



Manual of Procedures (MOP)

Section 1. Study Organization, Administration and Governance

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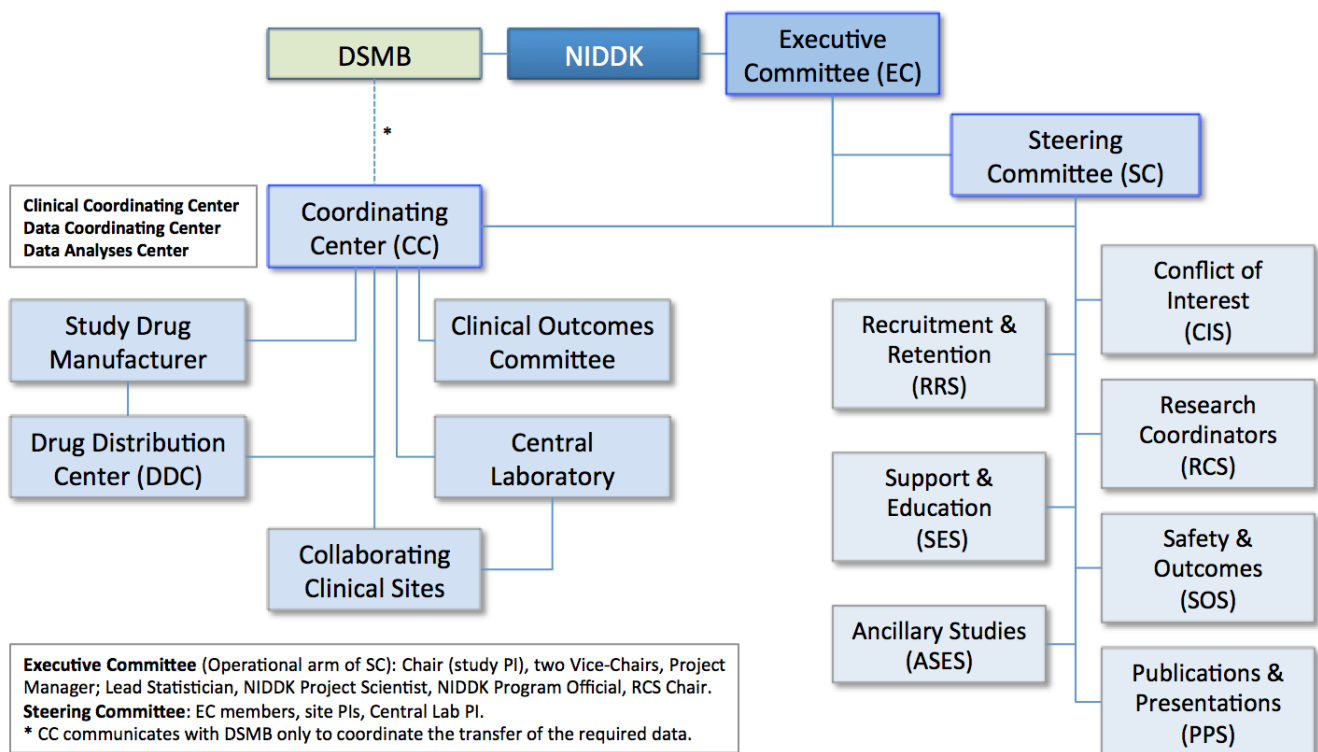
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1.1 OVERVIEW OF STUDY ORGANIZATION, ADMINISTRATION AND GOVERNANCE

The Vitamin D and type 2 diabetes (D2d) study is funded primarily by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) through the Multi-Center Clinical Study Cooperative Agreement (U01) funding mechanism to Tufts Medical Center (Boston, MA), which has established sub-award agreements with each collaborating clinical site and core units (i.e. central laboratory, drug distribution center).

The organization scheme of D2d is shown in Figure 1. Study leadership is provided by the Steering Committee while the Executive Committee acts as the operational arm of the Steering Committee. There are 7 standing subcommittees of the Steering Committee, which are established to monitor specific components of the trial conduct and to provide periodic status reports to the Steering Committee. The *D2d Coordinating Center (CC)* is established in the Division of Endocrinology at Tufts Medical Center. The CC provides study organization and administration, and manages day-to-day operations by working directly with the collaborating sites, other core units (central laboratory, drug distribution center), vendors, study committees and subcommittees and the sponsor. The *Drug Distribution Center (DDC)*, established at the VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (Albuquerque, NM), conducts the randomization and distribution of study drug to the sites. The *Central Laboratory*, established at the University of Vermont Laboratory for Clinical Biochemistry Research (Burlington, VT), coordinates collection of study specimens from collaborating sites, conducts laboratory measurements and serves as a repository for short and intermediate-term storage of human tissue samples. After the study is completed, long-term storage of specimens will be transitioned to the NIDDK Central Repositories.

