to ship medication directly to patients as long as the shipments do not contain any Personal Health Information. When shipping directly to patients the first time, a woken up MEMS cap with instructions on how to use the cap should also be provided and accountability maintained.

PROTECT requests that all pills and MEMS caps are returned at each clinic visit so that pills can be counted during the visit and MEMS data downloaded. If medication and/or MEMS are not brought back to study visits, the patient loses pills or there is some other reason why question 1e1 on the SMF cannot be answered, leave the question missing and enter an explanation in the DMS note log. The study coordinator should also call the participant to obtain a reasonably close estimate and enter that estimate on the SMF.

A.2.3 Disposal of Excess or Expired Medication

Study medication should not be discarded or destroyed without approval from the CCMC department of pharmacy. In general, medications will be disposed of on a regular schedule before, but near, the time that a batch is expiring. Following authorization from the CCMC department of pharmacy, the coordinator will arrange for disposal according to the policy of the local institution. Disposal will include unused medications returned by a participant, medications unusable because of the expiration date, and drugs remaining at the conclusion of the study. Each Project Coordinator must send CCMC department of pharmacy the disposal policy at their institution (incinerate, bury, etc.). A copy of the

destruction policy should be maintained in the regulatory files. At the conclusion of the study, the study drug should be inventoried and prepared to be destroyed in accordance with the requirements of the state board of pharmacy. All documentation regarding receipt, storage, dispensing, and destruction must be complete and accurate.

Attachment 1:

Pentasa Package Insert

PENTASA®

(mesalamine)

Controlled-Release Capsules 250 mg and 500 mg

Prescribing Information as of June 2008 Rx only

DESCRIPTION

PENTASA (mesalamine) for oral administration is a controlled-release formulation of mesalamine, an amino-salicylate anti-inflammatory agent for gastrointestinal use.

Chemically, mesalamine is 5-amino-2-hydroxybenzoic acid. It has a molecular weight of 153.14.

Each 500 mg capsule contains 500 mg of mesalamine. It also contains the following inactive ingredients: acetylated monoglyceride, castor oil, colloidal silicon dioxide, ethylcellulose, hydroxypropyl methylcellulose, starch, stearic acid, sugar, talc, and white wax. The capsule shell contains FD&C Blue #1, gelatin, titanium dioxide, and other ingredients.

CLINICAL PHARMACOLOGY

Sulfasalazine is split by bacterial action in the colon into sulfapyridine (SP) and mesalamine (5-ASA). It is thought that the mesalamine component is therapeutically active in ulcerative colitis. The usual oral dose of sulfasalazine for active ulcerative colitis in adults is 2 to 4 g per day in divided doses. Four grams of sulfasalazine provide 1.6 g of free mesalamine to the colon.

The mechanism of action of mesalamine (and sulfasalazine) is unknown, but appears to be topical rather than systemic. Mucosal production of arachidonic acid (AA) metabolites, both through the cyclooxygenase pathways, ie, prostanoids, and through the lipoxygenase pathways, ie, leukotrienes (LTs) and hydroxyeicosatetraenoic acids (HETEs), is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin (PG) production in the colon.

Human Pharmacokinetics and Metabolism

Absorption. PENTASA is an ethylcellulose-coated, controlled-release formulation of mesalamine designed to release therapeutic quantities of mesalamine throughout the gastrointestinal tract. Based on urinary excretion data, 20% to 30% of the mesalamine in PENTASA is absorbed. In contrast, when mesalamine is administered orally as an unformulated 1-g aqueous suspension, mesalamine is approximately 80% absorbed.

Plasma mesalamine concentration peaked at approximately 1 mcg/mL 3 hours following a 1-g PENTASA dose and declined in a biphasic manner. The literature describes a mean terminal half-life of 42 minutes for mesalamine following intravenous administration. Because of the continuous release and absorption of mesalamine from PENTASA throughout the gastrointestinal tract, the true elimination half-life cannot be determined after oral administration. N-acetylmесalamine, the major metabolite of mesalamine, peaked at approximately 3 hours at 1.8 mcg/mL, and its concentration followed a biphasic decline. Pharmacological activities of N-acetylmесalamine are unknown, and other metabolites have not been identified.

Oral mesalamine pharmacokinetics were nonlinear when PENTASA capsules were dosed from 250 mg to 1 g four times daily, with steady-state mesalamine plasma concentrations increasing about nine times, from 0.14 mcg/mL to 1.21 mcg/mL, suggesting saturable first-pass metabolism. N-acetylmесalamine pharmacokinetics were linear.

Elimination. About 130 mg free mesalamine was recovered in the feces following a single 1-g PENTASA dose, which was comparable to the 140 mg of mesalamine recovered from the molar equivalent sulfasalazine tablet dose of 2.5 g. Elimination of free mesalamine and salicylates in feces increased proportionately with PENTASA dose. N-acetylmесalamine was the primary compound excreted in the urine (19% to 30%) following PENTASA dosing.

CLINICAL TRIALS

In two randomized, double-blind, placebo-controlled, dose-response trials (UC-1 and UC-2) of 625 patients with active mild to moderate ulcerative colitis, PENTASA, at an oral dose of 4 g/day given 1 g four times daily, produced consistent improvement in prospectively identified primary efficacy parameters.

The 4-g dose of PENTASA also gave consistent improvement in secondary efficacy parameters, namely the frequency of trips to the toilet, stool consistency, rectal bleeding, abdominal/rectal pain, and urgency. The 4-g dose of PENTASA induced remission as assessed by endoscopic and symptomatic endpoints.

In some patients, the 2-g dose of PENTASA was observed to improve efficacy parameters measured. However, the 2-g dose gave inconsistent results in primary efficacy parameters across the two adequate and well-controlled trials.

INDICATIONS AND USAGE

PENTASA is indicated for the induction of remission and for the treatment of patients with mildly to moderately active ulcerative colitis.

CONTRAINDICATIONS

PENTASA is contraindicated in patients who have demonstrated hypersensitivity to mesalamine, any other components of this medication, or salicylates.

PRECAUTIONS

General

Caution should be exercised if PENTASA is administered to patients with impaired hepatic function.

Mesalamine has been associated with an acute intolerance syndrome that may be difficult to distinguish from a flare of inflammatory bowel disease. Although the exact frequency of occurrence cannot be ascertained, it has occurred in 3% of patients in controlled clinical trials of mesalamine or sulfasalazine. Symptoms include cramping, acute abdominal pain and bloody diarrhea, sometimes fever, headache, and rash. If acute intolerance syndrome is suspected, prompt withdrawal is required. If a rechallenge is performed later in order to validate the hypersensitivity, it should be carried out under close medical supervision at reduced dose and only if clearly needed.

Renal

Caution should be exercised if PENTASA is administered to patients with impaired renal function. Single reports of nephrotic syndrome and interstitial nephritis associated with mesalamine therapy have been described in the foreign literature. There have been rare reports of interstitial nephritis in patients receiving PENTASA. In animal studies, a 13-week oral toxicity study in mice and 13-week and 52-week oral toxicity studies in rats and cynomolgus monkeys have shown the kidney to be the major target organ of mesalamine toxicity. Oral daily doses of 2400 mg/kg in mice and 1150 mg/kg in rats produced renal lesions including granular and hyaline casts, tubular degeneration, tubular dilation, renal infarct, papillary necrosis, tubular necrosis, and interstitial nephritis. In cynomolgus monkeys, oral daily doses of 250 mg/kg or higher produced nephrosis, papillary edema, and interstitial fibrosis. Patients with preexisting renal disease, increased BUN or serum creatinine, or proteinuria should be carefully monitored, especially during the initial phase of treatment. Mesalamine-induced nephrotoxicity should be suspected in patients developing renal dysfunction during treatment.

Drug Interactions

There are no data on interactions between PENTASA and other drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week dietary carcinogenicity study of mesalamine, CD-1 mice were treated with doses up to 2500 mg/kg/day and it was not tumorigenic. For a 50 kg person of average height (1.46 m² body surface area), this represents 2.5 times the recommended human dose on a body surface area basis (2960 mg/m²/day). In a 104-week dietary carcinogenicity study in Wistar rats, mesalamine up to a dose of 800 mg/kg/day was not tumorigenic. This dose represents 1.5 times the recommended human dose on a body surface area basis.

No evidence of mutagenicity was observed in an in vitro Ames test and an in vivo mouse micronucleus test.

No effects on fertility or reproductive performance were observed in male or female rats at oral doses of mesalamine up to 400 mg/kg/day (0.8 times the recommended human dose based on body surface area).

Semen abnormalities and infertility in men, which have been reported in association with

sulfasalazine, have not been seen with PENTASA capsules during controlled clinical trials.

Pregnancy

Category B. Reproduction studies have been performed in rats at doses up to 1000 mg/kg/day (5900 mg/M²) and rabbits at doses of 800 mg/kg/day (6856 mg/M²) and have revealed no evidence of teratogenic effects or harm to the fetus due to mesalamine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, PENTASA should be used during pregnancy only if clearly needed.

Mesalamine is known to cross the placental barrier.

Nursing Mothers

Minute quantities of mesalamine were distributed to breast milk and amniotic fluid of pregnant women following sulfasalazine therapy. When treated with sulfasalazine at a dose equivalent to 1.25 g/day of mesalamine, 0.02 mcg/mL to 0.08 mcg/mL and trace amounts of mesalamine were measured in amniotic fluid and breast milk, respectively.

N-acetylmessalamine, in quantities of 0.07 mcg/mL to 0.77 mcg/mL and 1.13 mcg/mL to 3.44 mcg/mL, was identified in the same fluids, respectively.

Caution should be exercised when PENTASA is administered to a nursing woman.

No controlled studies with PENTASA during breast-feeding have been carried out.

Hypersensitivity reactions like diarrhea in the infant cannot be excluded.

Pediatric Use

Safety and efficacy of PENTASA in pediatric patients have not been established.

ADVERSE REACTIONS

In combined domestic and foreign clinical trials, more than 2100 patients with ulcerative colitis or Crohn's disease received PENTASA therapy. Generally, PENTASA therapy was well tolerated. The most common events (ie, greater than or equal to 1%) were diarrhea (3.4%), headache (2.0%), nausea (1.8%), abdominal pain (1.7%), dyspepsia (1.6%), vomiting (1.5%), and rash (1.0%).

In two domestic placebo-controlled trials involving over 600 ulcerative colitis patients, adverse events were fewer in PENTASA-treated patients than in the placebo group (PENTASA 14% vs. placebo 18%) and were not dose-related. Events occurring at 1% or more are shown in the table below. Of these, only nausea and vomiting were more frequent in the PENTASA group. Withdrawal from therapy due to adverse events was more common on placebo than PENTASA (7% vs. 4%).

Nervous System: depression, dizziness, insomnia, somnolence, paresthesia

Cardiovascular: palpitations, pericarditis, vasodilation

Other: albuminuria, amenorrhea, amylase increase, arthralgia, asthenia, breast pain, conjunctivitis, ecchymosis, edema, fever, hematuria, hypomenorrhea, Kawasaki-like syndrome, leg cramps, lichen planus, lipase increase, malaise, menorrhagia, metrorrhagia, myalgia, pulmonary infiltrates, thrombocytopenia, thrombocytopenia, urinary frequency

One week after completion of an 8-week ulcerative colitis study, a 72-year-old male, with no previous history of pulmonary problems, developed dyspnea. The patient was subsequently diagnosed with interstitial pulmonary fibrosis without eosinophilia by one physician and bronchiolitis obliterans with organizing pneumonitis by a second physician. A causal relationship between this event and mesalamine therapy has not been established.

