Manual of Procedures (MOP)
Section 3. Regulatory

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3.1 OVERVIEW

This D2d study is conducted in compliance with the Institutional Review Board (IRB)-approved protocol and related documents and in accordance with Good Clinical Practice guidelines, the applicable regulatory requirements of the Department of Health and Human Services, the International Conference on Harmonization (ICH) Guidelines, and state and local legal and ethical requirements to assure that the rights, safety and well-being of participants are protected.

Site Principal Investigators (PI) are responsible for the oversight of the study at their site and for ensuring that research staff training and education is complete and up to date, that local IRB approval is obtained and maintained, and that the policies and procedures governing human subject research are followed throughout the study. The Coordinating Center (CC) will work collaboratively with the PIs at each site to ensure all regulatory requirements are met.

The regulatory procedures that will be followed at each site are described next and a list of essential regulatory documents is shown in Table 3.1.

3.2 INSTITUTIONAL REVIEW BOARD (IRB)

The mandate of the IRB is to ensure that the rights and welfare of human participants in research are protected, in accordance with the regulations established by the Department of Health and Human Services (45 CFR46) and the Food and Drug Administration (FDA – 21 CFR 50 & 56).

3.2.1 Initial Review

Prior to the shipment of study pills by the Drug Distribution Center (DDC) and the initiation of participant recruitment, the site IRB must approve the protocol, informed consent forms, and all associated documents, including recruitment processes and materials (e.g. script that will be read to participants, advertisements). Sites are encouraged, but not required, to utilize the IRBshare System option for initial approval. For details about IRBShare, contact the CC and/or visit irbshare.org.

- ✓ A copy of the IRB initial review submission must be kept on file at the site.
- ✓ The original of the IRB initial review approval letter must be kept on file at the site and an e-copy submitted to the CC.

3.2.2 Continuing Review and Amendments

The protocol, informed consent forms and associated documents must undergo a continuing review by the site IRB, at a minimum, annually. Protocol amendments, changes to consent forms and other documents relevant to participants (e.g. advertisements) must be submitted to the IRB and approved prior to implementation.

⇒ It is the responsibility of the site PI to submit an application for continuing review to the site IRB in a timely fashion well before the study's current approval lapses. *If study approval lapses, all D2d study related activities must stop*, including recruitment and enrollment of participants, and follow-up of enrolled participants. The study cannot continue until continuing review approval has been granted.

- ✓ A copy of the IRB annual continuing review submission must be kept on file at the site.
- ✓ A copy of IRB amendment submissions must be kept on file at the site.
- ✓ The original of the IRB annual continuing review approval letter must be kept on file at the site and an e-copy submitted to the CC.
- ✓ The original of each protocol amendment approval letter must be kept on file at the site and an e-copy submitted to the CC.
- ✓ All major correspondence with IRB must be kept on file at the site.

3.2.3 Informed Consent Forms

The site IRB must approve all informed consent forms, which are generally valid for 1 year. *Only currently approved consent forms may be used.* Sample informed consent forms are included as an appendix to the D2d protocol. These samples will be used as templates (guides) and may need to be modified to meet the site's IRB requirements.

Informed consent forms may be translated to languages other than English. Translation of English-IRB approved consent forms must be done according to local policies and procedures. Frequently, IRB will allow a shorter version of the informed consent to be translated to a non-English language.

- ✓ Site-specific informed consent forms must be submitted to and approved by the CC prior to submission to the site IRB. Although sites are permitted to make minor alterations to text to meet the requirements of the site IRB, the content of the consent forms cannot be changed.
- ✓ The CC will review site-specific consent forms and approve submission or request clarifications/modifications within 2 business days of receipt.
- ✓ All IRB-approved informed consent forms must be kept on file at the site and an e-copy submitted to the CC.
- ✓ The site must maintain the original informed consent forms signed by the participant in the D2d participant source documents folder. In addition, a copy of the signed informed consent form must be provided to each participant. These procedures are described in more detail in the Manual of Procedures (MOP) section 6.

3.2.4 Adverse Event Reporting

Please see MOP section 14 for the D2d study Data Safety and Monitoring Plan and the procedures that the sites will follow to report adverse events.