Figure 1. D2d study organizational scheme



1.2. STUDY ROLES AND RESPONSIBILITIES

1.2.1 Role of the Sponsor

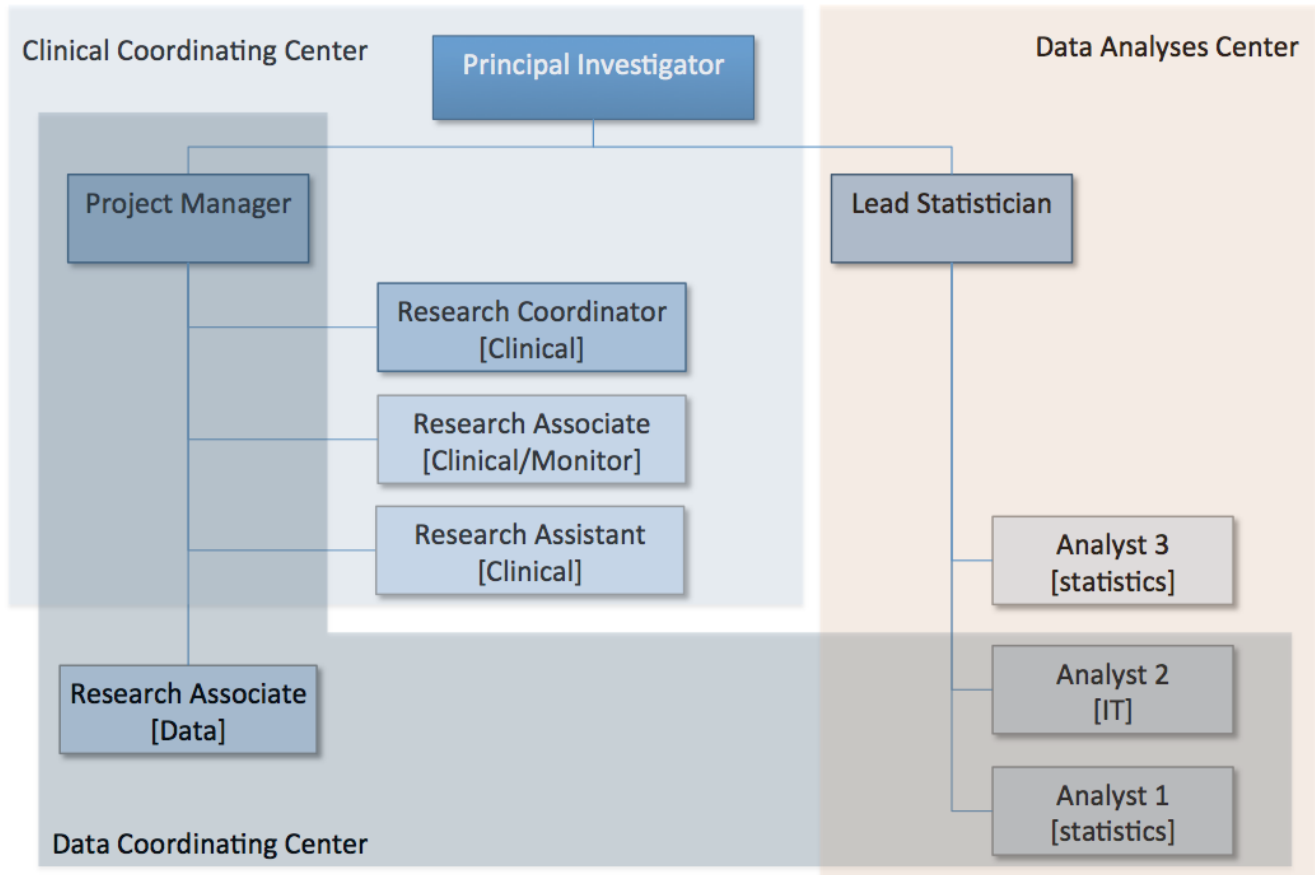
The D2d study is funded primarily by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) through the Multi-Center Clinical Study Cooperative Agreement (U01) funding mechanism to Tufts Medical Center, which has established sub-award agreements with each collaborating clinical site and core units (i.e. central laboratory and drug distribution center) to reimburse each site and core unit for their activities related to the D2d study. The funding agency (NIDDK) and the study investigators work as partners; however, the primary responsibility for the study planning and conduct is with the study's Principal Investigator (PI) and the CC. Representatives from NIDDK (Project Scientist and Program Official), as members of the Executive and Steering Committees, participate in all phases of the planning, development of the protocol, policies and procedures, implementation and monitoring of study performance and safety, data analyses and dissemination of study findings. Representatives from NIDDK also participate in the general organization and fiscal management of the study. The funding agency has established the Data and Safety Monitoring Board (DSMB) to oversee the safety and other regulatory and scientific aspects of the study. The NIDDK Program Official serves as the Executive Secretary to the DSMB and acts as a direct liaison to the NIDDK Director concerning issues relating to data and safety monitoring issues.

