PROTOCOL REGISTRATION MANUAL

Office for Policy in Clinical Research Operations
Division of AIDS

VERSION 3.0
April 2015

TABLE OF CONTENTS

PROTOCOL REGISTRATION MANUAL

SUMMARY OF CHANGES TO THE DAIDS PROTOCOL REGISTRATION MANUAL DATED MAY 2015 4

I. INTRODUCTION 5

II. DEFINITIONS 6

III. DAIDS PROTOCOL REGISTRATION OFFICE CONTACT INFORMATION AND DPRS ACESS 11

IV. PROTOCOL REGISTRATION REQUIRED DOCUMENTS 12

A. FORM FDA 1572 13

B. DAIDS INVESTIGATOR of RECORD (IoR) FORM 20

C. CURRICULUM VITAE (CV) 26

D. DOCUMENTATION OF INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE (IRB/EC) & OTHER REGULATORY ENTITY (RE)/APPROVING ENTITYAPPROVALS 27

i. IRB/EC Approvals 27

ii. Other RE/Approving Entity Approvals 28

iii. Documentation of Pediatric Risk/Benefit Category 29

iv. Institutional Biosafety Committee (IBC) Approval 29

v. Suspension or Termination of IRB/EC Approval 30

E. SITE-SPECIFIC INFORMED CONSENT FORMS (ICFs) 31

i. Types of ICFs and Protocol Registration requirements 32

ii. . Health Insurance Portability and Accountability Act (HIPAA) – Privacy Rule 34

V. CLINICALTRIALS.GOV INFORMED CONSENT REQUIREMENTS 34

VI. TRANSLATION REQUIREMENTS 35

i. Form FDA 1572, IoR Form and CVs 36

ii. IRB/EC, other RE/Approving Entity, and IBC approval letters 36

iii. Site-specific ICFs 36

VII. PROTOCOL REGISTRATION SUBMISSIONS 37

A. INITIAL REGISTRATION 38

B. AMENDMENT REGISTRATIONS 40

i. Full Version Protocol Amendment Registration 40

ii. Letter of Amendment (LoA) Registration 42

C. SUB-STUDY REGISTRATION 45

D. OTHER SUBMISSIONS 45

i. Requested Materials 45
ii. Disapprovals 46
iii. Registrations with Required Corrections 47
iv. Administrative Registration 48
v. Change of Investigator of Record (IoR) 49
vi. Continuing/Annual Review 50
vii. Site Initiated Revisions to Site Informed Consent Forms (ICFs) 52
viii. Updated Form FDA 1572 or DAIDS IoR Form 53
ix. Deregistration 54

VIII. APPENDIX A - INSTRUCTIONS ON HOW TO ACCESS & SUBMIT PROTOCOL REGISTRATION MATERIALS THROUGH THE DAIDS PROTOCOL REGISTRATION SYSTEM (DPRS) 56

SUMMARY OF CHANGES TO THE DAIDS PROTOCOL REGISTRATION MANUAL DATED

This manual has been reviewed for accuracy and updated to meet 508 compliance guidelines. Several sections have been updated to be consistent with current NIAID (DAIDS) requirements. Key changes to note in this version of the Manual are:

1. Requirements of Financial Disclosure by clinical investigators.
2. Additional explanations on “how to complete the Form FDA 1572/DAIDS IoR Form”.
3. Information on inclusion of IRB/EC/RE required language in Site-Specific ICFs
4. Updated Appendix A:Instructions on How to Submit Protocol Registration Materials through the DAIDS PROTOCOL REGISTRATION SYSTEM with the most current information on DPRS Submissions

This Manual supersedes the version 2.0 dated May 2012.

I. INTRODUCTION

The Division of AIDS (DAIDS) Office for Policy in Clinical Research Operations (OPCRO) has established a protocol registration process to ensure that all clinical research sites (CRSs) conducting NIAID (DAIDS)-supported and/or -sponsored clinical research do so in accordance with DAIDS Clinical Research Policies and Standard Procedures in addition to all applicable regulations for human subjects protection and the use of investigational drugs, biologics and/or devices.

The DAIDS protocol registration process verifies that CRSs have received the necessary Institutional Review Board (IRB)/Ethics Committee (EC) and other applicable Regulatory Entity (RE)/Approving Entity approvals and have provided to DAIDS all documentation pertaining to investigator qualifications and responsibilities that are required by the U.S. federal regulations and the National Institutes of Health (NIH). The DAIDS protocol registration process also verifies that site-specific informed consent forms contain the necessary information to comply with U.S. federal regulations. This includes the basic and additional informed consent form elements as required by U.S. federal regulations at 45 CFR 46.116 and 21 CFR 50.25.

Sites cannot begin the protocol registration process until the protocol has completed the DAIDS protocol development requirements. All protocols must receive final DAIDS approval either after DAIDS Clinical Sciences Review Committee (CSRC) or Prevention Sciences Review Committee (PSRC) or after regulatory review and DAIDS Medical Officer sign-off. In addition, for those protocols conducted under a DAIDS held Investigational New Drug (IND) Application, the final DAIDS approved version of the protocol must be submitted to the U.S. Food and Drug Administration (FDA).Each CRS will complete the protocol registration process for all clinical research supported and/or sponsored by NIAID (DAIDS) that is reviewed by CSRC or PSRC.

The DAIDS Protocol Registration Manual is a reference tool to help CRSs successfully complete the DAIDS protocol registration process. This manual explains the different types of protocol registration submissions as well as a list of the required documents for each type of submission.