3.3 TRAINING OF RESEARCH STAFF AT CLINICAL SITES

All research staff participating in the D2d study must be qualified and trained to perform their assigned role(s) in the study. Study-specific training includes:

3.3.1 Human Subject Protection Training

All research staff must complete Human Subject Protection training before beginning human subject research. Sites should offer Human Subject Protection training either locally or through the Collaborative Institutional Training Initiative (CITI). The National Institutes of Health also offers an online training program titled, Protecting Human Research Participants (*http://phrp.nihtraining.com*)

- ✓ Human Subject Protection certificates of training for all research staff must be kept on record at the site for review by the CC monitor.
- ✓ Prior to the start of the study, the site PI and all key personnel (NIH criteria) need to submit an e-copy of their Human Subject Protection training certificate to the CC.

3.3.2 Laboratory Specimen Shipping Training

All research staff responsible for the packaging and shipping of laboratory samples must have completed training to comply with Department of Transportation and International Air Transport Association (IATA) shipping regulations. Sites should offer such training to their staff.

- ✓ A Laboratory Specimen Shipping certificate of training must be kept on record at the site for review by the CC monitor.

3.3.3 Electronic Data Capture (EDC) System

Users will be required to complete training on the use of the EDC system prior to being granted full access to the system. General training on the EDC system (Medidata) will be completed on-line via web-based modules and D2d specific e-CRF training will be conducted in person (at the study kick off meeting) or via a webinar. Please see MOP section 15 for details.

Training on the use of EDC will be documented by the CC.

3.3.4 Study Pill Inventory and Randomization System (SPIRS)

Users will be required to complete training on the use of SPIRS prior to being granted full access to the system. The training may be conducted in person (at the Investigators meeting) or via a webinar. Please see MOP section 7 for details.

Training on the use of SPIRS will be documented by the CC.

3.4 REGULATORY DOCUMENTS AT CLINICAL SITES - GENERAL

Regulatory documents will be maintained at the sites and (selected ones) at the CC. The following is a list of general regulatory documents, the rationale for their collection and location where they will be saved.

3.4.1 Protocol

The study protocol includes the study design and objectives, and describes the way in which the study will be conducted (21CFR312.23, 312.60, FDA Guidance E6 GCP)

- ✓ Site research staff must use the most currently approved version of the protocol.
- ✓ A copy of the current version of the protocol must be kept on site with the regulatory documents.
- ✓ Prior versions (archives) of the protocol must be kept on site. In addition, the CC will maintain prior versions (archives) on the D2d web portal (D2d protocol archive folder) for access by all D2d research staff.
- ✓ The original of the Protocol Signature Page signed by the PI must be kept on site in the regulatory binder. A copy of the signed Protocol Signature Page is provided to the CC. The site PI must sign the Protocol Signature Page of every new version of the protocol.

3.4.2 Biosketches

A biosketch is a way to demonstrate that an investigator is qualified (e.g. education, training and experience) to conduct the trial (21CFR312.53).

- ✓ Prior to the start of the study, each site will provide the CC with the biosketch of the site PI and all key personnel (NIH definition, see below).
- ✓ Biosketches need to be formatted according to NIH criteria (http://grants.nih.gov/grants/funding/phs398/biosketchsample.pdf) and submitted in PDF format.

  According to the NIH, key personnel include the site PI and other individuals who contribute to the scientific development or execution of a project in a substantive, measurable way, whether or not they receive salaries or compensation under the grant. Typically these individuals have doctoral or other professional degrees, although individuals at the masters or baccalaureate level may be considered senior/key personnel if their involvement meets this definition. Key personnel must have been defined as such in the D2d sub-award budget application.

- ✓ When a new key person joins the D2d study, the site will provide the CC with their biosketch.
- ✓ The most up-to-date biosketch should be maintained on site in the regulatory file.

3.4.3 Medical License(s)

A medical license demonstrates that the persons acting as study physicians are licensed to practice medicine and are qualified to treat study participants as needed.

- ✓ The CC will access the medical licensure information from online sources. However, if the CC is unable to access medical license information online, the site study physician(s) will be asked to provide a copy of their current medical license to the CC.
- ✓ A copy of the currently valid medical license should be maintained on site.

3.4.4 Federal Wide Assurance (FWA) Number

The Office of Human Research Protection of the Department of Health and Human Services issues a Federal Wide Assurance (FWA) number to an institution that provides written assurance that the institution will comply with the DHHS regulations (45CFR46). All institutions engaged in human participant research conducted or supported by DHHS must have a FWA (45CFR46.103, 46.107, FDA Guidance E6 GCP).

No action is required by the site because the CC will obtain the site IRB's FWA number and expiration from the Office of Human Research Protections (OHRP) website.