1.2.2 Role of the Coordinating Center (CC)

The CC is established in the Division of Endocrinology at Tufts Medical Center (Boston, MA). The CC is responsible for the execution of D2d in cooperation with the Executive Committee, the sponsor (NIDDK) and the NIDDK-appointed DSMB (Figure 1). The CC provides study organization and administration, and manages day-to-day operations by working directly with the collaborating sites, other core units (central laboratory, drug distribution center) and vendors (drug manufacturer, electronic data capture vendor), study committees and subcommittees, the sponsor and the DSMB.

The CC is led by the study PI and is composed of three subdivisions, the Clinical Coordinating Center, the Data Coordinating Center and the Data Analyses Center (Figure 2). The Clinical Coordinating Center, led by the Project Manager, is responsible for all aspects of study conduct, except for data management and data analyses. The Data Coordinating Center, led by the Project Manager, concentrates on data management. The Data Analyses Center, led by the Lead Statistician, focuses on study design and analytical issues. The CC subdivisions interact continuously with each other, as required.

Figure 2. Structure of the D2d Coordinating Center



1.2.3 Role of the Collaborating Clinical Sites

The D2d study is conducted at multiple collaborating clinical sites throughout the United States. Sites are which will be responsible for screening, recruiting, enrolling, randomizing, treating, retaining and following participants throughout the study according to the study protocol. The site PI is responsible for all aspects of the study at her site. The site PI oversees the work of co-investigators and research staff and is responsible for ensuring all site research staff is appropriately trained in Good Clinical Practices and in study-specific protocol procedures. The site PI serves as a member of the Steering Committee and is expected to serve in subcommittees based on her interest and expertise.

1.2.4 Role of the Central Laboratory

The Central Laboratory, established at the University of Vermont Laboratory for Clinical Biochemistry Research (Burlington, VT), coordinates collection of study specimens from clinical sites, conducts laboratory measurements and also serves as a central repository for short and intermediate-term storage of human tissue samples from D2d participants. After the study has been completed, long-term storage of human tissue samples will be transitioned to the NIDDK central Repositories. In collaboration with the CC, the Central Laboratory is responsible for development and distribution of laboratory-specific protocols.

1.2.5 Role of the Drug Distribution Center

The Drug Distribution Center is responsible for the development and implementation of plans for study drug acquisition from the manufacturer, packaging, labeling, dispensing to sites and randomization of participants according to the study protocol.

1.3 STUDY LEADERSHIP AND GOVERNANCE

Overall study leadership is provided by the Steering Committee while the Executive Committee acts as the operational arm of the Steering Committee. There are 7 standing subcommittees of the Steering Committee, which are established to monitor specific components of the trial conduct and to provide periodic status reports to the Steering Committee. The Clinical Outcomes Committee reports to the CC and its responsibility is to adjudicate the diagnosis of diabetes that is made outside of study procedures. Below is a brief description of each committee and subcommittee. Detailed descriptions can be found in the committee and subcommittee charters (see MOP1 Appendix).