II. 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): Distinct locations (i.e., 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 Sciences Review Committee (CSRC): The Division of AIDS internal scientific review committee responsible for the programmatic review of therapeutic protocols sponsored by DAIDS. The review will include careful assessment of the scientific objectives, design, safety, ethics, and feasibility of proposed research protocols. Scientific representatives from collaborating NIH Institutes and Centers participate as appropriate. (DAIDS)

Clinical trial: A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes (NIAID)

Code of Federal Regulations (CFR): Published by the U.S. Office of the Federal Register National Archives and Records Administration, these are detailed procedures for meeting requirements authorized by law:

> ***Title 21*:** Food and Drugs (covers regulations administered by FDA as authorized by the Food, Drug and Cosmetic Act).
>
> ***Title 45*:** Public Welfare (includes regulations administered by Office for Human Research Protections (OHRP) relating to the protection of human subjects). (DAIDS)

Curriculum Vitae (CV): A statement of investigator's qualifications including professional experience accomplishments, educational background, and any publications. This document is required for all initial protocol registrations. (DAIDS)

Division of AIDS (DAIDS): One of six divisions within the National Institute of Allergy and Infectious Diseases. DAIDS is responsible for the initiation, management, and oversight for the clinical trials and research that is sponsored and/or supported by NIAID (DAIDS). (DAIDS)

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 Protocol Registration System (DPRS): An internet-based system that allows DAIDS Clinical Research Sites (CRS) to submit and track all documents submitted to the DAIDS Protocol Registration Office (PRO).(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:

1. 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 DAIDS-supported award to another institution
2. 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, management and distribution services.
3. DAIDS-supported central laboratory or data management center receives from other organizations specimens or data for processing or analysis and the results or analyses, will be used to direct involvement of participants in clinical research activities. (DAIDS)

Electronic Protocol Registration (EPR): An alternate way CRSs can submit registration materials via email to the DAIDS PRO if they encounter problems when trying to submit registration materials through the DPRS. (DAIDS)

Food and Drug Administration (FDA): A public health agency within the United States (U.S.) Department of Health and Human Services. FDA's mission is to promote and protect public health by helping safe and effective products reach the market in a timely way and monitoring products for continued safety after they are in use as authorized by The Federal Food, Drug and Cosmetic Act. (DAIDS)

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

Full Version Protocol Amendment: Protocol modifications that result in a change in protocol version number. This new protocol version incorporates any currently proposed changes in addition to those made in all Clarification Memos (CMs) and Letter of Amendments (LOAs) that have been approved since the finalization of the previous protocol version. (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 bio hazardous research, including select agents. (NIAID)

Institutional Review Board/Ethics Committee (IRB/EC): Committee used by an institution to ensure the protection of human subjects by independently approving, modifying, or disapproving research protocols. (NIAID)

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 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 U.S. FDA has not approved the route of administration, dosage level, 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.

Investigator of Record (IoR) Form: A document required by DAIDS for non-IND studies. By signing the document, the IoR accepts full responsibility for conduct of the trial at their CRS. (DAIDS)

Letter of Amendment (LoA) - A revision to a protocol made by the Protocol Team/Chair/Awardee through a letter that requires DAIDS final approval/sign-off before implementation. Changes described in a LoA are listed in a document that is separate from the protocol document itself and will NOT result in the change to the DAIDS protocol version number. (DAIDS)

National Institute of Allergy and Infectious Diseases (NIAID): NIH institute that conducts and supports research to understand, treat, and prevent infectious, immunologic, and allergic diseases. (NIAID)

National Institutes of Health (NIH): A Federal agency whose mission is to improve the health of the people of the United States. NIH is a part of the Public Health Service, which is part of the U.S. Department of Health and Human Services. (NIH)

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 Human Research Protections (OHRP): U.S. Department of Health and Human Services (DHHS) office overseeing human subject protection regulations for HHS-supported research. (NIH)

Office for Policy in Clinical Research Operations (OPCRO): An office in DAIDS that provides a variety of clinical research management resources and oversight to the

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)

Prevention Sciences Review Committee (PSRC): The Division of AIDS internal scientific review committee responsible for the programmatic review of vaccine and prevention protocols sponsored by DAIDS. The review will include careful assessment of the scientific objectives, design, safety, ethics, and feasibility of proposed research protocols. Scientific representatives from collaborating NIH Institutes and Centers participate as appropriate. (DAIDS)

Protocol Registration Notifications: The following are notifications that a CRS may receive from the DAIDS PRO:

1. Confirmation of Submission - A notification sent out to the CRS Coordinator and IoR confirming that registration materials have been successfully submitted to the DAIDS PRO. If a CRS does not receive a Confirmation of Submission Notification within 24-48 hours of submitting registration documents to the DAIDS PRO, the CRS should contact the DAIDSPRO to find out how to proceed.
2. Registration Notification - A final notification from the DAIDS PRO indicating that a CRS has successfully completed the protocol registration process.
3. Registration with Required Corrections Notification -A notification from the DAIDS PRO indicating that a CRS must make required corrections and submit them to their IRB/EC for review and approval *OR* must submit justification for why the required correction will not be made within 120 calendar days of the date the Registration with Required Corrections Notification was issued. A Registration with Required Corrections Notification indicates that a CRS may begin using the site-specific informed consent forms (ICFs) after protocol activation by the appropriate Operations Center, Data Management/Statistical Center or DAIDS Program.
4. Disapproval Notification - A notification from the DAIDS PRO indicating that the site-specific informed consent forms (ICFs) do not include all the required basic and additional elements to comply with U.S. federal regulations and DAIDS policy. The Disapproval Notification will outline the deficiencies that must be revised/corrected before a final Registration Notification can be issued. All revised site-specific ICFs must be approved by the IRB/EC prior to submission to the DAIDS PRO. A disapproval notification is *NOT* a final notification since corrective materials must be resubmitted.
5. Deregistration Notification - A final notification from the DAIDS PRO indicating that a CRS is no longer registered to a study and all associated sub-studies.
6. Change of IoR Approval Notification – A final notification from the DAIDS PRO indicating that DAIDS has approved the change of IoR for a protocol at a CRS.
7. Requested Materials Notice - A message from the DAIDS PRO indicating that additional/corrected materials are required as a result of an incomplete or inaccurate submission to the DAIDS PRO.

   A Materials Request Notification stops the registration review process until the requested materials have been received at the DAIDS PRO. (DAIDS)

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

Regulatory Entity (RE)/Approving Entity - Any group other than the local IRB/EC responsible, for reviewing and/or approving a clinical research protocol and site- specific ICFs prior to implementation at a site. For example, in some states within the U.S., institutional approvals are required since these states have research regulations in addition to the federal human subjects protection regulations detailed in U.S. federal regulations (45 CFR 46).In addition, at many non-U.S. sites, other approvals may be required in addition to the local IRB/EC approval, which include but are not limited to approvals from ministry of health, national regulatory agency, in-country drug control council, national IRB/EC, or other government agency. (DAIDS)

Sub-Investigator: Any member of the clinical research team designated and supervised by the CRS Leader/IoR of a protocol at a CRS to perform critical trial related procedures and/or to make important clinical trial-related decisions. (DAIDS)

Sub-Study: A sub-study asks a separate research question from the parent protocol and may or may not contribute to the parent protocol's objectives but uses all or a subset of study participants or specimens. A sub-study can be included as part of the main/parent protocol document or may not be included in the main protocol but requires current or previous participation in the main protocol. (NIAID)

The following are different types of sub-studies that a site may protocol register:

1. Embedded Sub-study - A sub-study that is part of a main protocol that may or may not have a separate ICF. Embedded sub-studies have the same protocol version number as the main study and have a separate protocol number and/or DAIDS protocol ID number. If the main study amends, when protocol registering to the amendment, sites are required to protocol register to all embedded sub-studies. A CRS will receive a registration notification for each embedded sub-study that is submitted for protocol registration.
2. Stand Alone Sub-study - A sub-study that is not part of the main protocol but requires participants to be enrolled in the main study or have previously participated in the main study. A stand-alone sub-study is an independent protocol that may or may not have the same protocol version number/date as the main study and will always have a separate protocol number and/or DAIDS protocol ID number. A CRS should submit all required documents (i.e. IRB/EC approval letter[s], site-specific informed consent form[s], Form FDA 1572 and/or DAIDS IoR Form, and IoR CV) when registering to a stand-alone sub-study. A CRS will receive a registration notification for each stand-alone sub-study that is submitted for protocol registration. (DAIDS)

III. DAIDS PROTOCOL REGISTRATION OFFICE CONTACT INFORMATION and DPRS ACCESS

The DAIDS Protocol Registration Office (PRO) has two different e-mail addresses: one for submission of protocol registration documents and a second for questions and general correspondence.

Contact Information for Questions and General Correspondence:

EMAIL: protocol@tech-res.com
PHONE: 301-897-1707
OFFICE HOURS: Monday through Friday 8:30 AM to 5:00 PM
(U.S. Eastern Standard Time)

Effective January 2012, all sites participating in NIAID (DAIDS)-supported and/or -sponsored clinical research that requires protocol registration, are required to submit protocol registration materials to the DAIDS PRO through the DAIDS Protocol Registration System (DPRS). Information on the DPRS and how to access the system is available on the DPRS website or information on how to submit protocol registration materials through the DPRS once a CRS has received a user name and password, refer to Appendix A of this manual.

In order to gain access to the DPRS, site personnel must complete the DPRS training that's available online at DAIDS Learning Portal.
First, log in to the DAIDS Learning Management System (LMS) with your user name and password. Then enter DPRS into the search field, and select the DPRS training course. If you do not have a DAIDS LMS account click to request account access.
At the time of completion of the DPRS training, a username and password will be provided to the person who completed the training. If DPRS login details have not been received, contact DAIDS-ES Support at DAIDS-ESSupport@niaid.nih.gov.

If a CRS encounters problems when submitting protocol registration materials through the DPRS, a CRS can submit protocol registration materials via e-mail to the DAIDS Electronic Protocol Registration (EPR) mailbox. If a CRS submits materials through the EPR mailbox, the email message must outline the details of what is being submitted, and the kind of registration that is being submitted.

Information on protocol registration timelines is available on the RSC web site under the "Protocol Registration" section.

IV. PROTOCOL REGISTRATION REQUIRED DOCUMENTS

DAIDS reviews and approves the final version of each protocol and Sample Informed Consent (SIC) before distribution to the CRSs. CRSs are required to submit the initial version and all subsequent versions of a NIAID (DAIDS) -supported and/or -sponsored protocol, including the DAIDS-approved SIC and site-specific ICFs, to their local IRB/EC and other applicable RE/Approving Entity(ies) for review and approval.