Published case reports and/or spontaneous postmarketing surveillance have described infrequent instances of pericarditis, fatal myocarditis, chest pain and T-wave abnormalities, hypersensitivity pneumonitis, pancreatitis, nephrotic syndrome, interstitial nephritis, hepatitis, aplastic anemia, pancytopenia, leukopenia, agranulocytosis, or anemia while receiving mesalamine therapy. Anemia can be a part of the clinical presentation of inflammatory bowel disease. Allergic reactions, which could involve eosinophilia, can be seen in connection with PENTASA therapy.

Postmarketing Reports

The following events have been identified during post-approval use of the PENTASA brand of mesalamine in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for

inclusion due to a combination of seriousness, frequency of reporting, or potential causal connection to mesalamine:

Gastrointestinal: Reports of hepatotoxicity, including elevated liver enzymes (SGOT/AST, SGPT/ALT, GGT, LDH, alkaline phosphatase, bilirubin), hepatitis, jaundice, cholestatic jaundice, cirrhosis, and possible hepatocellular damage including liver necrosis and liver failure. Some of these cases were fatal. One case of Kawasaki-like syndrome which included hepatic function changes was also reported.

Other: Postmarketing reports of pneumonitis, granulocytopenia, systemic lupus erythematosus, acute renal failure, chronic renal failure and angioedema have been received in patients taking PENTASA.

OVERDOSAGE

Single oral doses of mesalamine up to 5 g/kg in pigs or a single intravenous dose of mesalamine at 920 mg/kg in rats were not lethal.

There is no clinical experience with PENTASA overdosage. PENTASA is an aminosalicylate, and symptoms of salicylate toxicity may be possible, such as: tinnitus, vertigo, headache, confusion, drowsiness, sweating, hyperventilation, vomiting, and diarrhea. Severe intoxication with salicylates can lead to disruption of electrolyte balance and blood-pH, hyperthermia, and dehydration.

Treatment of Overdosage. Since PENTASA is an aminosalicylate, conventional therapy for salicylate toxicity may be beneficial in the event of acute overdosage. This includes prevention of further gastrointestinal tract absorption by emesis and, if necessary, by gastric lavage. Fluid and electrolyte imbalance should be corrected by the administration of appropriate intravenous therapy. Adequate renal function should be maintained.

DOSAGE AND ADMINISTRATION

The recommended dosage for the induction of remission and the symptomatic treatment of mildly to moderately active ulcerative colitis is 1g (4 PENTASA 250 mg capsules or 2 PENTASA 500 mg capsules) 4 times a day for a total daily dosage of 4g. Treatment duration in controlled trials was up to 8 weeks.

HOW SUPPLIED

PENTASA controlled-release 250 mg capsules are supplied in bottles of 240 capsules (NDC 54092-189-81). Each green and blue capsule contains 250 mg of mesalamine in controlled-release beads. PENTASA controlled-release capsules are identified with a pentagonal starburst logo and the number 2010 on the green portion and PENTASA 250 mg or S429 250 mg on the blue portion of the capsules.

PENTASA controlled-release 500 mg capsules are supplied in bottles of 120 capsules (NDC 54092-191-12). Each blue capsule contains 500 mg of mesalamine in controlled release beads. PENTASA controlled-release capsules are identified with a pentagonal starburst logo and PENTASA 500 mg or S429 500 mg on the capsules.

Store at 25°C (77°F) excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Manufactured for Shire US Inc. 725 Chesterbrook Blvd., Wayne, PA 19087, USA

Licensed U.S. Patent Nos. B1 4,496,553 and 4,980,173 189 0107 009

Licensed from Ferring A/S, Denmark

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Rev. 06/2008

PEN-00042

Table 1. Adverse Events Occurring in More Than 1% of Either Placebo or PENTASA Patients in Domestic Placebo-controlled Ulcerative Colitis Trials. (PENTASA Comparison to Placebo)

PENTASA Placebo

Event n=451 n=173

Diarrhea 16 (3.5%) 13 (7.5%)

Headache 10 (2.2%) 6 (3.5%)

Nausea 14 (3.1%) ---

Abdominal Pain 5 (1.1%) 7 (4.0%)

Melena (Bloody Diarrhea) 4 (0.9%) 6 (3.5%)
Rash 6 (1.3%) 2 (1.2%)
Anorexia 5 (1.1%) 2 (1.2%)
Fever 4 (0.9%) 2 (1.2%)
Rectal Urgency 1 (0.2%) 4 (2.3%)
Nausea and Vomiting 5 (1.1%) ---
Worsening of Ulcerative Colitis 2 (0.4%) 2 (1.2%)
Acne 1 (0.2%) 2 (1.2%)
Attachment 2.

Attachment 2

Subject Specific Product Dispensing/Return Log

Protocol: Predicting Response to Standardized Pediatric Colitis Therapy (**PROTECT**)

Investigator Name	Clinical Study Site	Study Site ID	Subject ID	MEMS Cap Serial Number

Date	Prescription Number	Quantity Dispensed or Received	Manufacturer Lot Number	Manufacturer Expiration Date	Recorders Initials

APPENDIX B
INSTALLATION GUIDE



INSTALLATION GUIDE **FOR ACTIVE X** **COMPONENT**

**THE SOFTWARE MUST BE INSTALLED
PRIOR TO THE FIRST MEMS READING**

You will need a personal login for www.medamigo.com.
Request it at techsupport@ aardexgroup.com

Table of contents		
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Requirements for medAmigo		4
Software installation procedure		5
Check whether the installation was successful		7
Troubleshooting	Internet Security Settings	9
	Trusted Sites	10
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medAmigo is not fully compatible with Internet Explorer 11		12
Technical details (for IT department)		13

HELPDESK:

techsupport@ardexgroup.com

Website for the MEMS download:

www.medamigo.com

BEFORE YOU START USING THE MEMS CAPS AND THE MEDAMIGO WEBSITE

- Request a login for www.medamigo.com at the helpdesk
- Proceed with the installation of the software (instructions are provided in the Installation Guide)

medAmigo PLATFORM

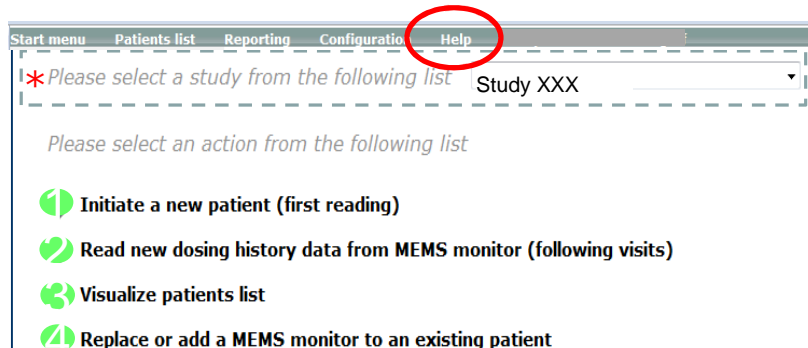
GENERAL INFORMATION

1. The **medAmigo** (med=medicine, Amigo=friend) web platform is a website which allows the study staff to read the MEMS caps on a secured website.

www.medamigo.com home page



2. Frequently asked questions and general support documents are available in the "help" tab upon login to the website.



3. If you are already participating in another study using the www.medamigo.com website, you do not need to install the software again. Moreover, you can use your current login for several studies. You just need to have the additional study activated in your profile and select the appropriate study in the main menu upon login to the website (*).

If you have any questions, send an email to the dedicated AARDEX

Group helpdesk:

techsupport@ aardexgroup.com

SOFTWARE INSTALLATION PROCEDURE

REQUIREMENTS FOR medAmigo

- ❑ **Software installation** The software 'AARDEX reader setup' must be installed on **each computer** which will be used to read the MEMS caps. The installation must be done **before the first subject is enrolled**.

This Software is required to register and read a MEMS cap on the www.medamigo.com website ; **all MEMS caps** which you received **are**, however, **activated and fully functional!** They do not need to be activated on the website.

The installation procedure is described in the following pages. A personal login for the www.medAmigo.com website is required for the installation. If you haven't received a login yet, you might download the software from the link provided on page 10.
- ❑ **Personal login** Each user should receive a **personal** login and password by email to access the medAmigo website. You may have received it in your junk-mailbox. If not received, please send an email to the AARDEX Group helpdesk (address provided on page 2).
- ❑ **Internet Connection** The medAmigo portal is a web-based application. The software 'medAmigo ReadMonitor setup' component used to read the MEMS caps is **only** compatible with Microsoft **Internet Explorer version 8 or higher**.
- ❑ **Hardware** Minimal requirements:
 - Computer running Windows 32bits or 64bits with internet connection
 - MEMS Reader (or other compatible devices)
 - Free USB port
- ❑ **Software**
 - Microsoft Windows 8 (recommended)
 - Microsoft Windows 7 (recommended)
 - Microsoft Windows Vista
 - Microsoft Windows XP Pro SP2
 - Microsoft Internet Explorer 8 or higher, only 32bits version supported
 - Microsoft Internet Explorer desktop version only on Microsoft Windows 8Non validated platforms
 - Windows 2000, Windows 98 SE, Windows ME, Windows XP Home

SOFTWARE INSTALLATION PROCEDURE

Please note that the software is for an internet application; you will not find a shortcut on your desktop after the installation.

Depending on your network security policy, the involvement of the IT team may be required to proceed with this installation (*administrator rights are required for the installation*).

1. Connect the MEMS reader on a free USB port (Windows will automatically find the MEMS reader).

2. Log in to www.medamigo.com

Welcome to AARDEX medAmigo online system.
Please enter your login and password below.

Login

Password

[Sign-in](#)

[Forgot password ? Help](#)

3. Upon login, click on the following item in the main menu:

- Initiate a new patient (first reading)
- Read new dosing history data from MEMS monitor (following visits)**
- Visualize patients list
- Replace or add a MEMS monitor to an existing patient

4. Click on "Installation".

Installation

A component must be installed on your computer in order to communicate with our hardware devices.

If you have already installed the component and still see this message, you should activate the component by clicking in the yellow information bar on top of the page.

Please make sure that you have sufficient rights to install an ActiveX component on the computer. To install the software click on the installation button below.

[Return to the main page](#)

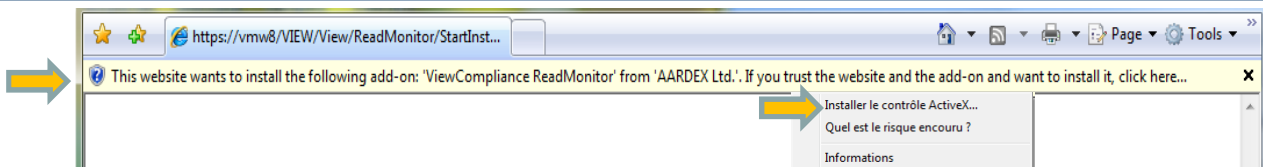
Before installing the software please check your browser Internet Options:

- **Download signed ActiveX controls.** This should be Prompt or Enable
- **Run ActiveX controls and plug-ins.** This should be Enable or Prompt
- **Script ActiveX controls marked safe for scripting.** This should be Enable or Prompt

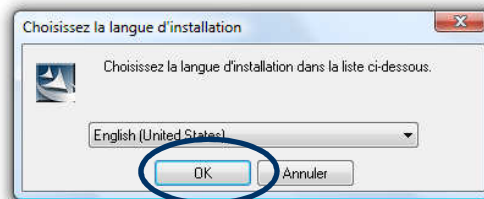
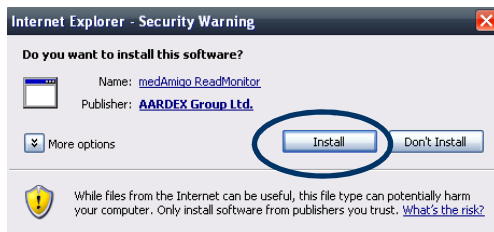
If you still have installation problems or cannot find/detect our online reader, [click here](#) to see the most likely reasons.