1.3.1 Executive Committee (EC)

The EC acts as the operational arm of the Steering Committee (SC) and makes scientific, administrative and fiscal decisions, on behalf of the SC, for day-to-day operational issues requiring prompt action. The committee is accountable to the Steering Committee and the primary study sponsor (NIDDK). The committee is comprised of the Chairman (D2d study Principal Investigator), two Vice-Chairpersons, the D2d study Project Manager (CC representative), the Lead Statistician, the Chairperson of the Research Coordinator subcommittee, the NIDDK Project Scientist and the NIDDK Program Official. The committee develops timelines for the accomplishment of tasks, appoints (and disbands) subcommittees as the need arises and selects subcommittee members and chairs, presents information to the sponsor, and develops Steering Committee meeting agendas. The committee meets weekly at the same day and time by conference call, and annually in person, to discuss the progress of the study, provide overall guidance and make recommendations to the CC, Steering Committee and subcommittees.

1.3.2 Steering Committee (SC)

The SC provides scientific leadership for the study. The committee works closely with its operational arm, the EC, and its subcommittees. The committee reports to the primary study sponsor (NIDDK), via the EC. The committee is comprised of all standing members of the EC in addition to the PI of each collaborating site and the Central Laboratory. The committee meets every month, as needed, by conference call, and annually in person, to discuss major scientific and programmatic issues.

1.3.3 Steering Committee Subcommittees

Subcommittees are established to monitor specific components of the study conduct and to provide periodic status reports to the Steering and Executive Committees. The EC appoints (and disbands) subcommittees as the need arises and selects subcommittee members and chairs. Subcommittee members are selected from among site Principal Investigators, co-investigators and research

coordinators, the CC and Central Laboratory. Several subcommittees also include representatives from NIDDK (Program Scientist and/or Program Official). Subcommittees may occasionally seek the input of outside consultants. The CC will schedule subcommittee meetings, record minutes and post agendas and minutes on the web portal.

Below is an overview of the 7 standing D2d subcommittees.

1.3.3.1 Conflict of Interest Subcommittee (CIS)

The subcommittee reviews all conflict of interest forms in which there has been a disclosure. The committee will determine if a potential conflict of interest exists, and will develop and implement a management plan that will specify the actions that have been and/or will be taken to eliminate or limit the potential impact of such conflict(s) on the study's credibility. The subcommittee works closely with the sponsor to evaluate and mitigate conflicts of interest.

1.3.3.2 Recruitment and Retention Subcommittee (RRS)

The subcommittee reviews and approves the collaborating sites' recruitment plans prior to the start of the study and monitors recruitment progress and retention and adherence to study procedures. Rates of participant retention and prompt and complete data capture will serve as quality measures of performance by the sites. Pre-specified site-specific targets for optimal performance are defined and should be met to achieve high quality of trial conduct. The subcommittee reviews these measures regularly and makes recommendations (general or site-specific) to improve these rates and ensure that sites meet their target recruitment goals. The subcommittee makes recommendations to the EC regarding the need for additional sites, if recruitment is slower than anticipated.

1.3.3.3 Support and Education Subcommittee (SES)

The subcommittee develops the Support and Education Program (SEP) that will be implemented during the study. The subcommittee reviews and approves the education materials on the current lifestyle recommendations for prevention of type 2 diabetes that will be provided to all participants at baseline. The subcommittee also develops program themes and content for use during the SEP group meetings that will be held at each site twice a year. The goals of the SEP meetings are the following: (1) to provide participants with up-to-date information on the lifestyle recommendations for the prevention of type 2 diabetes and (2) to promote participant retention. Towards these goals, the SES works closely with the RRS.

1.3.3.4 Research Coordinators Subcommittee (RCS)

The subcommittee is comprised of the research coordinators from each site and representatives from the CC. The major objectives of the subcommittee is to assure communication among the sites with respect to overall study coordination, share best ideas and problem solve. The coordinators are closest to the day-to-day issues at the sites; therefore, they are expected to be an invaluable resource to the study and are encouraged to make recommendations regarding the study conduct to the SC & EC for review and consideration. The Chairperson of the RCS is a member of the EC.

1.3.3.5 Safety and Outcomes Subcommittee (SOS)

The subcommittee implements the Data Safety Monitoring Plan. The subcommittee reviews all serious adverse events (SAE) and unanticipated problems (UAP) as they are reported, reviews periodic safety reports of all adverse events (AE) and oversees study safety. The subcommittee chair or designee assesses each SAE and UAP to determine if immediate action is required in response to the event. The subcommittee meets three times a year (or more frequently if needed) by conference call. During these meetings, the subcommittee discusses SAE, UAP and summary reports of non-serious AE. The subcommittee also evaluates whether there is any clustering of AEs, SAEs or UAPs by clinical site. The subcommittee remains masked to patient treatment group during these evaluations. The subcommittee considers whether changes in the protocol (monitoring, consent process, etc.) are needed based on the occurrence, frequency, or severity of AE, SAE or UAP and provides its recommendations to the Steering and Executive Committees for further discussion and subsequently to the DSMB for approval and implementation. The subcommittee also provides adjudication for secondary outcomes.

