

POLICY

Protocol Registration

Approval Date: 26 MAR 2010

No.: DWD-POL-RA-011.03

Effective Date: 26 APR 2010

NOTE: This Policy has been reviewed for accuracy and updated to meet 508 compliance guidelines. DAIDS has revised and more clearly defined roles and responsibilities related to the protocol registration process, as well as the types of notifications sites may receive. Updates also include modifications to submission timeline requirements for protocol amendment registrations when notifying local IRB/ECs for both US and non-US sites, and a new implementation requirement for sites once final IRB/EC/RE approval for a full version protocol amendment or LoA has been received. In addition, this policy explains protocol registration requirements for each of the most common types of submissions that a CRS may send to the DAIDS Protocol Registration Office (PRO). This version supersedes version 2.0 dated 20 DEC 06.

1.0 PURPOSE

The purpose of this policy is to describe the protocol registration requirements for National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS)-supported and/or -sponsored clinical research that is reviewed and approved by a DAIDS Scientific Review Committee.

2.0 SCOPE

This policy applies to all clinical research supported and/or sponsored by NIAID (DAIDS) that is reviewed by DAIDS Scientific Review Committees, namely the Prevention Sciences Review Committee (PSRC) and the Clinical Sciences Review Committee (CSRC).

3.0 BACKGROUND

NIAID (DAIDS) sponsors and provides support for clinical research conducted within the U.S. and around the world. In order to ensure that this research is conducted in compliance with applicable standards and regulations, DAIDS has developed specific protocol registration requirements and a web-based Protocol Registration (PR) System.

The PR System receives and tracks certain regulatory documents that must be submitted by Clinical Research Sites (CRSs) throughout the conduct of a study. The DAIDS PR process verifies that CRSs have received the necessary Institutional Review Board (IRB)/Ethics Committee (EC) and Institutional Biosafety Committee (IBC) approvals and have provided to DAIDS all documentation pertaining to investigator qualifications and responsibilities required by the U.S. Food and Drug Administration (FDA) or the National Institutes of Health (NIH) and DAIDS. In addition, all IRB/EC-approved site-specific informed consent forms must be submitted.

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This policy describes when a CRS must submit certain materials to DAIDS through the PR System (i.e., the time period from initial protocol registration through deregistration) and the communications the CRS will receive in response to their submissions.

4.0 DEFINITIONS

Clinical research: Research conducted on participants, material, or data of human origin with an identifiable person as the source. Clinical research includes exploratory, behavioral and observational studies. All clinical trials are a subset of clinical research. (DAIDS)

Clinical Research Site (CRS): Discrete locations (e.g., hospitals, outpatient clinics, health maintenance organizations, community health centers, private practices, clinics) supported and/or sponsored by NIAID (DAIDS) where qualified professionals conduct clinical research in accordance with good clinical practice (GCP) and applicable regulations. (DAIDS)

Clinical Research Site (CRS) leader: The onsite senior research scientist responsible for the administrative and scientific components of the CRS. The CRS leader is responsible for overall site activities, including day-to-day operations, performance, and compliance at the site level. (DAIDS)

Clinical trial: A prospective study of human subjects designed to answer questions about biomedical or behavioral interventions, e.g., investigational drugs or investigational medical devices, or new ways of using known treatments to determine whether they are safe and effective. (NIAID)

DAIDS Protocol Registration Office (PRO): An office within the DAIDS Regulatory Support Contract (RSC) that receives and processes all protocol registration materials for DAIDS. (DAIDS)

DAIDS Regulatory Support Contract (RSC): A contract that provides clinical, regulatory, and technical support services for NIAID (DAIDS)-supported and/or -sponsored clinical trials. (DAIDS)

DAIDS-sponsored: DAIDS is responsible for the management (including submission of the Investigational New Drug Application (IND) and Investigational Device Exemption (IDE) Application to FDA, and initiation of the study), and oversight for the trial. (DAIDS)

DAIDS-supported: Clinical research activities would be considered to be supported by NIAID (DAIDS) under one or more of the following circumstances:

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1. NIAID (DAIDS) provides direct funding to an institution via a grant, contract or cooperative agreement for the clinical research activities; or indirect funding via a subcontract executed under a NIAID (DAIDS) -supported award to another institution,
2. NIAID (DAIDS) provides other tangible support for the clinical research activities which includes, but is not limited to, regulatory support, site monitoring services, study product supply, and management and distribution services,
3. NIAID (DAIDS)-supported central laboratory or data management center receives from another organization either specimens or data for processing or analysis, and the results or analyses will be used to direct involvement of some or all participants in clinical research activities. (DAIDS)