SOFTWARE INSTALLATION PROCEDURE

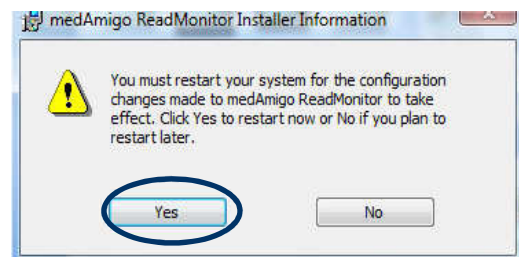
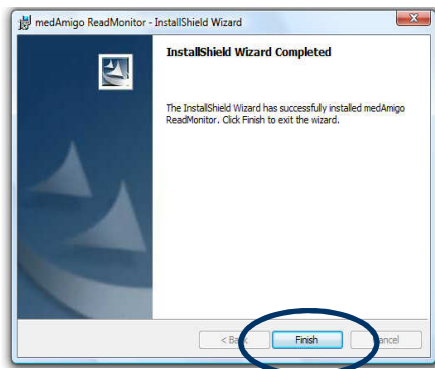
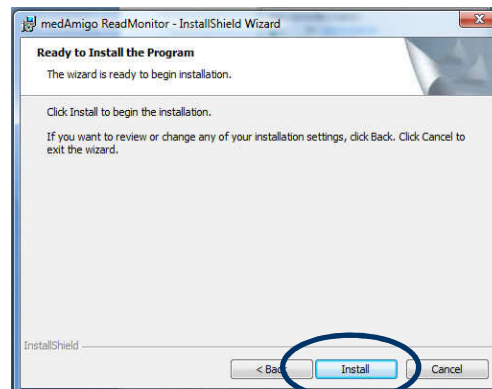
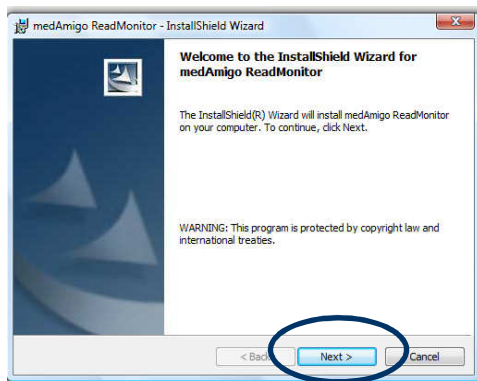
5. If the following screen appears, click on the yellow bar (right mouse button), and « Install ActiveX controls ».



6. Click on « Install ». Then, choose your language.







7. Follow the installation procedure until you are asked to restart your computer. Click on « yes » to restart your computer.



CHECK WHETHER THE INSTALLATION WAS SUCCESSFUL

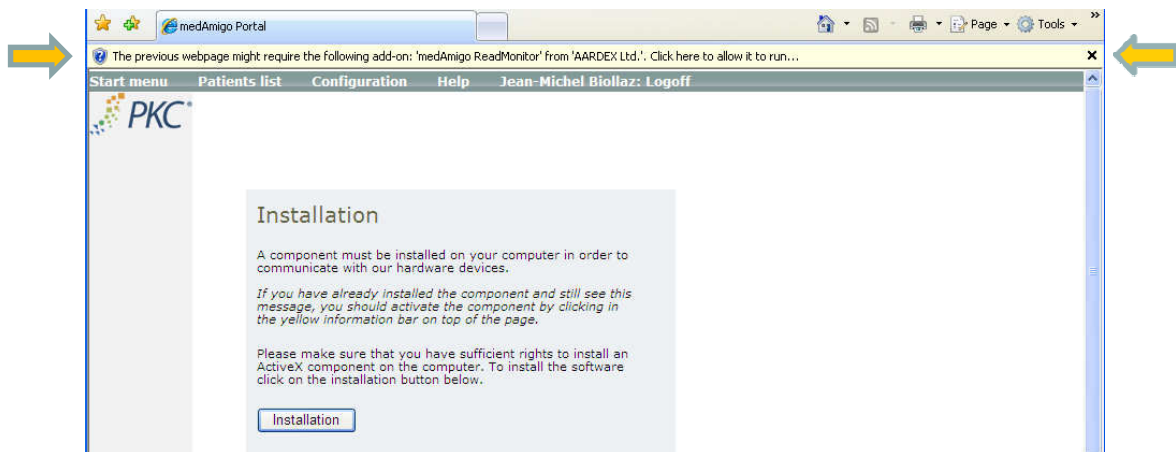
1. After having installed the software and restarted your computer, open the windows session with the end-users login, then open Internet Explorer and log in to www.medamigo.com.

2. Click on the following item in the main menu:

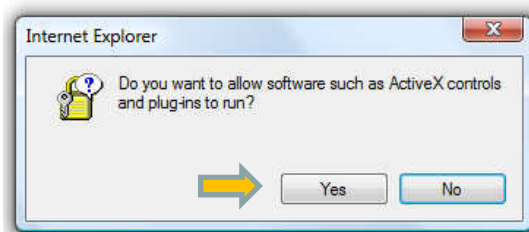
-  **Initiate a new patient (first reading)**
-  **Read new dosing history data from MEMS monitor (following visits)**
-  **Visualize patients list**
-  **Replace or add a MEMS monitor to an existing patient**

3. The first execution of the ActiveX may require a **user's confirmation**. If you see again the Installation-page, check if a confirmation is displayed on the top of your Internet Explorer. Click on the yellow bar and select **Run ActiveX Control** to allow the software's execution.

Depending on your Internet Explorer version, this yellow bar might appear in the bottom of the page.



4. If necessary, confirm the security warning by clicking on **Yes**.

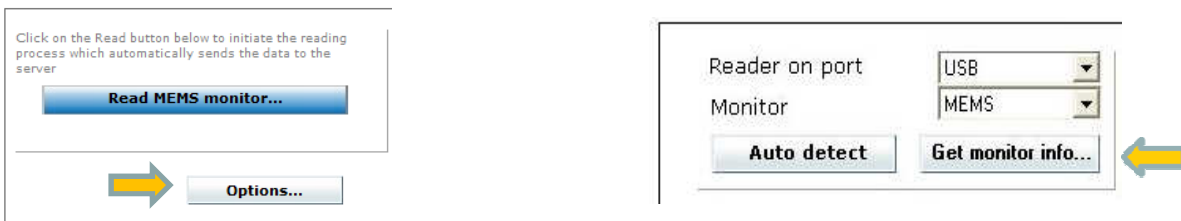


CHECK WHETHER THE INSTALLATION WAS SUCCESSFUL

- Put a MEMS cap on the MEMS reader (upside down).

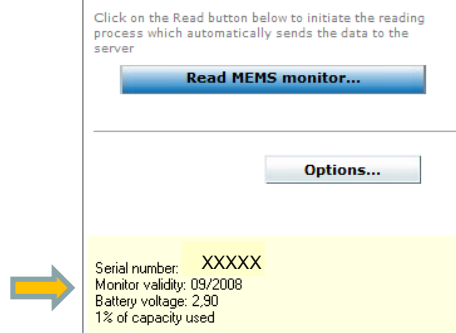


- Click on Options, then on **Get Monitor Info**

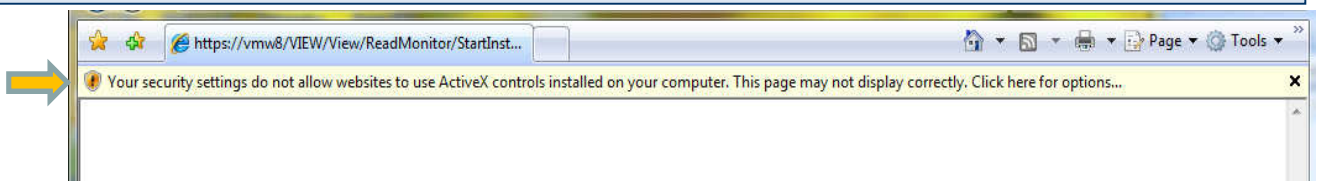


- If you see the blue button « Read MEMS monitor », the installation was successful.

Moreover, the website displays the information about the MEMS cap (as shown below), the connection to the MEMS cap was thus successful and proves that the installation is completed.



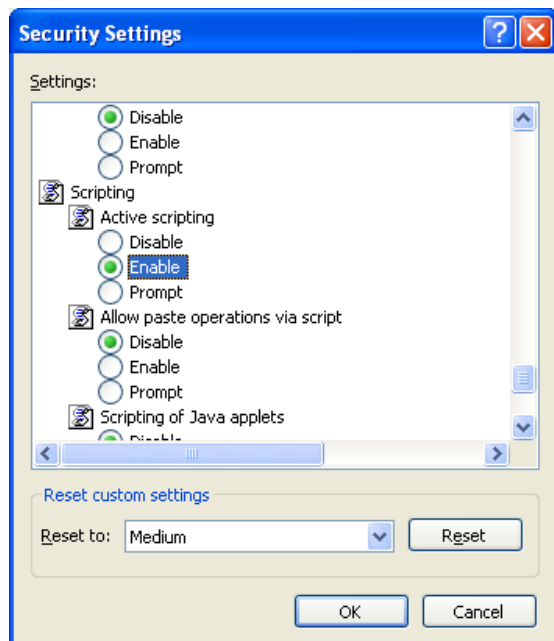
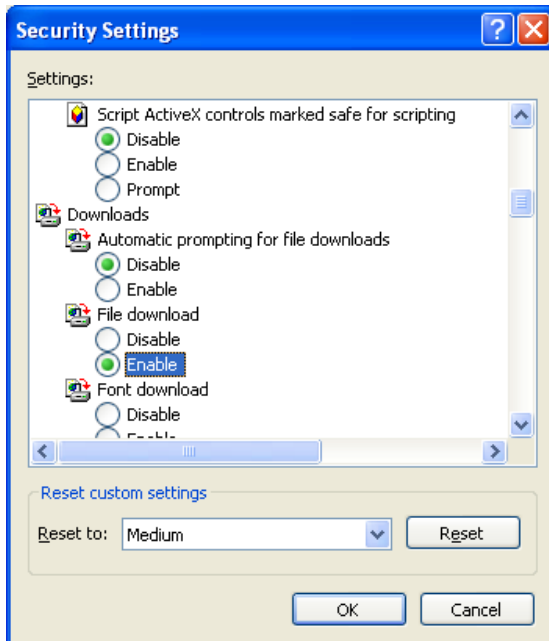
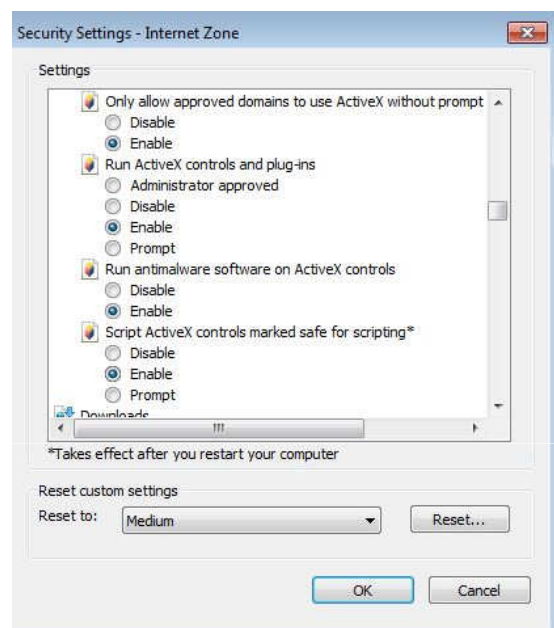
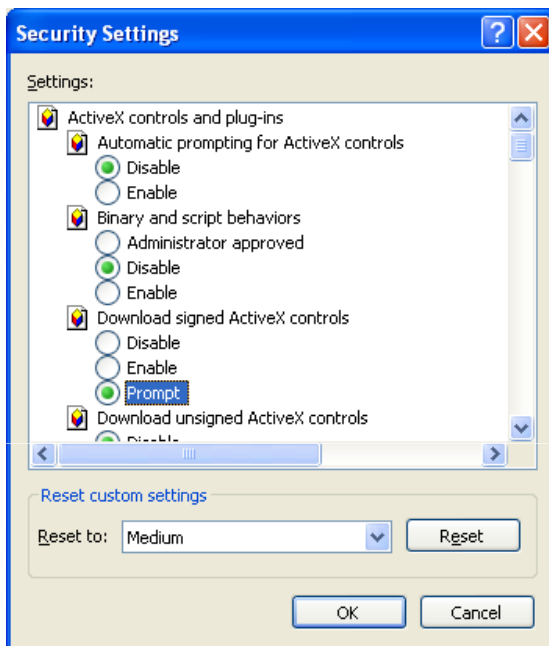
REMARK: If the following screen appears after a successful installation, you need to check your internet security settings and the configuration of your trusted sites. Instructions are provided in the following pages.