Prior to implementing the protocol and enrolling participants, a CRS must receive approval from their IRB/EC and other applicable RE/Approving Entity(ies). In addition, the CRS must successfully complete the DAIDS protocol registration process. However, a Registration Notification from the DAIDS PRO *DOES NOT* authorize a CRS to begin enrollment of participants. CRSs will be notified by the appropriate DAIDS scientific program (i.e., Program/Contracting Officer Representative), Operations Center or Data Management Center when enrollment may begin.

Detailed information on specific requirements for each required document for protocol registration is included in sub-sections A-E of this section of the manual. Refer to Section VII – “Protocol Registration Submissions” for more information on the different types of submissions that can be made to the DAIDS PRO.

NOTE: Failure to include any required documents for protocol registration at the time of submission to the DAIDS PRO will result in processing delays until all the required documents are received.

A. FORM FDA 1572

REQUIRED FOR ALL INITIAL REGISTRATIONS FOR STUDIES BEING CONDUCTED UNDER AN IND APPLICATION AND WHEN THERE IS ANY MAJOR CHANGE TO THE INFORMATION ON THE CURRENT FORMD FDA 1572

A signed Form FDA 1572 is required for each investigator that participates in any clinical trial (drug or biologic) that is conducted under an Investigational New Drug (IND) Application filed with the U.S. FDA. By signing the Form FDA 1572, the Investigator of Record (IoR) affirms that he/she will conduct the clinical trial according to the research protocol and all applicable U.S. federal regulations. Investigators at non-U.S. sites must affirm to DAIDS their commitment to comply with local laws and requirements throughout the course of the clinical trial by signing the Form FDA 1572.

All CRSs participating in a NIAID (DAIDS)-supported and/or -sponsored clinical trial conducted under an IND must submit a copy of the signed and dated Form FDA 1572 to the DAIDS PRO as part of the protocol registration submission for review and for submission to the U.S. FDA if DAIDS is the IND sponsor.

NOTE: CRSs are required to retain the original signed Form FDA 1572 in their regulatory files at the site. Original Form FDA 1572s should not be sent to the DAIDS PRO.

CRSs requiring more space than what is provided on the Form FDA 1572 can use a supplemental page. The supplemental page provides additional space to document: additional research locations and addresses; laboratory facilities and addresses; and the names of additional sub-investigators. The supplemental page should identify the CRS and protocol number. If used, a copy of the supplemental page must also be sent to the DAIDS PRO as part of the protocol registration submission.

A CRS must update and submit within 30 calendar days a revised copy of the Form FDA 1572 when there is *ANY major* change to the information on the current Form FDA1572 submitted to the DAIDS PRO. Any correction or revision requires the IoR to sign and date the newly revised form. CRSs must submit *BOTH* pages of the revised Form FDA 1572 to the DAIDS PRO even if the changes only affect one page of the form.

NOTE: Examples of major changes to the Form FDA 1572 include but are not limited to:

- *Change in IoR*
- *Change in Sub-IoR*
- *Addition of a new or additional DAIDS approved location where the research will be conducted*
- *Addition of a laboratory*
- *Addition or change in an IRB/EC/RE that is responsible for review and approval*

of the clinical research protocol

NOTE: An updated Form FDA 1572 that has the same date as the original or previous version will not be accepted.

The most current version of the Form FDA 1572 is available for download on the RSC Web site under the "Protocol Registration" section or from the U.S. FDA website (www.fda.gov).

How to complete the Form FDA 1572

The Form FDA 1572 is comprised of 11 sections, 10 of which require data entry. Below is detailed information to assist the CRS in completing the Form FDA 1572.

Section 1 - Name and Address of Investigator of Record (IoR)

This section must contain the complete legal name (first and last name) and address of the IoR at the CRS that is responsible for the conduct of the clinical trial. The complete legal name of the IoR and the IoR's complete office address (complete physical location/street address) should be included in Section 1. Non-U.S. CRSs should include the complete physical address, including the country.

If a CRS has more than one IoR sharing responsibilities for a clinical trial being conducted under an IND, the CRS has the following options:

- The CRS can submit a separate Form FDA 1572 for each IoR that is responsible for the study at that CRS(s) and other DAIDS approved location(s). The CRS must provide documentation explaining that the investigators listed on the two Form FDA 1572s are sharing responsibilities for the conduct of the study at the CRS and DAIDS approved satellite location(s).

OR

- The CRS can submit one Form FDA 1572 that lists both investigators in section 1 of the Form FDA 1572. This indicates that both investigators are sharing equal responsibilities for the conduct of the study at the CRS(s) and other DAIDS approved location(s). Each investigator must sign and date sections 10 and 11 of the Form FDA 1572. The CRS must provide documentation stating that the two investigators listed on the Form FDA 1572 are sharing responsibilities for the conduct of the study at the CRS(s) and other DAIDS approved location(s).