1.3.3.6 Ancillary Study Subcommittee (ASS)

The subcommittee is responsible for establishing and overseeing the Ancillary Studies Policies and Procedures and ensuring that the policy is followed. The subcommittee is responsible for evaluating ancillary study applications and making recommendations to the Steering Committee regarding the proposals and monitors progress of approved ancillary studies.

1.3.3.7 Publications & Presentations Subcommittee (PPS)

The subcommittee develops and oversees the policies and procedures by which D2d investigators will interpret data analyses and will coordinate publications and presentations of study results. The subcommittee is responsible for establishing and overseeing the Publications and Presentations Policy and ensuring that the policy is followed. The subcommittee reviews and approves all publications and presentations related to the D2d study, including those from ancillary studies, prior to submission. The subcommittee monitors the progress of all proposed manuscripts to ensure prompt completion and publication.

1.3.4 Clinical Outcomes Committee (COC)

The committee, which is independent of the D2d Study Group, is formed to review and adjudicate the diagnosis of diabetes that is made outside of the D2d study or initiation of diabetes-specific medication (for any reason) when study-specific glycemic data are not available. The COC is composed of clinical diabetes experts who have no real or perceived conflict of interest related to the D2d study, D2d Study Group, sponsor or study core units.

1.4 COMMUNICATION

1.4.1 Collaborating Clinical Site – CC Communication

The CC will assign a primary contact (liaison) for each collaborating clinical site. The CC contact will establish a working relationship with the site Research Coordinator to facilitate communication between the CC and the site, maximize study conduct efficiency and troubleshoot issues as they develop.

1.4.2 Study Meetings

1.4.2.1 Collaborating Clinical Site – CC Conference calls

Prior to study initiation: A weekly phone meeting is set-up with each site to establish timelines for IRB submission, discuss status of regulatory documents, discuss the recruitment plan, ensure all site personnel have completed the necessary training (EDC, Study Pill Inventory and Randomization System, Protocol and MOP review) and have access to the electronic web-based systems, as well as coordinate the shipment of supplies. The PM, CRC and CRA will represent the CC on these calls.

Intra-study: The weekly phone meetings will continue but as the study progresses, the focus of the meetings will change. It is expected that as soon as possible after the Investigators' meeting and after IRB approval, recruitment will start; therefore, recruitment progress will be the focus of early meetings. As the study progresses, participant retention, data collection, and planning for the support and education program meetings will become the focus. Importantly, these meetings will be an opportunity for discussion, troubleshooting and problem solving.

Meeting minutes will be saved at the CC in the site-specific folder and copies will be sent to the sites.

1.4.2.2 Committee and Subcommittee Conference Calls

Committee and subcommittee meetings are scheduled on a date/time that accommodates as many members as possible. Meetings will be scheduled with sufficient advance notice and the CC will send each member a reminder before each meeting. Most committee meetings are conducted via teleconference and/or web-conference. The call-in information will be sent to members ahead of time. Meetings begin and end on time. Meeting minutes will be posted on the web portal.

1.4.2.3 Investigator Meetings

An Investigators' study start-up meeting will take place prior to the initiation of the study. It is expected that, at a minimum, an investigator and coordinator from each site will be present at the start-up meeting. Additional in-person Investigators' meetings will take place annually. The dates for the meeting will be selected as far in advance as possible.

1.4.3 Study Documents and Version Control

All D2d study documents will have a version date, and certain documents (e.g. protocol, MOP) will also have a version number. The version number and date will be in the footer of the document and on the cover page, when available. If a document is undergoing modifications, it will be labeled with the next sequential version number followed by the word "-draft" and a watermark (DRAFT) will be inserted across every page. The draft version of the document will undergo review by the appropriate committees and subcommittees before being finalized. Once final, the word "Draft" will be removed from the version number, the Draft watermark will be removed from the pages and the date of final approval will be added in the version date.