Troubleshooting: Internet Security Settings

Check your internet security settings with your IT. All functionalities of medAmigo will work properly only if the following security parameters are turned on.

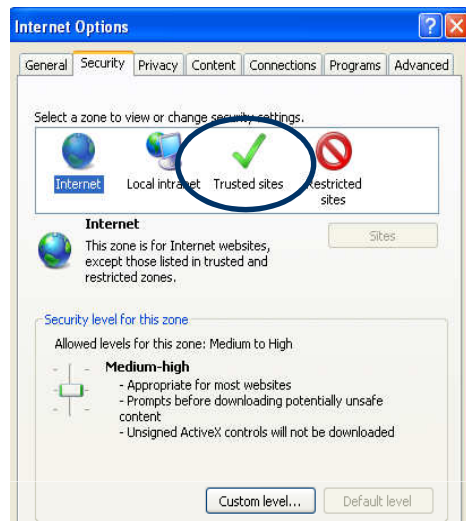
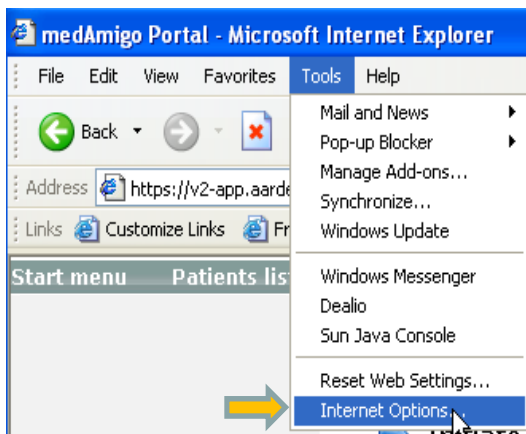
1. Set the security level for the zone as « Medium high ».
2. Set the following security settings as shown below.



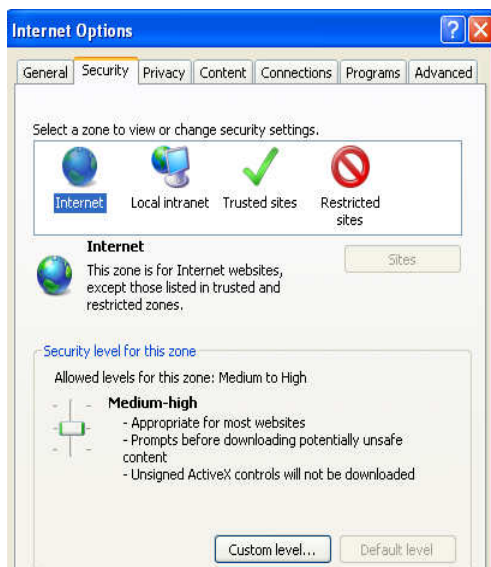
Troubleshooting: Trusted Sites

If you still have difficulties to access the "Read MEMS monitor" button, please check if the website is listed as a trusted site on your computer.

Go to « Internet options »
Click on Trusted sites.



In the new window which pops up, enter the internetlinks www.medAmigo.com and *.aardexgroup.com in the empty field. Click on « add » and then on « Close ».



E. ALTERNATIVE SOFTWARE INSTALLATION

1. If the installation from the website is not possible or if you haven't received a login yet, you might download the software from the following link:

<http://helpdesk.aardexgroup.com/index.php?/Default/Knowledgebase/Article/View/102/11>

2. Check if the software 'AARDEX Reader setup' is installed in your control panel
3. Check if you are using Internet Explorer 8 or higher (only the 32bits version is supported). Install a shortcut for Internet Explorer 32 bit on your computer. Once this is done, please install the Active X 32 bit application.
 - a. On a Win7 64-bit computer, two versions of Internet Explorer are available: IE 32-bit (the default) and IE 64-bit (cannot be the default). Shortcuts to both versions should be listed in your Start menu, you just need to open IE 32-bit shortcut.

If you need to check the target of your shortcut, the executable for IE8 32-bit is located here:

- C:\Program Files (x86)\Internet Explorer\iexplore.exe

and the executable for IE8 64-bit is located here:

- C:\Program Files\Internet Explorer\iexplore.exe

If you cannot find a shortcut to IE 32-bit, please follow these steps to create a shortcut:

1. Right click on the desktop.
 2. Click on New, and then click on Shortcut.
 3. Once you click on Shortcut, you will get a box as Type the location of the item.
 4. Type the following command "C:\Program Files (x86)\Internet Explorer\iexplore.exe"
 5. Click next and finish the process.
- Then you can open a 32-bit Internet explorer.

4. In Windows 8, start Internet Explorer from the desktop and not from the start screen (with the tiles).
5. Check in the 'Tools - Manage add-ons' menu, that the 'ActiveX control' is enabled. If that's not the case, you can activate it by clicking on the 'enable' button.

medAmigo is not fully compatible with Internet Explorer 11

If the following message is displayed in your Internet Explorer 11, you need to add the aardexgroup.com to Compatibility view as shown below.

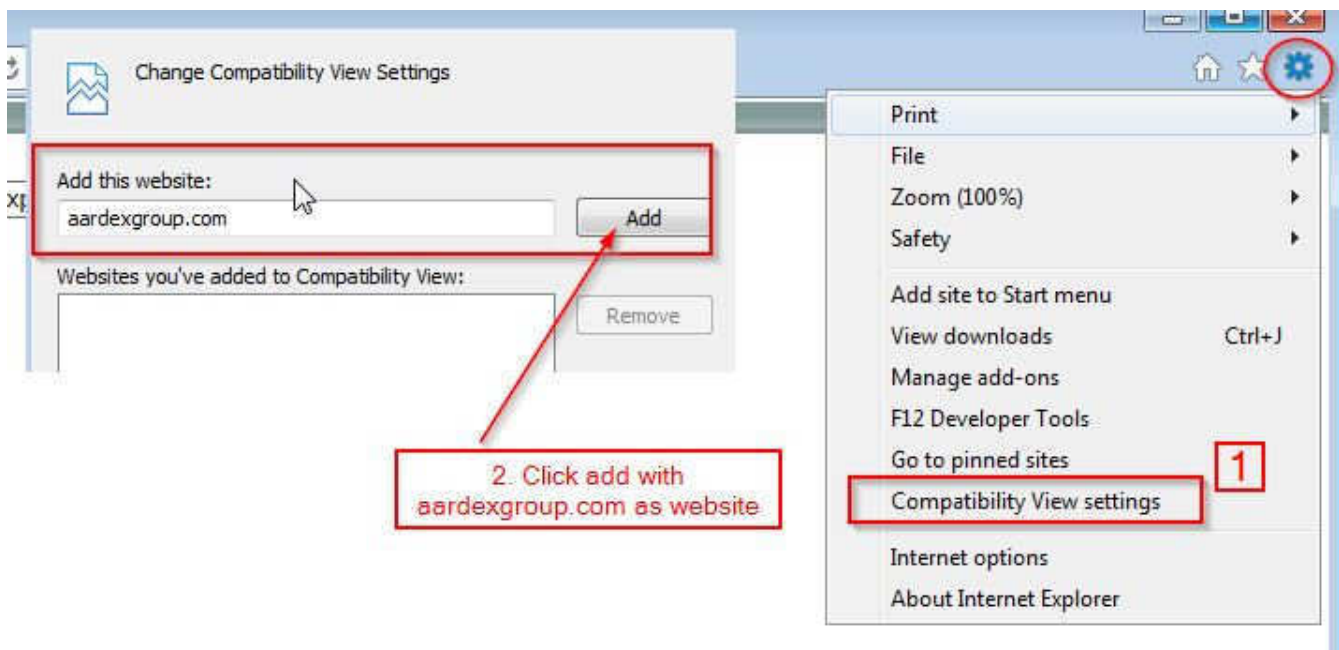
Please select an action from the following list

Information :

medAmigo is not fully compatible with **Internet Explorer 11**.
To use medAmigo, you will need to activate the compatibility mode in your browser.

1. Click the Tools button, and then click Compatibility View settings.
2. Under Add this website, enter "aardexgroup.com" and then click Add.

- ➔ **Initiate a new patient (first reading)**
- ➔ **Read new dosing history data from MEMS monitor (following visits)**
- ➔ **Visualize patients list**
- ➔ **Replace or add a MEMS monitor to an existing patient**



1. Objectives

This document describes the steps required to install the AARDEX ReadMonitor ActiveX component.

2. System requirements

2.1. Hardware

Minimal requirements:

Computer running Windows 32bits or 64bits with internet connection

MEMS Reader (or other compatible devices)

Free USB port

2.2. Software

- Microsoft Windows 8 (*recommended*)
- Microsoft Windows 7 (*recommended*)
- Microsoft Windows Vista
- Microsoft Windows XP Pro SP2

- Microsoft Internet Explorer 8 or higher, only 32bits version supported
- Microsoft Internet Explorer desktop version only on Microsoft Windows 8

Non validated platforms

Windows 2000, Windows 98 SE, Windows ME, Windows XP Home

3. What is AARDEX ReadMonitor ActiveX

- AARDEX ReadMonitor ActiveX is needed to communicate with our hardware device on the USB port. This part of the software will only capture data on the device and put them in a working directory from which they will be transferred to the medAmigo online system.
- No internet communication will be made by the ActiveX except for device data upload.
- The default working directory is "[Current user]\Application Data\AARDEX\ViewCompliance". The user needs read/write access in this directory. This directory can be changed in ReadMonitor Settings if needed. All readings made on the system are stored incrementally in this working directory. They can be manually deleted if needed. There are no other disk writing needs.
- Working files are encrypted and signed and do not contain any private data.
- AARDEX ReadMonitor ActiveX is signed by the trusted Verisign Code Signing Certificate.
- medAmigo http communication is secured by an SSL certificate covering *.aardexgroup.com. So if you are using an Internet filtering solution (Websense, etc), please allow the following addresses: www.medamigo.com and *.aardexgroup.com.

4. Installation procedures

1. Login on the medAmigo website and choose one of the "Read Monitor" links in the proposed menu. You will be automatically forwarded to the installation page where you can click on the "Installation" button. Alternatively you can start on the provided CD-ROM the medAmigo ReadMonitor setup.
2. Both installations need install rights on the computer for All Users. ActiveX can be installed with an Administrative account and then used by a standard user account.
3. To launch the online installation and to later use the Read Monitor ActiveX component, signed ActiveX must be authorized on your Internet Explorer:
 - Download signed ActiveX controls: this should be Enable or prompt.
 - Run ActiveX controls and plug-ins: this should be Enable or prompt.
 - Script ActiveX controls marked safe for scripting: this should be Enable or prompt
4. Online installation may ask the user to confirm that the system wants to install a signed ActiveX component.
5. Follow the instructions on screen to complete the installation.