3.4.5 Conflict of Interest (COI)

To execute the sub-award, each collaborating clinical site must assure that its institution complies with 42CFR50 subpart F. In addition, the D2d study Conflict of Interest Policy must be followed (see MOP section 2.1). The site Principal Investigator and each research team member are to complete the D2d study COI form. The PI is to submit his/her completed form to the D2d Coordinating Center, and maintain a copy in his/her files. The PI will review all forms from all other research team members in his/her site and any form(s) with "yes" responses are also to be submitted to the CC by the PI, and a copy maintained in his/her files. The PI will retain in his/her study files the completed Form(s) for research team members who answer "no" to all questions. Note: the completed forms do not need to be maintained in the site regulatory binder, but must be maintained in a secure site accessible to the PI and be available for review during CC visits.

3.5 REGULATORY DOCUMENTS AT THE CLINICAL SITES – D2d SPECIFIC

3.5.1 Participant Recruitment (Screening and Enrollment) Reports

The D2d study will record and monitor recruitment (screening and enrollment) progress through the EDC system. Screening and enrollment reports may be obtained and printed out as needed. Monthly, the CC and the Recruitment and Retention subcommittee (RRS) will review recruitment reports.

- The CC and the RRS will prepare recruitment reports and submit to DSMB and NIDDK.

3.5.2 Laboratory Specimen Records

These records document the collection of laboratory samples, including date of shipment to and date of receipt by the Central Laboratory. Laboratory specimen records will be maintained in the EDC system. Please see MOP section 9 and section 15 for details.

3.5.3 Study Pill Accountability

A secure web-based system (SPIRS) will be used to track and maintain study pill accountability. Please see MOP section 7 for details. The following will be recorded in the system (relevant to the sites):

- Shipment information from the DDC (e.g. date of shipment, number and identification of bottles shipped to the sites)
- Receipt information by the sites (e.g. date of receipt, quantity and condition of bottles received)
- Dispensation information to participants (e.g. date and ID of bottle dispensed, participant ID)
- Disposition of unused study pills

✓ The number of study pills returned by the participant will be recorded in the EDC system

3.5.4 Adverse Events

All adverse events, serious adverse events and unanticipated problems will be reported to the CC via the EDC system.

✓ Sites may need to submit supplemental information to the CC beyond what is recorded in the EDC system.

The CC and the Safety and Outcomes Subcommittee (SOS) will produce study-wide safety reports, for SAEs that are possibly or probably related and unexpected, and all UAPs. Safety reports [PDF format] will be distributed to all site PIs and research coordinators (RC) via email.

✓ Research staff must submit safety reports to the site IRB. Documentation that safety reports were submitted must be maintained on site in the regulatory file. Please see MOP section 14 for details.

3.5.5 Breaking of Randomization Code (Unmasking)

At no time will the code of the treatment assignment be broken without the expressed knowledge and consent of the site PI and the CC. It is expected that unmasking will be exceedingly rare as it will be restricted to situations in which knowing the assignment will change the course of care of the participant. Please see MOP section 7 for details.

✓ The site PI will review and report the circumstances that led to the unmasking to the CC and site IRB, per local policy.

✓ The occurrence of unmasking will be recorded in the EDC, on the adverse event form and detailed documentation of unmasking will be recorded in the participant source document folder, and should include the following: date, participant's study ID, staff involved, rationale for unmasking and procedures followed.

3.5.6 Contact Information

- The CC will maintain up to date contact information for all entities and research staff on the D2d study web-portal.

- ✓ Sites are encouraged to download the D2d Contacts document and keep a hard copy easily available on site.
- ✓ Sites will use the site contact information spreadsheet (see MOP section 1) to communicate to the CC changes in research staff at the site.

6 SITE MONITORING

Proper monitoring is necessary to assure adequate protection of the rights and safety of human participants in clinical research, accurate and timely reporting of adverse events, and the quality and integrity of research data.

A representative from the CC will visit the collaborating clinical sites yearly to conduct a monitoring visit. During these visits, emphasis will be placed on appropriate collection of data, adherence to the study protocol and regulatory requirements. The CC representative will review the source files of a minimum of 10 percent of participants enrolled at the site. More frequent monitoring and/or additional participant source files may be monitored if warranted based upon previous monitoring visit findings or upon request by the Executive Committee, DSMB, or NIDDK. The first monitoring visit will be scheduled after the first 2 participants have been enrolled. Clinical site monitoring early in the enrollment period will provide the site with the opportunity to ask questions and have any protocol related issues or challenges addressed. During monitoring visits, for each participant selected for review, the source documentation verification will be completed for all e-CRF data collected up until the date of the most recent visit. Emphasis will be placed on the informed consent process and documentation, study pill storage and accountability and primary outcome assessment.