Form FDA 1572: FDA required document in which clinical investigators agree to conduct the clinical trials according to federal regulations. The Form FDA 1572 is signed and submitted to the IND sponsor. (DAIDS)

Institutional Biosafety Committee (IBC): Committee set up by an institution under NIH guidelines to review recombinant DNA research and ensure its appropriate use. IBCs may also review other biohazardous research, including select agents. (NIAID)

Institutional Review Board/Ethics Committee (IRB/EC): The board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of participants in research. IRB/EC reviewing DHHS sponsored research must be registered with OHRP and identified on the institute FWA. (DAIDS)

Investigational Device Exemption (IDE): Similar to an IND, allows an unapproved medical device to be used for investigational purposes. For more information, go to 21 CFR 812.1 and NIAID Human Subjects Resources portal. (NIAID)

Investigational New Drug (IND): A drug or biological product that is used in a clinical investigation. The terms "investigational new drug" and "investigational drug" are deemed to be synonymous within DAIDS policies. (DAIDS)

Investigational New Drug (IND) Application: A request for authorization from the FDA to administer an investigational drug or biological product to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug or biological product that is not the subject of an approved New Drug Application or

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Biologics/Product License Application. (FDA) An IND application is required by the FDA before clinical trials of an investigational drug or biological agent may be initiated. An IND is also generally required if the US FDA has not approved the route of administration, dosage level, indicated use, or patient population for the drug or biological agent. (DAIDS)

Investigator of Record (IoR): The individual at the CRS responsible for ensuring that a clinical trial is conducted in accordance with the protocol, applicable U.S. federal regulations, in-country regulations and any provisions imposed by the reviewing IRB/EC/other regulatory entity. This person is the signatory for the Form FDA 1572 for studies conducted under an IND or the DAIDS Investigator of Record Form for non-IND studies. (DAIDS)

Investigator of Record (IoR) Form: A document required by DAIDS for Non-IND studies. The IoR is required to sign and date this document accepting full responsibility for the conduct of the trial at their CRS. (DAIDS)

Observational study: A type of study in which individuals are observed or certain outcomes are measured, but no treatments or interventions are assigned by the study. (DAIDS)

Office for Policy in Clinical Research Operations (OPCRO) – An office in DAIDS that provides a variety of clinical research management resources and oversight to DAIDS clinical research portfolio. This includes overseeing the development, standardization, implementation and execution of policies, procedures and standards of conduct for all of DAIDS domestic and international clinical research. (DAIDS)

Principal Investigator (PI): The qualified person designated by the applicant institution to direct the funded research program. PIs oversee the scientific and technical aspects of an award and the day-to-day management of the research.

Protocol registration(PR): The process established by DAIDS to ensure that all sites participating in NIAID (DAIDS)-supported and/or -sponsored clinical research that is reviewed by a DAIDS Scientific Review Committee conduct the research in accordance with requirements for human subjects protection and the use of investigational new drugs (where applicable). The process includes initial protocol registration, amendment registration, continuing review documentation, deregistration and submission of other required documents. (DAIDS)

Protocol registration submissions: The most common types of submissions that a CRS may send to the DAIDS Protocol Registration Office (PRO) include the following:

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1. Initial – The first time a CRS submits a consent type, language and/or version of a protocol to the PRO.
2. Amendment – A revision to a protocol made by the Protocol Team/Chair/Awardee that requires DAIDS review and final approval/sign-off before implementation; amendments are also referred to as “full version amendments.” The changes to the protocol are incorporated into the protocol document itself and will result in the change to the DAIDS protocol version number (e.g. 2.0, 3.0).
3. Letter of Amendment (LoA) - A revision to a protocol made by the Protocol Team/Chair/Awardee through a short letter that requires DAIDS final approval/sign-off before implementation. Changes described in a LoA are listed in a document which is separate from the protocol document itself and will NOT result in the change to the DAIDS protocol version number.
4. Continuing/Annual Reviews – An IRB/EC re-review of a protocol conducted on at least an annual basis as required by 45 CFR 46 for all federally funded research studies as well as by 21 CFR 56 for IND studies.
5. Change of IoR – When there is a change in the Investigator of Record at a CRS for a protocol.
6. Deregistration- When a CRS no longer has participants on study (all follow-up has been completed) and does not plan to enroll additional subjects and /or if no participants were ever enrolled at the CRS and the study has closed to accrual. (DAIDS)

Protocol Registration Team (PRT): A Team within OPCRO responsible for managing the PR System, which includes oversight of the DAIDS PRO. (DAIDS)

Scientific Review Committee (SRC): A reviewing body within DAIDS to review the concepts and protocols developed by various programs within DAIDS (e.g., Clinical Sciences Review Committee (CSRC) and Prevention Sciences Review Committee (PSRC)). (DAIDS)

For additional definitions see DAIDS Glossary:

<http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Glossary.htm>.