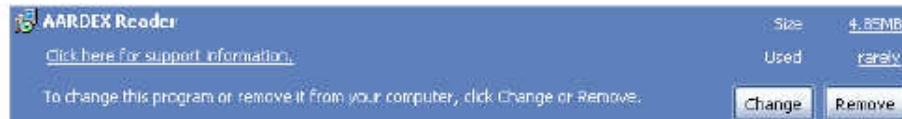
5. How to check that the installation is working

Steps to ensure the installation will work correctly:

- It's recommended, but not mandatory, to restart your computer to ensure there are no startup scripts that will interfere with the installation
- Login with the end user account
- Open your Internet Explorer, login to medAmigo (<http://www.medamigo.com>) and choose one of the "Read" links proposed in the menu. You must see here the ReadMonitor component with a Read button. If hardware devices are available, click on the Read button to start a test reading.
- In a centrally managed environment, ensure with the IT department that the medAmigo ReadMonitor component installation will be included in the basic workstation image.

6. Uninstallation procedures

1. From the Windows Start menu, choose Settings and open the Control panel
2. Launch "Add/remove programs"
3. Select the appropriate AARDEX ReadMonitor entry and click on the remove button



7. Installed files

The following files are installed by AARDEX ReadMonitor setup:

Filename	Date	Size	MD5
ReadMonitorProj.ocx	31.01.2013 14:38	2*831*872	97044d4973db224a9e16d4e0942cf5f
Sedc.dll	30.04.2012 13:22	745*472	Bca7f90b506822645b77ca2d126b6f4d
MEMS7.dll	29.01.2013 15:42	535*040	e2593a0147e69e064ac3b0ac0348457a
PPSrvProxy.dll	01.10.2007 19:34	135*168	007304f4d6c5d9d02d2349772ef95324
IDAS2.dll (optional)	06.06.2003 09:23	122*880	73696b5476356308f7a98c638b0cc4e9
IDAS1.dll (optional)	12.11.2008 11:04	729*088	8923715dbdf206cc9d74d71c0da96d8e

8. Version history

Changes in 2.8.0 (31.01.2013):

- Added support for MEMS 6.1

Changes in 2.7.0 (17.09.2008):

- Added support for HelpingHand

Changes in 2.6.0 (21.04.2008):

- Added MEMS Monitor information
- Added external devices support

Changes in 2.5.0 (08.11.2007):

- MEMS recycling support

Changes in 2.4.0 (19.04.2007):

- MEMS Reader support

Previous versions not listed here

9. More information and contact

More information can be obtained in the online help or by contacting our helpdesk techsupport@aardegroupp.com

APPENDIX C

MEMS GETTING STARTED



Getting started

MEMS® 6 WakeUp

v. 2.4 / USB only,
Windows XP, Vista, Windows 7, 8 compatible



MEMS® 6 WakeUp

1. Requirements

Minimal requirements:

Computer running Windows 32bits or 64bits

MEMS Reader (or other compatible devices)

Free USB port

2. Installation of the software

<u><i>Install from the CD</i></u>	<u><i>Download from our Website</i></u>
<ul style="list-style-type: none">• Insert the CD-ROM in the appropriate drive.• Open the File menu 'Start', select 'Run' and type the drive X:\SETUP.EXE, where "X" stands for the drive from which you are installing the program (normally D for CD-ROM drive).	<ul style="list-style-type: none">• The software can be downloaded on the following website: http://www.aardexgroup.com/helpdesk• Choose 'Download' and download the last version of MEMS 6 WakeUp software; fill in the registration fields.• Click on 'Start download', and then 'Save' the file on your computer.• Double-click on the file Mems6WakeUp2xx.exe.

- Select the directory where you want MEMS 6 WakeUp to be installed. The default location, suggested by the program, is **C:\Program Files\Aardex\MEMS6WakeUp**.
- If you wish to use another location, click on 'Browse' to select or create a new directory.
Click on 'Next' to continue.
- The program shows the selected installation parameters.
Click on 'Next' to finish.

IMPORTANT REMARK: Storing the MEMS monitors

If the monitors are not used by patients, but stocked in a warehouse, please make sure that they are either protected with the plunger protection, or completely screwed on a fitting plastic bottle.

3. Wake up your MEMS monitors

Installation of the material

➤ For **MEMS 6 Reader (green) (art. no. 1020-25-1)**

Please see the separate info sheet 'MEMS 6 USB Reader: Installation Procedure'.

➤ For **MEMS Reader (black) (art. no. 1070-20-1)**

Connect the MEMS reader to an USB port. No USB driver installation is requested.

Start the program

Double click on the icon 'MEMS 6 WakeUp'

Configuration of the application

- Check the actual date/time value and if necessary change it with the button "Change"
- Make sure the USB port configured is the same as previously connected.

Waking Up a MEMS 6 TrackCap (without LCD)

- Read carefully the 'Warning' and press OK.
- Place the MEMS 6 monitor top down in the well at the front of the reader.
- Press F2 for waking up the monitor.
- Unscrew the plunger protection, screw the monitor on a bottle completely, and place the MEMS 6 monitor top down in the well at the front of the reader.
- Press F4 for checking event creation.
- Remove the sticker and press F8.



Waking Up a MEMS 6 SmartCap (with LCD)

- Read carefully the 'Warning' and press OK.
- Place the MEMS 6 monitor top down in the well at the front of the reader.
- Press F2 for waking up the monitor.
- Select the time zone in which the MEMS 6 monitor will be used.
- Select the hour at which the doses counter must be reset to zero.
- Press F3 for validate selected parameters.
- Unscrew the plunger protection, screw the monitor on a bottle completely, and place the MEMS 6 monitor top down in the well at the front of the reader.
- Press F4 for checking event creation.
- Remove the sticker and press F8.



Appendix D: MEMS Quick Start Manual

Table of Contents

D.1	MEMS QUICK START MANUAL.....	2
D.2	CHANGE REGIMEN INSTRUCTIONS.....	21
D.3	NON-MONITORED PERIOD INSTRUCTIONS.....	24
D.4	MEMS FAQ.....	27

QUICK START MANUAL





HELPDESK	4
Remove closure protection	5
Instructions for patients	6
The medAmigo main menu	7
Initiate a new patient	8
Read a MEMS	10
Patient data	12
Replace a MEMS for an existing patient	13
Add a MEMS for an existing patient	16
Close patient	19

HELPDESK:

techsupport@ardexgroup.com

Website for the MEMS download:

www.medamigo.com

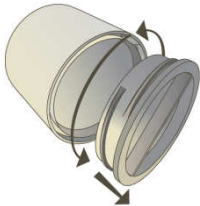
**BEFORE YOU START USING THE MEMS CAPS AND THE
MEDAMIGO WEBSITE**

- Request a login for www.medamigo.com at the helpdesk
- Proceed with the installation of the software (instructions are provided in the Installation Guide)

REMOVE THE CLOSURE PROTECTION

Each MEMS caps has a unique 6 digit serial number. This number is stored in the memory of the MEMS cap and it is printed on the side of the cap.

1. Remove the closure protection from the MEMS cap.



Turn and pull.
Push down and turn if child resistant system



2. Place the MEMS cap on the medication bottle.



"Push down and turn"
if child resistant system



3. Initiate the patient on the medAmigo website and read the MEMS cap for the first time. Follow the instructions described in "How to initiate a new patient?"

www.medamigo.com



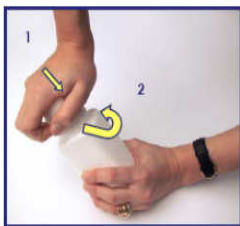
4. Give the dosing dispenser with the MEMS cap to the patient with the following instructions:

- No other dosing dispenser should be used besides the medication bottle with the MEMS cap. No pocket dosing.
- Bring the MEMS cap to each visit.
- When it is time to take the medication:
- Open the bottle
- Remove the dose and promptly close the package
- Ingest the prescribed dose



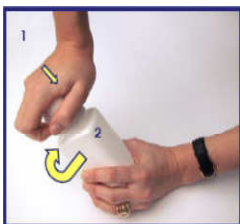
INSTRUCTIONS FOR THE PATIENT

You will use a MEMS monitor during the course of this study. Each time you open and close the MEMS monitor, it registers the date and time of opening.



To open your MEMS® monitor, turn the MEMS® monitor counter-clockwise (Push down and turn if child resistant system).

Your MEMS® monitor can now be easily removed from the bottle. Take your tablet from the bottle.



To close your medication bottle, turn clockwise (Push down and turn if child resistant system).

You can now take your pill.

Special remarks:

- ❖ Data recorded by the MEMS monitor are important information. As each opening of the pillbox will be recorded, please **do NOT open the pillbox unnecessarily.**
- ❖ **No other dosing dispenser** should be used besides the medication bottle with the MEMS cap. No pocket dosing.
- ❖ Promptly close the bottle with the MEMS cap after removing each dose. **Never leave the medication bottle with the MEMS cap open.**
- ❖ **Do not immerse the MEMS cap in any liquid;** do not clean it with detergent or alcohol. The exterior may be wiped with a slightly damp cloth.
- ❖ **Always bring all assigned MEMS caps to each visit.**

medAmigo MAIN MENU

1. The **medAmigo** (med=medicine, Amigo=friend) web platform is an internet portal which allows the study staff to read the MEMS caps on a secured website.



www.medamigo.com home page

2. Once you are logged in to the medAmigo platform, you will be directed to the main menu. Select the appropriate procedure in the main menu to read the MEMS caps.

If you are involved in **multiple studies using medAmigo, you need to select the appropriate study before reading the MEMS caps.*

**Please select a study from the following list*

Please select an action from the following list

- 1 **Initiate a new patient (first reading)**
- 2 **Read new dosing history data from MEMS monitor (following visits)**
- 3 **Visualize patients list**
- 4 **Replace or add a MEMS monitor to an existing patient**

Explanations of the main menu

- 1 *Click here to include a new patient.*
- 2 *Click here to read the MEMS data of an already included patient.*
- 3 *Click here to see data of a patient without reading a MEMS.*
- 4 *Click here if you want to replace or add a MEMS cap for an existing patient.*






INITIATE A PATIENT

1. Log on internet web-page: [www. medAmigo.com](http://www.medAmigo.com) using your personal login and password



2. On the start page, click on *Initiate a new patient (First reading)* - (*Visit 0 of your patients*)

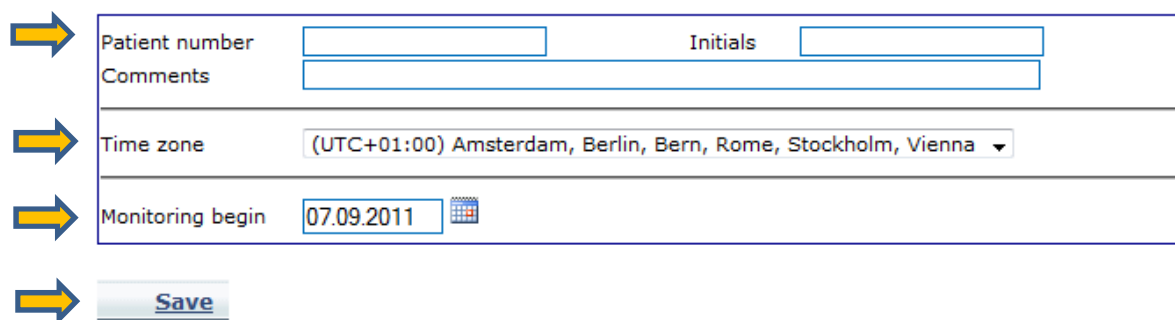
Please select an action from the following list

-   **Initiate a new patient (first reading)**
-  **Read new dosing history data from MEMS monitor (following visits)**
-  **Visualize patients list**
-  **Replace or add a MEMS monitor to an existing patient**

3. Patient data form:

- Enter the Patient number
- Select the appropriate time zone
- Enter the MEMS monitoring begin date. This is the date when the monitoring of the patient's medication intake is supposed to start. The default is set as the date of the patient's initiation. Verify and change this date if necessary.

Click on *Save* to have the data entries registered.