NOTE: Requirements of the documentation can be fulfilled in one of the following ways:

- *Provide a written document that specifies how responsibilities will be shared and the role of each IoR at their respective location(s)*
- *Provide a copy of the site's delegation of responsibility log that indicates how responsibilities will be shared and the roles of each IoR at their respective location(s).*
- *Provide a statement in item 1 of the Form FDA 1572 that specifies that the two IoRs are Co-Investigators and how responsibilities will be shared and the role of each IoR at their respective location(s).*

Section 2 - Education, Training, and Experience

This section requires the IoR to check the appropriate box on how they plan to verify their education, training and experience that qualifies them as an expert in the clinical investigation of the study product (drug or biologic) being tested. The box marked "Curriculum Vitae" should be checked and a copy of the IoR's CV must be included in the registration packet that is submitted to the DAIDS PRO. DAIDS does not require the submission of CVs for sub-investigators. However, sites should keep a copy of all sub-investigator CVs in the regulatory files at the site. DAIDS requires that all CVs be submitted in English and must be signed and dated.

Section 3 - Name and Address of Location(s) Where the Study Will be conducted

This section must list the complete name and address of all locations where the clinical trial will be conducted and where clinical data will be generated or collected. The complete name and physical address of all the locations (medical school, hospital, clinics, satellite sites, or research facility) should be listed in Section 3.This includes facilities where participants will be seen and study procedures performed. Non-U.S. CRSs should include the country in addition to the complete physical address.

If a CRS utilizes a DAIDS-approved pharmacy, it is not necessary to list the pharmacy on the Form FDA 1572. If a CRS out-sources the pharmacy responsibilities for the clinical trial the CRS must list the name and complete physical address of the contracted pharmacy in Section 3.

If an IoR is conducting the same research protocol at more than one CRS overseen by the same IRB/EC, then it is acceptable to submit one Form FDA 1572 which lists all locations where the clinical trial will be conducted. If more than one CRS is included in Item 3, include the DAIDS site ID (if available) for each CRS.

Section 4 - Name and Address of Clinical Laboratory

This section must list the complete name(s) and complete physical address of ALL clinical laboratories or testing facilities which will be used for the clinical trial to process study related and/or study defined samples that will directly contribute to or support the clinical trial (i.e., diagnostic labs performing blood work, imaging centers, cardiology labs, non-local labs). This may include analytical labs that provide pharmacokinetic analysis, and laboratories supplying efficacy data. The official name of the laboratory (i.e., Department of Pathology) should be included. If multiple CRSs and/or locations are listed on the Form FDA 1572, the corresponding clinical laboratories must be listed for each CRS and/or location.

Exceptions for not including ALL clinical laboratories or testing facilities include:

- If a primary laboratory is sending samples to a satellite or other contract labs for additional testing, or
- If a laboratory is being used only to store study samples.

The additional labs do not need to be listed as long as the primary laboratory can trace, through written records, the samples to the additional labs where the tests were performed.

Section 5 - Institutional Review Board (IRB)/Ethics Committee (EC) and All Other Regulatory Entity(ies) (RE)/Approving Entity(ies) and Institutional Biosafety Committees (IBCs)

This section must list the complete name and address of all IRBs, ECs and other applicable REs/Approving Entity(ies) and IBCs which are responsible for the review and approval of clinical trials at a CRS prior to the CRS's initiation of the protocol. The official name (refer to the title provided on the IRB/EC and other applicable RE/Approving Entity approval letter(s)) and complete physical address of the IRBs/ECs and other applicable REs/Approving Entity(ies) which reviewed the protocol should be included in Section 5. IRBs/ECs reviewing and approving the clinical trial do not have to be at the same location as the research being conducted. In addition to U.S. FDA requirements, DAIDS requires that all sites participating in NIAID (DAIDS)-supported and/or -sponsored clinical trials also list all regulatory entities that must review and approve the clinical trial prior to implementation at a CRS in section5.

NOTE: The DAIDS PRO must receive an approval letter for each entity listed in section 5 of the Form FDA 1572. If the other RE/Approving Entity is not responsible for the review and approval of full version protocol amendments, LoAs or changes to the CRS's site-specific ICF(s), RE/Approving Entity should not be removed/omitted from FORM FDA 1572. However, the CRS Leader or IoR should document in a memo to the DAIDS PRO or in the comments section of the IRB/EC/RE field in the DPRS when submitting registration materials if the other RE/Approving Entity is not responsible for approvals.

Section 6 - Names of Sub-Investigators

This section must list the complete legal name (first and last name) of all study staff at a CRS, and DAIDS approved additional study location(s) that are responsible for making a "direct and significant contribution to the data". A direct and significant contribution includes any persons directly responsible for the treatment or evaluation of research participants. This includes site personnel who have more than minimal involvement with the conduct of the research (performing study evaluations or procedures or providing intervention) or more than minimal study conduct-related contact with study participants or confidential study data, records, or specimens.

Hospital staff, including nurses, residents, fellows, and office staff who provide ancillary or intermittent care but who do not make a direct and significant contribution to the data do not need to be listed. It is not necessary to include in Section 6 a person with only an occasional role in the conduct of the research (i.e., an on-call physician who temporarily dealt with a possible adverse event or a temporary substitute for any research staff). If a number of residents on rotation will participate in the clinical trial, a general statement regarding their planned participation may be included in Section 6.

The decision about whether to list a pharmacist or research coordinator on the Form FDA 1572 is the responsibility of the IoR at the CRS and should be based on the contribution that the individual makes to the study. For example, a research pharmacist may prepare test articles and maintain drug accountability for many clinical trials that are ongoing concurrently at an institution. Because the pharmacist is not making a direct and significant contribution to the data for a particular study, it would not be necessary to list the pharmacist as a sub-investigator in Section 6, but he/she should be listed in the investigator's study records.