For additional information about the PR process, see the DAIDS Protocol Registration Manual:

http://rcc.tech-res-intl.com/DAIDS%20RCC%20Forms/HighlightOff_PROManual_v04b.pdf

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5.0 RESPONSIBILITIES

CRS Leader

For Network studies, the *CRS Leader* is responsible for ensuring that his/her site adheres to the Protocol Registration policy. The CRS Leader may delegate PR-associated tasks to another qualified individual, such as the IoR.

IoR/Grant PI/Contract PI

After receiving final IRB/EC approval, IBC approval and other applicable regulatory approval of the protocol and site-specific informed consent, the *IoR/Grant PI/Contract PI* will ensure that their clinical research site submits all the required PR documents to the DAIDS PRO and all PR requirements are met, as specified in the Protocol Registration manual.

Program Officer/Contracting Officer's Technical Representative (COTR)

For non-network studies, the *Program Officer/COTR* or designee will make the Grant/Contract PI aware of PR requirements at the time of protocol development and the need to include language in the initial version of the protocol pertaining to PR requirements. The Program Officer/COTR or designee will refer the Grant/Contract PI to the DAIDS Protocol Registration manual for additional information.

DAIDS RSC

The PRO at the *DAIDS RSC* implements and manages the day-to-day operations of the PR process. All required PR documents are submitted to the DAIDS PRO. RSC personnel, under DAIDS PRT oversight, review the registration materials.

DAIDS PRT

The *PRT* manages the PR System, including oversight of the DAIDS PRO. The DAIDS PRT is responsible for determining protocol registration requirements for each protocol at the time of DAIDS SRC review or regulatory review. The DAIDS PRT makes final decisions regarding "exceptions" from the PR process.

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Director of OPCRO or designee

Under circumstances when a decision cannot be reached by the DAIDS PRT and DAIDS Program staff, the *Director of OPCRO* or designee will make the final decision regarding an “exception” from the PR process.

6.0 POLICY

Each CRS will complete the PR process for all clinical research supported and/or sponsored by NIAID (DAIDS) reviewed and approved by a DAIDS Scientific Review Committee. See the Protocol Registration manual¹ for instructions and additional information on the PR process.

- 6.1 Upon receiving IRB/EC approval(s) and IBC approval if applicable, the CRS will submit all required PR documents to the DAIDS PRO via the DAIDS PR System.

Upon making *ANY* submission to the DAIDS PRO, a CRS will receive a confirmation of submission notice that indicates that the DAIDS PRO has received materials.

The CRS must place a copy of all final PR notifications from DAIDS in the site’s regulatory files.

6.1.1 Initial Protocol Registration

Prior to implementing the protocol and enrolling participants, the CRS must receive approval to conduct a study from their IRB/EC and other applicable regulatory entity(ies). In addition, the CRS must successfully complete the PR process with the DAIDS PRO. Requirements for initial PR will be decided during the review of the protocol at the time of the DAIDS SRC assessment. Information on the PR process will be included in each protocol.

In rare cases, requests to modify the type of PR process determined at the SRC review will be submitted, via email, from DAIDS staff to the DAIDS PRT.

Final decisions regarding modification of the PR process will be made by the DAIDS PRT and appropriate DAIDS staff. All final decisions will be

¹ Available at: http://rcc.tech-res-intl.com/DAIDS%20RCC%20Forms/HighlightOff_PROManual_v04b.pdf

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documented and shared with the DAIDS staff and Protocol Team/Protocol PI/Grant PI/Contract PI, as applicable.

OPCRO staff will serve as consultants as needed.

Under circumstances when a decision cannot be reached by the DAIDS PRT and DAIDS Program staff, the Director of OPCRO or designee will make the final decision regarding an exception from the determined PR process.

Successfully completing the PR process *does not* authorize the CRS to begin enrollment of participants. CRSs will be notified by the appropriate DAIDS scientific program (i.e., Program Officer, Contracting Officer's Technical Representative), Operations Center or Data Management Center when enrollment may begin.

A CRS will receive a Registration Notification from the DAIDS PRO that indicates successful completion of the initial PR process. See the Protocol Registration manual for further details.

NOTE - A Disapproval Notification is not a final Registration Notification since corrective materials must be resubmitted to the DAIDS PRO. See the Protocol Registration manual for further details.

6.1.2 Protocol Amendment Registration

CRSs will submit the amended protocol including the sample informed consent form(s) (ICFs), site - specific ICF(s) and other required materials to their local IRBs/ECs within 45 calendar days for U.S. sites or 75 calendar days for non-U.S. sites from the date the amendment was approved by DAIDS and distributed to the sites. Sites must also submit the required materials to any additional regulatory entity(s) in a timely manner.