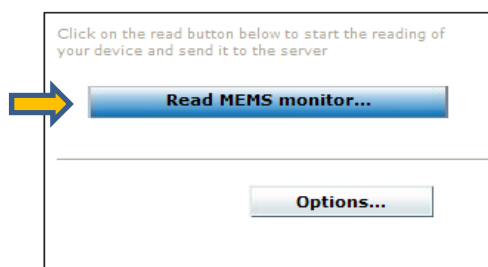


INITIATE A PATIENT

- 4. Put the MEMS monitor on the MEMS Reader (upside down) and click on the *Read MEMS monitor* button.**



1. Put the MEMS monitor on the MEMS reader (head down)
2. Proceed with reading the data from the MEMS monitor



- 5. Indicate the *drug name, the regimen and the number of tablets per dose* (if applicable). Click on *Continue*, and you will be directed to the patient data.**

Reading MEMS monitor 1 from 1

	Monitor number	202794
	Indication / pathology	MEMS 1 ▾
➔	Drug name	Drug A ▾
➔	Regimen	<input checked="" type="radio"/> Fixed 1x/day Regimen ▾ <input type="radio"/> Every
➔	Number of tablets per dose	<input type="text"/>
	Data transfer successful	
➔	Continue	






READ A MEMS

1. Log on internet web-page: [www. medAmigo.com](http://www.medAmigo.com) using your personal login and password

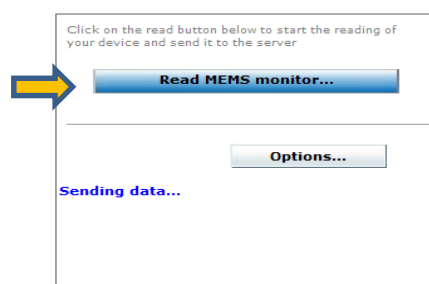


2. On the start page, click on *Read new dosing history data from MEMS monitor (following visits)*.

Please select an action from the following list

-  **Initiate a new patient (first reading)**
-   **Read new dosing history data from MEMS monitor (following visits)**
-  **Visualize patients list**
-  **Replace or add a MEMS monitor to an existing patient**

3. Put the MEMS monitor on the MEMS Reader (upside down) and click on the *Read MEMS monitor* button.



READ A MEMS

4. After reading a MEMS you will be asked if there was a change in the regimen. Change the regimen if necessary and click on Continue. The « change regimen » option at this stage might not be available in all studies.

Reading MEMS monitor 1 from 1

Monitor number 202794
Indication / pathology MEMS 1 ▾
Drug name Drug A ▾
Regimen Fixed 1x/day Regimen ▾
 Every
Number of tablets per dose 1
If there was a change of pathology, drug or regimen, since when
21.05.2010

Data transfer successful



Continue

5. You are automatically forwarded to the patient data.

Access patient data without reading a MEMS

1. Log on internet web-page: [www. medAmigo.com](http://www.medAmigo.com) using your personal login and password.

2. On the start page, click on *Visualize patients list*.

Please select an action from the following list

- Initiate a new patient (first reading)
- Read new dosing history data from MEMS monitor (following visits)
- Visualize patients list
- Replace or add a MEMS monitor to an existing patient

3. Here you will see an overview of all of your patients, visits dates and the next planned visit dates. To access data of a particular patient, click on the patient's code or the patient's assigned monitor number.

Patient code	Monitor number	Site name	Last visit	Next expected visit	Program ended	Search
11007	500000	Demo Patients	16/09/2007			
1DH	500006	Demo Patients	30/11/2007			
1Int	36569	Demo Patients	15/11/2007	12/07/2008		
1TV	500002	Demo Patients	30/10/2007	19/02/2009		
1WE	500004	Demo Patients	12/08/2007	21/06/2008		



Patient number



MEMS monitor number



Site name



Date of last reading



Date of next visit

REPLACE A MEMS CAP

Replace a MEMS: A MEMS cap should only be replaced when it is defective or definitely lost. Take a new MEMS cap and initiate this new MEMS with the following procedure.

1. **Log on internet web-page: [www. medAmigo.com](http://www.medAmigo.com) using your personal login and password.**

2. **On the start page, click on *Replace or add a MEMS monitor to an existing patient.***

Please select an action from the following list

- Initiate a new patient (first reading)**
- Read new dosing history data from MEMS monitor (following visits)**
- Visualize patients list**
- Replace or add a MEMS monitor to an existing patient**

REPLACE A MEMS CAP

- 3. To select the patient for whom a MEMS has to be replaced, you may either enter the patient number, or choose the patient number from the patients list by clicking on Patients list.**

a. enter the patient number

Replace or add a MEMS monitor to an existing patient

Select the patient number for whom you want to replace or add a MEMS monitor:

or choose in patient list: **Patients list**

b. select the patient from the patients list by clicking on Patients list.

Replace or add a MEMS monitor to an existing patient

Select the patient number for whom you want to replace or add a MEMS monitor:

or choose in patient list: **Patients list**

Replace or add a MEMS monitor to an existing patient

Choose a patient from the list

Patient code↓	Monitor number	Site name	Last visit
13201	320118, 320119	Internal	8/2/2013
400009	400009	Internal	7/23/2013

Select the patient from the patient list by clicking on the patient number. You will be directed automatically to the next screen.

REPLACE A MEMS CAP

- Put the “new” MEMS cap on the MEMS reader (upside down). Then, click on the *Read MEMS monitor* button.



Click on the Read button below to initiate the reading process which automatically sends the data to the server

Read MEMS monitor...

Options...

- Select the serial number of the MEMS cap that needs to be replaced and choose the date when the new MEMS cap is supposed to be used for the first time. Click on Continue.

Monitor number 252340

Monitor to be replaced

Begin date of use of the new MEMS monitor: 

End date of use of the previous MEMS monitor: 

Continue

The “End date of use of the previous MEMS monitor” is set by default and corresponds to the last reading of the broken/lost MEMS that will be replaced.

- You will be redirected to the patient data.

ADD A MEMS FOR AN EXISTING PATIENT

Add a MEMS: This procedure can be used if you need to add an additional MEMS for an existing patient (e.g. multiple medications that will be monitored).

1. Log on internet web-page: [www. medAmigo.com](http://www.medAmigo.com) using your personal login and password.

AARDEX group

Welcome to AARDEX medAmigo online system.
Please enter your login and password below.

Login

Password

Sign-in

[Forgot password?](#) [Help](#)

medAmigo

2. On the start page, click on *Replace or add a MEMS monitor to an existing patient.*

Please select an action from the following list

- Initiate a new patient (first reading)**
- Read new dosing history data from MEMS monitor (following visits)**
- Visualize patients list**
- Replace or add a MEMS monitor to an existing patient**

ADD A MEMS FOR AN EXISTING PATIENT

3. To select the patient for whom a MEMS has to be added, you may either enter the patient number, or choose the patient number from the patients list by clicking on Patients list.

a. enter the patient number

Replace or add a MEMS monitor to an existing patient

Select the patient number for whom you want to replace or add a MEMS monitor:

or choose in patient list: **Patients list**

b. select the patient from the patients list by clicking on Patients list.

Replace or add a MEMS monitor to an existing patient

Select the patient number for whom you want to replace or add a MEMS monitor:

or choose in patient list: **Patients list**

Replace or add a MEMS monitor to an existing patient

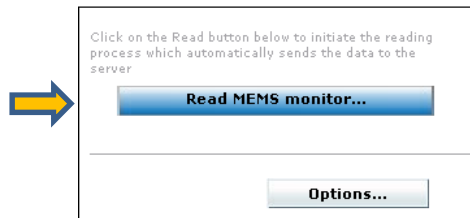
Choose a patient from the list

Patient code↓	Monitor number	Site name	Last visit
13201	320118, 320119	Internal	8/2/2013
400009	400009	Internal	7/23/2013

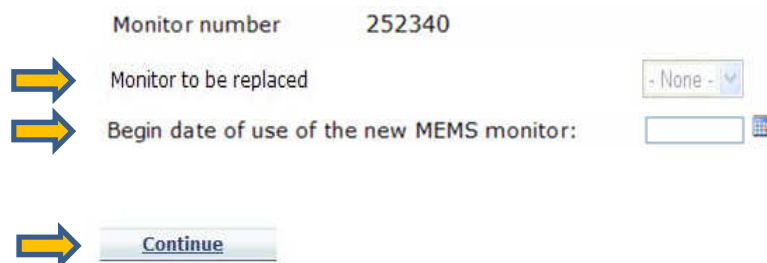
Select the patient from the patient list by clicking on the patient number. You will be directed automatically to the next screen.

ADD A MEMS FOR AN EXISTING PATIENT

- Put the “new” MEMS cap on the MEMS reader (upside down). Then, click on the *Read MEMS monitor* button.



- Set the Monitor to be replaced to “none” because there isn’t any cap to be replaced.
Choose the date when the new MEMS cap is supposed to be used for the first time.



- Click on Continue. You will be redirected to the patient data.

CLOSE PATIENT FORM

This option might not be activated in your study.

- Once finished with a patient, click on Close patient. You will then be guided to the following screen.



- Every time you close the patient you have 2 options:
 - A. The patient continues with the study: you may enter the next visit date which will then be visible in the patients list.
 - B. The patient stops the study: you may enter the drop out date and the reason for this drop out. The drop out date will appear in the patients list as well.

It is not mandatory to fill out this formulary and you can just click on *Skip*.

Patient 1WE	medAmigo platform, Demo Patients		
Monitor	Last visit	Print report	Options ▼
500004 ...	12.08.2007		

Close patient

- A** Patient continues with the medAmigo service

Next visit expected in month(s) or on

- B** Patient ended the medAmigo service definitely

When Reason

Save **Skip**

CLOSE PATIENT FORM

- 3. The previously entered data (next visit date or drop out date) are available in the patient list. Those information allow a better overview and follow-up of your patients.**

Patient code ↓	Monitor number	Site name	Last visit	Next expected visit	Program ended
11007	500000	Demo Patients	16.09.2007		
1DH	500006	Demo Patients	30.11.2007		
1Int	36569	Demo Patients	15.11.2007	12.07.2008	
1TV	500002	Demo Patients	30.10.2007	19.02.2009	
1WE	500004	Demo Patients	12.08.2007	21.06.2008	
testJD	202794, 202796	Intervention	25.05.2010		

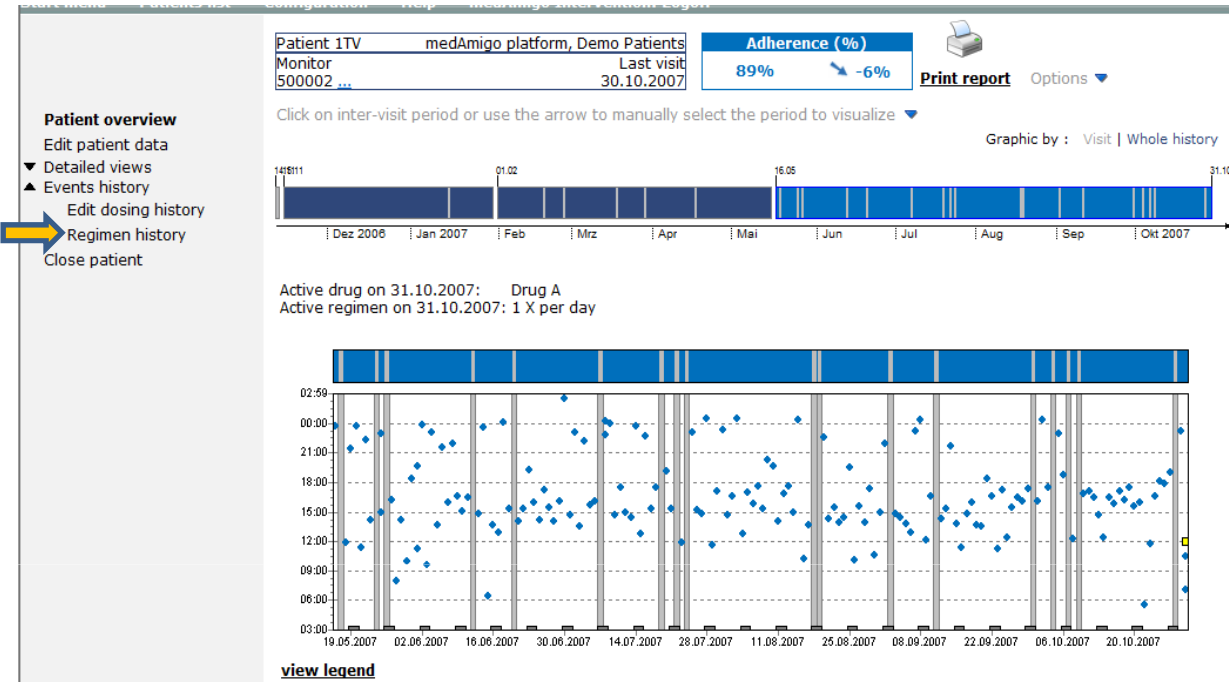
IMPORTANT NOTE:

Once you have entered that a patient has definitely ended the medAmigo service, it is not possible to re-activate him/her, unless you read the patient's MEMS cap again !