CRSs are required to list, at a minimum, one sub-investigator who will be responsible for fulfilling the requirements of the IoR should the IoR not be able to meet his/her requirement for any given reason. The complete legal name(s) of the sub-investigators who will assist the IoR in the conduct of the protocol should be listed in Section 6.

The IoR is responsible for determining the sub-investigators to be included on the Form FDA 1572. Individuals who will sign study medication prescriptions and physicians who submit SAE/EAEs to DAIDS must be listed on the Form FDA 1572. The IoR must designate a physician as a sub-investigator who will be responsible for backing up the IoR.

NOTE: Any physician who is responsible for the review and submission of SAE/EAEs to DAIDS must be listed in Section 6 of the Form FDA 1572. Safety

reports cannot be submitted by a physician who is not listed in section 6 of the Form FDA 1572.

NOTE: CRSs must list the CRS Leader as a Sub-investigator in Section 6 on all Form FDA 1572s if the IoR for the protocol, listed in Section 1, is not the CRS Leader. If the CRS Leader is the same person listed in Section 1 on the Form FDA 1572 (Protocol IoR) then the CRS Leader does NOT need to be listed again as a sub-investigator.

NOTE: Personnel at facilities where the study uses certain tests (e.g. cardiologist reading ECG or personnel at ECG facilities) do not have to be listed if they are not considered to be engaged in research activities. Per B1 of *OHRP's guidance document on engagement*; not all personnel are considered engaged in research activities unless they have other activities, such as administering study interventions being tested or evaluated or being a collaborator on the publication.

Section 7 - Protocol Name and Protocol Number:

The DAIDS ES/Network protocol ID number and the complete protocol title should be included in Section 7.

NOTE: Short titles cannot be accepted and will result in the CRS having to submit a revised Form FDA 1572 which will delay protocol registration. CRSs should not include the DAIDS protocol version number, and/or protocol date in Section 7.

Section 8 - Clinical Protocol Information:

As the IND sponsor, DAIDS submits the protocol and all relevant information to the FDA on behalf of investigator. This section should be left blank for both boxes. If DAIDS is not the IND sponsor for a trial, the IND sponsor is responsible for submitting the protocol and all relevant information including the Form FDA 1572 to the FDA and can determine the appropriate information for this section.

Sections 9, 10 and 11:

The IoR must read Section 9, date Section 10 and sign Section 11.The complete legal handwritten signature of the IoR should be included in Section 11 and should correspond with the name in Section 1 of the Form FDA 1572.*NOTE: If more than one IoR is listed in section 1 of the Form FDA 1572, both IoR's must sign and date this section.*

NOTE: If a CRS updates their Form FDA 1572, the IoR(s) is responsible for signing and dating the new document even if the change(s) only affect page 1.

NOTE: An updated Form FDA 1572 that is dated the same as the original or previous version will not be accepted.

Financial Disclosure (FD) by clinical investigators

Effective July 1, 2014, any investigator (including sub-investigators) listed on the Form FDA 1572 must complete a financial disclosure (FD) form/statement for all DAIDS sponsored and/or supported studies where DAIDS holds the IND.

Per the regulatory requirements of 21 CFR 54, a person listed as an investigator or sub-investigator on the Form FDA 1572 must complete and submit financial disclosure information for all DAIDS sponsored and/or supported studies where DAIDS holds the IND. Each clinical trials network (i.e., ACTG, IMPAACT, HPTN, HVTN, MTN) has developed a generic financial disclosure form/statement for all network studies that are conducted under DAIDS held IND. These forms should be used unless DAIDS or the protocol team provides sites with a different FD Form/statement.

For all Non-Network studies that are conducted under a DAIDS held IND, DAIDS has developed a financial disclosure form/statement and this form will be available on the Regulatory Support Center (RSC) DAIDS RSC, under protocol registration.

All original, completed and signed DAIDS approved network financial disclosure Forms/statements or the drug company-specific financial disclosure forms/statements must be filed and retained in a CRS's regulatory binder along with the original and/or updated, signed Form FDA 1572 for that study. These forms need not be submitted to DAIDS or the Network Operations Centers unless requested. For Non-DAIDS held INDs, investigators should follow the IND sponsor's instructions for the collection of financial disclosure form/statement (which may be a company, institution).

In the event that FD forms/statements are required for a regulatory submission, CRS Leaders are responsible for making sure that a financial disclosure form is completed and submitted to their appropriate Network Operations Center per affiliated network requirements for each individual listed in Sections 1 and 6 of the Form FDA 1572.

This process is not required for Non-IND/IDE studies.

Refer to the FAQs on DAIDS RSC website for additional information on the completion, implementation and collection of FD forms/statements.

B. DAIDS INVESTIGATOR of RECORD (IoR) FORM

SHOULD BE SUBMITTED FOR INITIAL REGISTRATION FOR STUDIES NOT BEING CONDUCTED UNDER AN IND APPLICATION AND WHEN THERE IS ANY MAJOR CHANGE TO THE INFORMATION ON THE CURRENT IoR FORM.

A signed DAIDS IoR Form should be submitted for each investigator who participates in a clinical trial that is sponsored and/or supported by DAIDS and is NOT conducted under an IND filed with the U.S. FDA. By signing the DAIDS IoR

Form, the IoR affirms that he/she will conduct the clinical trial according to the research protocol, applicable U.S. federal regulations, and all local laws and requirements, and DAIDS requirements/policies.