Documents will be available on the web portal (see below). When a document has changed, the latest version will replace the older version on the web portal and an e-mail notification will be sent to all

appropriate users. In addition, on the web portal, the document icon will be made to visibly stand out, highlighting that it is either a new document or a new version to an existing document.

The D2d Manual of Procedures (MOP) for the sites is divided into sections. If content in a single section changes, the section will have a new version number and the sites and core units will be instructed to go to the web portal to download only the revised section and replace it in their MOP.

1.4.4 Study website and social media

The D2d study will utilize websites and social media, described below, to meet the needs of the study. The CC is responsible for managing the content and keeping electronic media up to date. The CC collaborates with the sites and other core units to enhance the content and appearance of these electronic tools.

1.4.4.1 Public website

The D2d public website, www.D2dstudy.org will present general study information to the public.

1.4.4.2 Investigators' web portal

The www.D2dstudy.org website will have a restricted access section (web portal) for members of the D2d study group. Information on the web portal will include:

- Study documents: e.g. Protocol, Manual of Procedures.
- News and updates related to the D2d study that the D2d Study Group should be aware of.
- Information specific to committees, subcommittees and DSMB.

Access to the portal is restricted to authorized users. All users will have access to the general content and certain users will also have access to additional content depending upon committee and subcommittee membership. Users should protect their usernames or passwords. Committee schedules, agendas, information, and minutes will be posted in each committee's specific restricted folder. The CC will manage web portal registration.

To register for access to the web portal:

1. Go to www.D2dstudy.org

[when ready, insert directions on accessing and submitting registration, username and password]

1.4.4.3 Facebook

The D2d study has a Facebook page. General information about the study is included on the Facebook page and the public can follow and "like" the study on Facebook. There will also be a link to the public website (www.D2dstudy.org) for people interested in learning more about the study.

1.4.4.4 Twitter

The D2d study has a twitter account, @D2dstudy. A tweet is a message, 140 characters or less, that is sent to all followers of that account. Any person with a twitter account can "follow" the D2d study

twitter account. The @D2dstudy profile page includes general information about the study including: the D2d logo, a brief description of the study, a link to the D2d website (www.d2dstudy.org), and a history of all “tweets” created by @D2dstudy. The D2d study twitter account will be used to announce study milestones and achievements throughout the study, as well as general messages, such as ‘happy holidays.’

Sites may also create a twitter account that is site-specific. For example, the Tufts site has created the @Tufts_D2dstudy twitter account that will be used to communicate site-specific information to participants at the Tufts site, for example, reminding followers of an upcoming Support and Education Program meeting.

1.4.5 Electronic Data Capture

The EDC is hosted on a secure website by Medidata Solutions, Inc. This website provides access to the D2d study electronic data capture system. Data will be entered into the EDC by staff at the clinical sites and central laboratory. During monitoring visits, staff from the CC will document source document verification directly in the EDC system.

⇒ For details and for information on how to access the D2d EDC website, please refer to section 15.

1.4.6 Study Pill Inventory, Randomization and Distribution

The Study Pill Inventory and Randomization System (SPIRS) is hosted on a secure website by the DDC. This website is used to manage and track the study pills, and randomize participants into the study. Therefore, a limited number of users at each site have access to it. Staff with access typically includes the research pharmacist or person responsible for managing the study pill inventory and supply as well as the person responsible for randomizing participants (e.g. Research Coordinators).

⇒ For information on how to access the D2d Study Pill Inventory and Randomization System website, please refer to MOP 7.

1.5 COLLABORATING CLINICAL SITE PERSONNEL

1.5.1 Site Contact Form

All active site personnel should be listed on the site contact information form (MOP1 appendix 2). The form includes personnel contact information, site roles and responsibilities. When there is a change in personnel (addition or removal), the form must be updated and emailed to the CC at d2d@tuftsmedicalcenter.org. An electronic version of the form should be maintained at the site to allow updating as needed.

1.5.2 Coordinating Center Notification

The CC must be notified of any anticipated or planned change in personnel at a collaborating site. The site PI or Research Coordinator should contact their liaison at the CC with information regarding the addition or departure of staff. This will allow the site and CC to jointly plan for the training of new staff or any changes in roles and responsibilities that may result.

1.6 APPENDICES

Appendix 1. Committee and Subcommittee Charters

Appendix 2. Site Contact Information Form

Appendix 3. Coordinating Center Contact Information