Moreover, it is not possible to change the patient's drop out date.

Define regimen or dosing changes

You may change the regimen in the patient data.
Go to *Events history*, then *Regimen history*.



Click on *Add regimen change*.

Patient 1TV medAmigo platform, Demo Patients
 Monitor 500002 ... Last visit 30.10.2007

Print report Options ▾

List of regimen change

Date↓	Regimen	Drug
14.11.2006 03:00:00	24	Drug A

→ **Add regimen change**

Define regimen or dosing changes

Enter the Date, Drug name and the regimen. Click on **Save**.

Patient 1TV	medAmigo platform, Demo Patients	
Monitor	Last visit	
500002 ...	30.10.2007	Print report Options ▾

List of regimen change

→ Date

→ Drug name

→ Regimen Fixed Every

Number of tablets per dose

→ **Save** → **Cancel**

Define regimen or dosing changes

It is possible to enter a regimen change after each MEMS reading *if the study was configured so*. The medAmigo system will then ask you about regimen / dosing changes after each MEMS reading.

Enter the changes if there are any, enter the date since when the regimen was changed and click on *continue*.

Reading MEMS monitor 1 from 1

Monitor number	202794
Indication / pathology	MEMS 1 ▾
Drug name	Drug A ▾
Regimen	<input checked="" type="radio"/> Fixed <input type="radio"/> Every
	1x/day Regimen ▾
Number of tablets per dose	1

➡ If there was a change of pathology, drug or regimen, since when
21.05.2010

Data transfer successful





➡ **Continue**

Enter non-monitored periods (NMP)?






Periods might occur when the use of the monitor is inappropriate; for example, during a hospitalization. Without identifying such a period in the database, the software would assume that during this time period the subject was not adherent to the drug regimen.

Go to the patients list and select *Visualize patients list*.

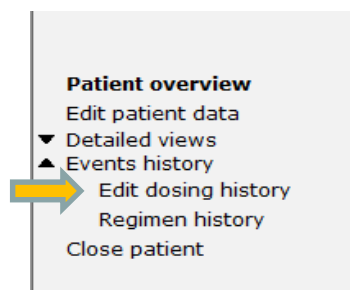
Please select an action from the following list

-  Initiate a new patient (first reading)
-  Read new dosing history data from MEMS monitor (following visits)
-  **Visualize patients list**
-  Replace or add a MEMS monitor to an existing patient

Choose the patient for whom you want to enter a non-monitored period in the patients list.

Patient code ↓	Monitor number	Site name	Last visit	Next expected visit	Program ended	Search
 11007	500000	Demo Patients	16/09/2007			
 1DH	500006	Demo Patients	30/11/2007			
 1Int	36569	Demo Patients	15/11/2007	12/07/2008		
 1TV	500002	Demo Patients	30/10/2007	19/02/2009		
 1WE	500004	Demo Patients	12/08/2007	21/06/2008		

On the patient overview page go to *Edit dosing history* in the *Events history* menu.



Enter non-monitored periods (NMP)?

Click on *Non monitored periods*

Events from 10.11.2006 03:00 to 16.03.2007 02:59

Date	Description	Monitor number	
14.03.2007 11:12		500004	Insert memo
13.03.2007 10:09		500004	Insert event
12.03.2007 10:25		500004	Non monitored periods
11.03.2007 10:27		500004	
10.03.2007 10:15		500004	
09.03.2007 16:40		500004	
08.03.2007 09:53		500004	
07.03.2007 10:28		500004	
06.03.2007 10:09		500004	

Click on *Add non monitored period*

Non monitored periods

Number Begin End

Add non monitored period

Reorganize

Quit

Enter the start and end date of the non monitored period. Use the calendar to select a date. Click on *OK*.

<https://v2-app.aardexgroup.com/?ContextKey=-129895886>

Non monitored periods

From: [] time 03:00:00

To: [] time 02:59:59

Type: Standard

Ok Cancel

Non monitored periods are listed and can be edited by clicking on the given period. To delete a non monitored period, click on the trash can.

Non monitored periods

Number	Begin	End
0	10.11.2006 03:00:00	20.11.2006 02:59:59

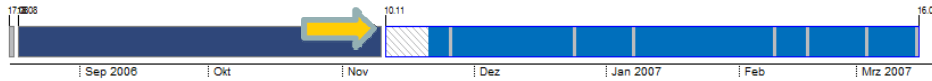
Add non monitored period

Reorganize

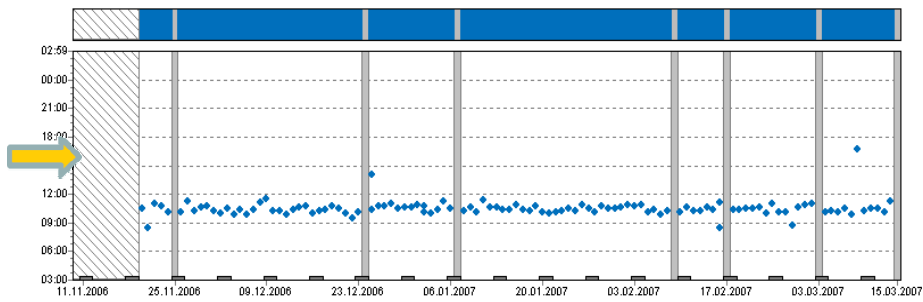
Quit

Enter non-monitored periods (NMP)?

Non monitored periods are displayed in the chronology and the calendar plot as hatched areas.



Active drug on 16.03.2007: Drug A
Active regimen on 16.03.2007: 1 X per day

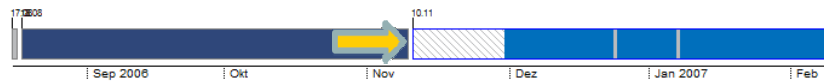


view legend



Key features

Medication omissions observed on (estimated over the entire follow-up): Saturday



November 2006							December 2006							January 2007						
Mon	Tue	Wed	Thr	Fri	Sat	Sun	Mon	Tue	Wed	Thr	Fri	Sat	Sun	Mon	Tue	Wed	Thr	Fri	Sat	Sun
											1 1	2 1	3 1	1 1	2 2	3 1	4 1	5 1	6 1	7 0
				10	11	12	4 1	5 1	6 1	7 1	8 1	9 1	10 1	8 1	9 1	10 1	11 1	12 1	13 1	14 1
13	14	15	16	17	18	19	11 1	12 1	13 1	14 1	15 1	16 1	17 1	15 1	16 1	17 1	18 1	19 1	20 1	21 1
20	21	22	23	24	25	26	18 1	19 1	20 1	21 1	22 1	23 1	24 0	22 1	23 1	24 1	25 1	26 1	27 1	28 1
27	28	29	30	1			25 2	26 1	27 1	28 1	29 1	30 1	31 1	29 1	30 1	31 1				
February 2007							March 2007													
Mon	Tue	Wed	Thr	Fri	Sat	Sun	Mon	Tue	Wed	Thr	Fri	Sat	Sun							
			1 1	2 1	3 1	4 1				1 1	2 1	3 0	4 1							
5 1	6 1	7 1	8 1	9 0	10 1	11 1	5 1	6 1	7 1	8 1	9 1	10 1	11 1							
12 1	13 1	14 1	15 1	16 2	17 0	18 1	12 1	13 1	14 1	15 0										
19 1	20 1	21 1	22 1	23 1	24 1	25 1														
26 1	27 1	28 1																		

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1. WHAT DO I NEED TO START THE STUDY ?
HOW TO REMOVE THE CLOSURE PROTECTION FROM THE MEMS CAP ?

- Hardware (MEMS cap & reader)
- Login and password for www.medamigo.com
- Successful installation of the ActiveX needed for the www.medamigo.com website

Before placing the MEMS cap on the medication bottle, remove the plastic protection. If the plastic protection cannot be removed, set the cap by and take a MEMS cap with the same color code from another patient's kit.

Please refer to the Quick Start Manual for further explanations on how to remove the MEMS plunger.

2. HOW TO IDENTIFY A MEMS CAP?

Each MEMS monitor has a unique 6 digit serial number imprinted on its side and stored in its electronic memory.

3. DO I NEED A NEW LOGIN IF I ALREADY HAVE ACCESS TO THE PLATFORM FOR OTHER STUDIES?

No. If you are already registered at www.medamigo.com as a user for other studies, and you do not have access to one study, just send an email to the AARDEX Group helpdesk (address provided on the "Welcome" page of the support documents).

Please mention the following information in your email:

- The study number/protocol you need to have access to
- Your contact details (name, phone, email)
- Your site name/ number

4. WHERE CAN I GET A LOGIN?

Write an email to the AARDEX Group Helpdesk (address provided on the "Welcome" page of the support documents).

Please mention the following information in your email:

- The study number/protocol
- The site name/ number
- The contact details of the new user (name, email, phone)

5. WHAT IF THE INSTALLATION WAS NOT SUCCESSFUL?

Check with your IT department if you have administrator rights and if the internet security settings are set as described in the Installation Guide.

Please note that the software is for an internet application; you will not find a shortcut on your desktop after the installation.

In the meantime, start the patient with the MEMS caps, they will work independently of the medAmigo web-platform. At the patient's next visit, initiate the patient on the medAmigo web-platform and adapt the monitoring begin date in the patient data form.

6. SOFTWARE INSTALLATION: THE 'INSTALLATION' BUTTON KEEPS POPPING UP

If the installation button pops-up after you restarted your computer, please check if all pop-ups are allowed to be displayed and if the internet security settings are set as described in the '*Installation Guide*' in 'Software installation'.

7. WHAT ABOUT THE SECURITY OF THE APPLICATION? WILL THERE BE PATIENT DATA TRANSFERRED?

The only data which are transferred to the website are the patient's dosing history data (date and time of medication intake) and the MEMS cap serial number. There isn't any transfer of patient's data.

For detailed information on the application, please read the 'Installation Guide'.

8. WHAT IF I CANNOT ACCESS THE WEBSITE TO INITIATE A PATIENT OR READ A MEMS CAP?

No access to the website at initiation visits:

The MEMS monitor is a standalone device that does not need any activation. All the data are immediately recorded in the MEMS cap.

Thus, you can give the MEMS cap to the patient with the medication bottle and do the initiation procedure when he / she comes back to the next visit.

Just make sure to note the serial number of the MEMS cap, the patient number and the monitoring begin date. At the patient's next visit, initiate the patient with the standard patient's initiation procedure. You just need to enter the monitoring begin date in the Patient data form, which is the date when the patient started using the MEMS cap.