The DAIDS IoR Form contains the same information as the Form FDA 1572 without the legal language that pertains only to studies conducted under an IND. All CRSs should submit a copy of the signed and dated DAIDS IoR Form to the DAIDS PRO as part of the initial protocol registration submission for review.

NOTE: CRSs are required to retain the original signed DAIDS IoR Form in their regulatory files at the site. Original DAIDS IoR Forms should not be sent to the DAIDS PRO. If a site submits an original DAIDS IoR Form to the DAIDS PRO, the form will be copied and the original returned to the site.

CRSs requiring more space than what is provided on the DAIDS IoR Form can use a supplemental page. The supplemental page provides additional space to document: additional research locations and addresses; laboratory facilities and addresses; and the names of additional sub-investigators. The supplemental page should identify the CRS and protocol number. If used, a copy of the supplemental page must also be included with the DAIDS IoR form as part of the initial protocol registration submission.

A CRS must update and submit within 30 calendar days a revised copy of the DAIDS IoR Form when there is *ANY* major change to the information on the current DAIDS IoR Form submitted to the DAIDS PRO. When there is any correction or revision to the original DAIDS IoR Form, the IoR should sign and date the revised form. CRSs should submit *BOTH* pages (and supplement page, if applicable) of the revised DAIDS IoR Form to the DAIDS PRO even if the changes only affect one page of the form.

NOTE: Examples of major changes to the DAIDS IoR Form include but are not limited to:

- *Change in IoR*
- *Change in Sub-IoR*
- *Addition of a new or additional DAIDS approved location where the research will be conducted*
- *Addition of a laboratory*
- *Addition or change in an IRB/EC/RE that is responsible for review and approval of the clinical research protocol*

NOTE: An updated DAIDS IoR Form that has the same date as the original or previous version will not be accepted.

The most current version of the DAIDS IoR Form is available for download on the RSC Web site under the "Protocol Registration" section.

How to complete the DAIDS IoR Form:

The DAIDS IoR Form is comprised of 10 sections, 9 of which require data entry. Listed below is detailed information to assist the CRS in completing the DAIDS IoR Form.

Section 1 - Name and Address of Investigator of Record (IoR)

This section must contain the complete legal name (first and last name) and address of the IoR at the CRS that is responsible for the conduct of the clinical trial. The complete legal name of the IoR and the IoR's complete office address (complete physical location/street address) should be included in Section 1. Non-U.S. CRSs should include the complete physical address, including the country.

If a CRS has more than one IoR sharing responsibilities for a Non-IND study, the CRS has the following options:

- The CRS can submit a separate DAIDS IoR Form for each IoR that is responsible for the study at that CRS(s) and other DAIDS approved location(s). The CRS must provide documentation explaining that the investigators listed on the two DAIDS IoR Forms are sharing responsibilities for the conduct of the study at the CRS and DAIDS approved satellite location(s).

OR

- The CRS can submit one DAIDS IoR Form that lists both investigators in section 1 of the DAIDS IoR Form. This indicates that both investigators are sharing responsibilities for the conduct of the study at the CRS(s) and other DAIDS approved location(s). Each investigator must sign and date sections 9 and 10 of the DAIDS IoR Form. The CRS must provide documentation stating that the two investigators listed on the DAIDS IoR Form are sharing responsibilities for the conduct of the study at the CRS(s) and other DAIDS approved location(s).

NOTE: Requirements of the documentation can be fulfilled in one of the following ways:

- *Provide a written document that specifies how responsibilities will be shared and the role of each IoR at their respective location(s)*
- *Provide a copy of the site's delegation of responsibility log that indicates how responsibilities will be shared and the roles of each IoR at their respective location(s).*

- *Provide a statement in item 1 of the IoR Form that specifies that the two IoRs are Co-Investigators and how responsibilities will be shared and the role of each IoR at their respective location(s).*

Section 2 – Education, Training, and Experience

This section requires the IoRs to check the appropriate box regarding how they plan to verify that their education, training and experience qualifies them as an expert in the clinical investigation of the study product (drug or biologic) being tested.

The box marked "Curriculum Vitae" should be checked and a copy of the IoR's CV must be included in the registration packet that is submitted to the DAIDS PRO. DAIDS does not require the submission of CVs for sub-investigators. However, sites should keep a copy of all sub-investigator CVs in the regulatory files at the site. DAIDS requires that all CVs be submitted in English and must be signed and dated.

Section 3 – Name, Address, and DAIDS CRS ID Number of Location(s) Where the Study Will be Conducted

This section must list the complete name and address of all locations where the clinical trial will be conducted and where clinical data will be generated or collected. The complete name and physical address of all the locations (medical school, hospital, clinics, satellite sites, or research facility) should be listed in Section 3. This includes facilities where participants will be seen and study procedures performed. Non-U.S. CRSs should include the country in addition to the complete physical address.

If a CRS utilizes a DAIDS-approved pharmacy, it is not necessary to list the pharmacy on the DAIDS IoR Form. If a CRS out-sources the pharmacy responsibilities for the clinical trial the CRS must list the name and complete physical address of the contracted pharmacy in Section 3.

If an IoR is conducting the same research protocol at more than one CRS overseen by the same IRB/EC, then it is acceptable to submit one DAIDS IoR Form which lists all locations where the clinical trial will be conducted. If more than one CRS is included in Item 3, include the DAIDS site ID for each CRS.