3.6.1 Monitoring Reports

- After each visit, monitoring reports will be written by the CC and sent to the site for review.
- The D2d clinical research associate will work with the site to resolve any pending or open issues included in the monitoring report.

✓ Copies of monitoring reports will be maintained on site in the regulatory binder.

3.6.2 Regulatory Binder

✓ Each site will maintain a regulatory binder (or file), which should be available for review by CC monitors and, if necessary, IRB auditors.

✓ The regulatory binder should follow the order shown in Table 3.1.

3.6.3 Source Documents

A source document is where information on a participant is first recorded. Per International Conference on Harmonization Good Clinical Practice (ICH E6. 1.52), source documents are: “Original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects’ diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.” (ICH E6, 1.52)

Excellent source documentation in a clinical trial allows an independent reviewer (monitor, auditor) to reconstruct the trial as it happened. The reviewer should be able to confirm all available data starting with the consent process, determination of eligibility, randomization and dispensation of the study pills

all the way to the last contact with the participant. Source documents should have the following characteristics (Bargaje C. Good documentation in clinical research. *Perspectives in Clinical Research.* 2011 Apr-Jun; 2(2): 59).

- Attributable: who documented the data
- Legible
- Contemporaneous: information should be documented in the time frame that it occurred or was collected in. If there is a delay in documentation and it is not documented chronologically, this should be noted.
- Original. If not possible, the source document should be an exact copy.
- Accurate

Source documents contain data that are entered into the EDC system and additional information illustrating how and when procedures were completed. For example, a participant's source documents should include information on the consent process including, who conducted the consent process, that the participant was given time to ask questions, the persons present during the process, the date and time consent was obtained, and that a copy of the informed consent form was given to the participant.

During the D2d study, some data may be entered directly into EDC, and the e-CRF will be considered the source document. Please see MOP section 15 for details.

3.6.3.1 Source Document Corrections

If a source document is found to be incorrect or incomplete, it may be corrected or additional information may be added. To make a correction, a single line should be placed through the erroneous content, allowing it to remain legible. The correct information should be recorded and the person making the documentation should initial and date the correction. Additional entries into source documents are permitted. However, the addenda must be signed and dated (representing the date of entry).

3.6.3.2 Source Document Worksheets

The CC has developed source document worksheets that may be customized by the site, see section MOP section 13.

Table 3.1 Essential regulatory documents and location

		Site [1]		CC [1]	Other (web-based)	Update
		Regulatory Binder	Back-up file			
Protocol	Current version	✓		✓	Portal	
	Protocol signature page	✓		✓		
	All prior versions		✓	✓	Portal	
Site Personnel	Site contact information form	✓		✓		
	Biosketches (NIH format) for site key personnel	✓		✓		
	Medical license study physician(s)	✓		(✓)		✓
	Conflict of interest		✓			
	Training					
	Human subject protection					
	Site PI & key personnel (NIH definition)	✓		✓ [2]		
	Other site research staff	✓				
	Laboratory Specimen Shipping	✓				
	EDC			✓		
	SPIRS			✓		
IRB	Federal Wide Assurance Number		✓	(✓)		
	Initial submission		✓			
	Initial approval letter	✓		✓		
	Continuing review submissions		✓			1y
	Continuing review approval letters	✓		✓		1y
	Protocol amendment submissions		✓			
	Protocol amendment approval letters	✓		✓		
	Approved informed consent and HIPAA forms	✓		✓		1y
	Other submissions (i.e. safety reports)		✓			
	Other approval letters	✓		✓[3]		
	Major correspondence with IRB	✓				
Safety	Data Safety Monitoring Plan		✓[4]			
	AE, SAE, UAP reporting	✓		✓	EDC	
	Study-wide safety reports	✓		✓		
	Un-masking	✓			EDC	
	Data Safety Monitoring Board Reports	✓		✓		
Site↕ CC	Major correspondence with CC	✓		✓		
	Monitoring Reports	✓		✓		
Other	Participant Screening and enrollment reports				EDC	
	Laboratory specimens records				EDC	
	Study pill accountability				SPIRS	

A (✓) sign indicates that the CC will obtain the information via a web-search.

[1] Original documents are saved on site. Copies are provided to the CC.
These categories may be used as tabs to organize the Regulatory Binder at each site.

[2] E-copy of human subject protection training required for PI and key personnel prior to the start of the study.

[3] Other approval letters may need to be submitted to the CC. Consult with CC as needed.

[4] The Data Safety Monitoring Plan is located in section 14 of the Manual of Operations.