NOTE: The 45 or 75 calendar day site requirement for submission of amendment materials is for local IRB submission only.

NOTE: If a CRS is unable to submit amendment materials within the designated timelines, the site should provide justification with the registration packet submission to the DAIDS PRO and a copy of the justification should be kept in the site's regulatory file.

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Once a CRS has received approval from their IRB/EC and other applicable regulatory entity, the amended protocol and site informed consent(s) must be implemented immediately.

NOTE - A final Registration Notification from the DAIDS PRO is not required prior to implementing an amendment.

A CRS must submit the required IRB/EC approved amendment registration documents to the DAIDS PRO within 14 calendar days after receipt of final written documentation of IRB/EC approval for the amendment. The submitted documents must include documentation of the date that the amended protocol and site informed consent(s) was submitted to the local IRB/EC.

A CRS will receive a Registration Notification from the DAIDS PRO that indicates successful completion of the amendment PR process.

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6.1.3 Letter of Amendment (LoA) Registration

CRSs will submit the LoA and other required materials to their local IRBs/ECs within 45 calendar days for U.S. sites or within 75 calendar days for non-U.S. sites from the date the LoA was approved by DAIDS and distributed to the sites. Sites must also submit the required materials to any additional regulatory entity(ies) in a timely manner.

NOTE: The 45 or 75 calendar day site requirement for submission of amendment materials is for local IRB submission only.

NOTE: If a CRS is unable to submit the LoA and other required materials within the designated timelines, the site should provide justification with the registration packet submission to the DAIDS PRO and a copy of the justification should be kept in the site's regulatory file.

Once a CRS has received approval from the IRB/EC and other applicable Regulatory entity, the LoA and any revised site informed consent(s) must be implemented immediately.

NOTE - A final Registration Notification from the DAIDS PRO is not required prior to implementing a LoA.

A CRS must submit the final IRB/EC approval letter(s) for the LoA and any revised site informed consent(s) to the DAIDS PRO within 14 calendar days after receipt of final written documentation of IRB/EC approval for the LoA. The submitted documents must include documentation of the date that the LoA and any revised site informed consent(s) were submitted to the local IRB/EC.

A CRS will receive a Registration Notification from the DAIDS PRO that indicates successful completion of the LoA registration process.

6.1.4 Continuing/Annual Review

CRSs are required to submit documentation of IRB/EC continuing/annual review to the DAIDS PRO.

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A CRS must submit the required IRB/EC approved Continuing/Annual review documentation to the DAIDS PRO within 14 calendar days after receipt of final written documentation of IRB/EC approval(s).

CRSs will *NOT* receive a final Registration Notification for continuing/annual review documentation submitted to the DAIDS PRO.

6.1.5 Change of IoR

When there is a change in the Investigator of Record listed in item 1 on the Form FDA 1572 or DAIDS IoR Form, a CRS must submit the required documentation to the DAIDS PRO to officially change the IoR for a protocol(s) at a CRS. The submission must be done within 30 calendar days from the time the CRS is informed that the current IoR will no longer serve as the IoR for the study.

A CRS *will* receive a final Change of IoR Approval Notification from the DAIDS PRO when the change of IoR has been approved by the DAIDS PRT.

NOTE – The Change of IoR is *NOT* official until the CRS receives the Approval notification for the change of IoR from the DAIDS PRO.

6.1.6 Deregistration

A CRS will notify the DAIDS PRO when a study is completed at the CRS by submitting a request for deregistration from the study and all associated sub-studies. See the Protocol Registration manual for additional information.

A CRS *will* receive a Deregistration Notification from the DAIDS PRO when the CRS has been deregistered from a study and all associated sub-studies.

NOTE – A CRS is not considered deregistered from a study/sub-study until the CRS receives the Deregistration notification from the DAIDS PRO.

NOTE - Upon completion of the deregistration process, a CRS will no longer receive safety information from DAIDS.

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7.0 REFERENCES

DAIDS Protocol Registration Manual

<http://www3.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/ClinicalSite.htm>

8.0 INQUIRIES

Questions and comments regarding this policy may be directed to the OPCRO Policy Group at: NIAIDOPCROPOLICYGROUP@mail.nih.gov

9.0 AVAILABILITY

This policy is available electronically at the following URL:

<http://www3.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/ClinicalSite.htm>

10.0 CHANGE SUMMARY

This policy supersedes version 2.0 dated 20 Dec 2006.

11.0 APPENDICIES

None

12.0 APPROVAL

/Richard Hafner, MD/
Richard Hafner