No access to the website at follow-up visits:

If you cannot access the website at a patient's follow-up visit, just postpone the download of the MEMS caps to the patient's next visit. The data are not lost if a download is postponed.

9. ERROR MESSAGE: MEMS NOT ASSIGNED FOR THE STUDY

If you get this message while you try to read a MEMS cap, please contact the AARDEX Group helpdesk (address provided on the "Welcome" page of the support documents).

Please mention the following information in your email:

- The study number/protocol
- The site name/ number
- Your contact details (name, email, phone)
- The error message
- The MEMS cap's serial number

10. WHAT IF I ASSIGNED A MEMS CAP TO A WRONG PATIENT?

If you assigned a MEMS cap to a wrong patient, send an email to the AARDEX Group helpdesk (address provided on the "Welcome" page of the support documents).

Please mention the following information in your email:

- The study number/protocol
- The site name/ number
- Your contact details (name, email, phone)
- The patient's ID
- The MEMS cap's serial number

11. HOW OFTEN DO I NEED TO READ THE MEMS CAPS?

It depends on the study protocol. But, ideally, the MEMS caps should be read at each patient's visit.

12. ARE THE DATA LOST IF I CANNOT READ THE MEMS CAPS AT ONE VISIT?

No. The data are stored in the internal memory of the cap itself. This memory can only be read and therefore raw data cannot be modified or erased. Thus, the data are not lost if you postpone the download to the next visit.

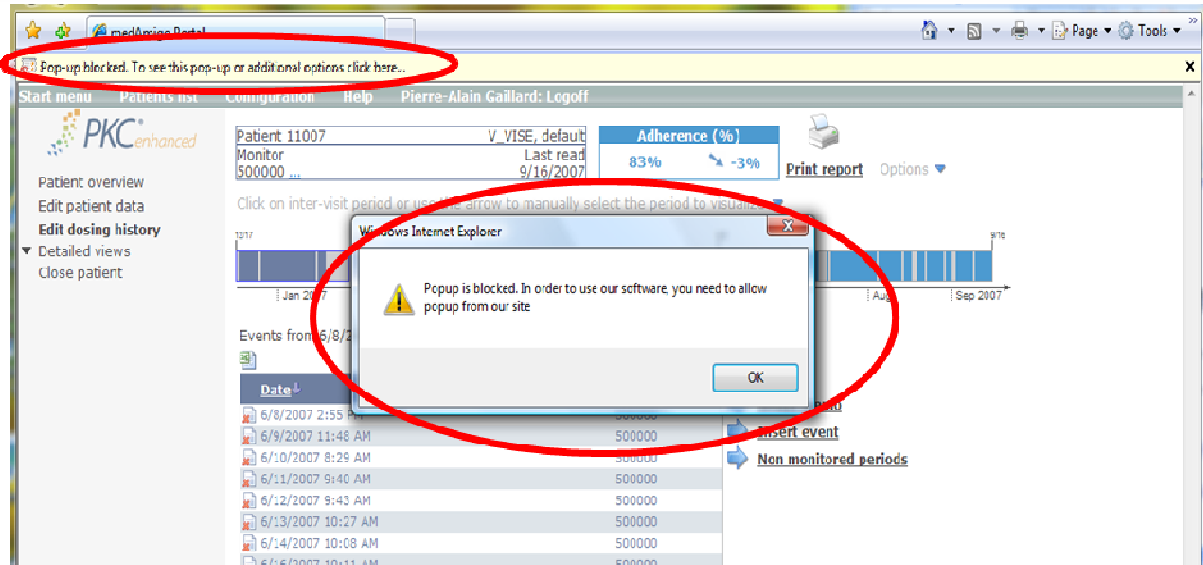
13. WHAT IF I CANNOT READ A MEMS CAP / ERROR 5000?

- Check if the reader is connected to your USB port.
- Check if the MEMS cap is placed properly on the MEMS reader (upside down).
- Check if other MEMS caps can be read.
 - If yes, the MEMS cap is probably broken and needs to be replaced. Take a MEMS cap with the corresponding color out of another patient's kit and initiate this new MEMS cap with the « *Replace or add a MEMS to an existing patient* » procedure. Contact the AARDEX Group helpdesk to organize the MEMS return. AARDEX Group will try to retrieve the missing data.
 - If none of the MEMS caps can be read take note of the error message and contact the AARDEX Group helpdesk (address provided on the "Welcome" page of the support documents).

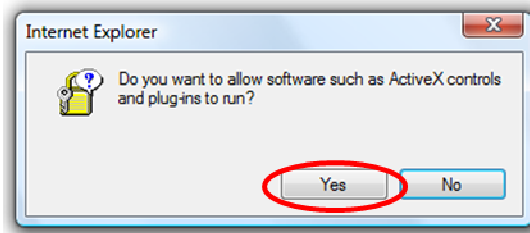
14. WHAT IF MY POP-UP FILTER PREVENTS ME FROM ACCESSING CERTAIN FUNCTIONALITIES ON THE WEBSITE?

In order to have access to all functionalities on the medAmigo website, you need to allow pop-ups from www.medamigo.com.

The pop-up filter may be activated in your Internet Explorer browser. If this is the case, please allow pop-ups from www.medamigo.com. If the following message appears, choose "Always allow pop-ups from this site".



A confirmation message can appear. Messages can be different depending on the configuration of your system.



**15. WHAT IF A PATIENT COMES BACK TO THE CLINIC WITH A DEFECTIVE MEMS CAP?
HOW TO REPLACE A MEMS CAP?**

MEMS caps should only be replaced if they are broken or definitely lost. If you suspect a cap to be broken, try to read it on the www.medamigo.com website.

- If it cannot be read, take a MEMS with the corresponding color out of another patient's kit and initiate this new MEMS cap with the « *Replace or add a MEMS to an existing patient* » procedure described in the 'Support Documents' tab.

Contact the AARDEX Group helpdesk to organize the return of the broken MEMS cap. AARDEX Group will try to retrieve the missing data.

- If a cap is readable, it is working fine and there is no need to replace it.

16. THE LCD DISPLAY OF THE MEMS CAP HAS TURNED OFF?

If the monitor has not been opened for more than 168 hours (1 week), the LCD display is automatically turned off, to conserve battery power. The display is reactivated, however, when the monitor is opened again.

Please refer to the 'LCD explanations' document for further explanations on the functioning of the MEMS cap with LCD.

17. WHERE CAN I CHANGE THE PATIENT'S ID?

You can change the patient's ID in the Patient/Data tab. Change the patient ID in the appropriate field and save the form.

Please refer to the 'Edit patient data' document for further explanations.

18. WHERE CAN I ADD A SPECIFIC COMMENT / MEMO?

You can add a comment/memo for a patient. A memo is a remark you would like to add for a specific day (refill, visit, occasional pocket dosing by the patient, etc.). This memo is depicted as a yellow square on the patient's chronology plot.

Please refer to the "Add a memo" document for further explanations.

19. WHERE CAN I CHANGE THE DRUG REGIMEN?

It might happen that the dosing regimen for a patient has to be changed (i.e. switch from once daily to twice daily regimen). If the regimen is not adapted on the medAmigo portal, the adherence data are not well calculated. Please modify the regimen on the medAmigo portal. Please refer to the "Define regimen changes" document for further explanations on how to change the regimen.

In some studies, it is possible to enter a regimen change after each MEMS reading if the study was configured so. The medAmigo system will then ask you about regimen / dosing changes after each MEMS reading.

20. WHAT IF MY PATIENT INTERRUPTED HIS/HER MEMS USE FOR A CERTAIN PERIOD?

Periods might occur when the use of the monitor is inappropriate; for example, during a hospitalization. Without identifying such a period in the database, the software would assume that during this time period the subject was not adherent to the drug regimen.

It is possible to introduce the start and end date of non-monitored periods (NMP) directly on the medAmigo portal.

A non monitored period is a time period during which the MEMS monitor has not been used by the patient either because he/she was not able to (e.g. hospitalization) or the treatment break was part of the prescription (e.g. 4 weeks intake, 2 weeks without intake).

Please refer to the « Enter non-monitored periods" document for further explanations on how to enter non-monitored periods.

21. WHAT IF I FORGOT OR LOST MY PASSWORD?

Go to www.medAmigo.com and click on **forgot password**. Follow the instructions described below and you will receive a new password to your registered e-mail address.

You have however to make sure that the sender address – medAmigo@aardexgroup.com – is allowed as secure sender, in order to avoid that the mail is blocked by some kind of filter.

Please refer to the « Forgot password” document for further explanations.

22. WHERE CAN I CHANGE MY PASSWORD?

Click on ‘Configuration’. Enter your current password once and your new password twice. Click on **Save**.

Please refer to the « Forgot password” document for further explanations.

23. CAN THE MEMS CAPS BE RE-USED?

No. The caps have a unique serial number which should be assigned to one patient only. The data stored in the caps cannot be erased and the re-use of a MEMS cap would require the segregation of dosing history data generated by a prior use, from the dosing history data generated by a subsequent use. Thus, there is a risk of data confusion from different uses of the MEMS monitor.

Moreover, there are potential risks of contamination arising from re-use of MEMS monitors.

24. ARE THERE ANY ISSUES WITH PASSING THE SECURITY CONTROL AT AIRPORTS WITH MEMS CAPS ?

The MEMS monitors are drug packages with integral electronic microcircuitry designed to compile the dosing histories of ambulatory patients’ prescribed medications. Each monitor consists of a conventional medicine bottle fitted with a special closure that records the time and date of each opening and closing of the container through integrated micro-circuitry.

The micro-circuitry is powered by a lithium battery, the size of a small coin, similar to those that power electronic wrist watches and hearing aids.

At airport security, the MEMS monitors should be considered as regular electronic devices and can go through X-rays.

25. HOW CAN THE MEMS CAPS BE DISPOSED?

First, check if the MEMS caps have been read on the www.medamigo.com website at the patient’s termination visit. **It is VERY important to download each cap before disposal.** Then, check if the caps have to be sent back to the study monitor at the end of the study.

If not, the disposal can happen at each investigational site. Once you have successfully downloaded the MEMS cap, it can be disposed as a regular electronic device according to local procedure, such as mobile phones for example.

The MEMS cap does not memorize any information about the study, the site or the patient. The only data recorded are the MEMS serial number and the dosing history data. They cannot be erased before disposal.

STUDIES WITH MULTIPLE MEMS PER PATIENT

26. WHAT IF I COULD NOT INITIATE MY PATIENT AT THE BASELINE VISIT AND MY PATIENT DID NOT BRING ALL THE MEMS CAPS TO THE NEXT VISIT AT WHICH I NEED TO INITIATE THE CAPS ON THE MEDAMIGO WEBSITE?

Initiate the caps which are available with the usual initiation procedure. Once you have read all the available caps, click on "*This is the last MEMS for this patient*".

Please refer to the "initiate patient" document for further details.

27. WHAT IF I COULD NOT INITIATE ALL THE MEMS CAPS FOR ONE PATIENT (E.G. LOSS OF INTERNET CONNECTION)?

If you could not initiate all the MEMS caps for one patient, you can add the missing ones with the procedure described in "*Add a MEMS cap for an existing patient*" in the "Support Documents" tab.

28. WHAT IF MY PATIENT IS RANDOMIZED FOR ONLY 3 OF THE 4 MEDICATIONS?

The respective number of treatments is to be entered on the medAmigo website in the patient data form during the patient's initiation.

If you received 4 caps whereas only 3 are used by the patient, put the fourth cap aside until the end of the study. It can eventually be used as a replacement for a patient randomized to the study arm with 4 caps/patient.

29. WHAT IF MY PATIENT DID NOT BRING ALL MEMS CAPS TO THE VISIT?

Download the caps which are available. The remaining ones should be read as soon as they are available. Dosing history data stored in the MEMS cap are NOT lost if the download is postponed to the patient's next visit.