Section 4 - Name and Address of Clinical Laboratory

This section must list the complete name(s) and complete physical address location of ALL clinical laboratories or testing facilities that will be used for the clinical trial to process study related and/or study defined samples that will directly

contribute to or support the clinical trial (i.e., diagnostic labs performing blood work, imaging centers, cardiology labs, non-local labs). This may include analytical labs that provide pharmacokinetic analysis, and laboratories supplying efficacy data. The official name of the laboratory (i.e., Department of Pathology) should be included. If multiple CRSs and/or locations are listed on DAIDS IoR Form, the corresponding clinical laboratories must be listed for each CRS and/or location.

Exceptions for not including ALL clinical laboratories and testing facilities include:

- If a primary laboratory is sending samples to a satellite or other contract labs for additional testing, or
- If a laboratory is being used only to store study samples.

The additional labs do not need to be listed as long as the primary laboratory can trace, through written records, the samples to the additional labs where the tests were performed.

Section 5 - Institutional Review Board (IRB)/Ethics Committee (EC) and All Other Entity(ies) (RE)/Approving Entity(ies) and Institutional Biosafety Committees (IBCs)

This section must list the complete name and address of all IRBs, ECs and other applicable REs/Approving Entity(ies) and IBCs, that are responsible for the review and approval of research at a CRS prior to the CRS's initiation of the protocol. The official name (refer to the title provided on the IRB/EC and other applicable RE/Approving Entity approval letter(s)) and complete physical address of the IRBs/ECs and other applicable REs/Approving Entity(ies) that reviewed the protocol should be included in Section 5. IRBs/ECs reviewing and approving the study do not have to be at the same location as where the research is conducted.

DAIDS requires that each site participating in NIAID (DAIDS)-supported and/or -sponsored clinical trials also list all entities that must review and approve the clinical trial prior to implementation at a CRS in section 5.

NOTE: The DAIDS PRO must receive an approval letter for each entity listed in section 5 of the Form FDA 1572. If the other RE/Approving Entity is not responsible for the review and approval of full version protocol amendments, LoAs or changes to the CRS's site-specific ICF(s), RE/Approving Entity should not be removed/omitted from FORM FDA 1572. However, the CRS Leader or IoR should document in a memo to the DAIDS PRO or in the comments section of the IRB/EC/RE field in the DPRS when submitting registration materials if the other RE/Approving Entity is not responsible for approvals

Section 6 - Names of Sub-Investigators

This section must list the complete legal name (first and last name) of all study staff at a CRS, and DAIDS approved additional location(s) that are responsible for making a "direct and significant contribution to the data." A direct and significant contribution includes any persons directly responsible for the treatment or evaluation of research participants. This includes site personnel who have more than minimal involvement with the conduct of the research (performing study evaluations or procedures or providing intervention) or more than minimal study conduct-related contact with study participants or confidential study data, records, or specimens.

Hospital staff, including nurses, residents, fellows, and office staff who provide ancillary or intermittent care but who do not make a direct and significant contribution to the data do not need to be listed. It is not necessary to include in Section 6 a person with only an occasional role in the conduct of the research (i.e. an on-call physician who temporarily dealt with a possible adverse event or a temporary substitute for any research staff). If a number of residents on rotation will participate in the study, a general statement regarding their planned participation may be included in Section 6.

The decision about whether to list a pharmacist or research coordinator on the DAIDS IoR Form is the responsibility of the IoR at the CRS and should be based on the contribution that the individual makes to the study. For example, a research pharmacist may prepare test articles and maintain drug accountability for many clinical trials that are ongoing concurrently at an institution. Because the pharmacist is not making a direct and significant contribution to the data for a particular study, it would not be necessary to list the pharmacist as a sub-investigator in Section 6, but he/she should be listed in the investigator's study records.

CRSs are required to list at minimum, one sub-investigator who will be responsible for fulfilling the requirements of the IoR should the IoR not be able to meet his/her requirement for any given reason. The complete name(s) of the sub-investigators who will assist the IoR in the conduct of the protocol should be listed in Section 6.

The IoR is responsible for determining the sub-investigators to be included on the DAIDS IoR Form. Individuals who will sign study medication prescriptions and physicians who submit SAE/EAEs to DAIDS should be listed on the DAIDS IoR Form. The IoR must designate a physician as a sub-investigator that will be responsible for backing up the IoR.

NOTE: Any physician who is responsible for the review and submission of SAE/EAEs to DAIDS should be listed in Section 6 of the DAIDS IoR Form. Safety reports cannot be submitted by a physician who is not listed in Section 6 of the DAIDS IoR Form.

NOTE: CRSs should list the CRS Leader as a Sub-investigator in Section 6 on all DAIDS IoR Forms if the IoR for the protocol, listed in Section 1, is not the CRS Leader. If the CRS Leader is the same person listed in Section 1 on the DAIDS IoR Form (Protocol IoR) then the CRS Leader does NOT need to be listed again as a sub-investigator.

NOTE: Personnel at facilities where the study uses certain tests (e.g. cardiologist reading ECG or personnel at ECG facilities) do not have to be listed if they are not considered to be engaged in research activities. Per B1 of OHRP's guidance document on engagement ; not all personnel are considered engaged in research activities unless they have other activities, such as administering study interventions being tested or evaluated or being a collaborator on the publication.

Section 7 –Study Title and Protocol ID Number:
The DAIDS ES/Network protocol ID number and the complete protocol title should be included in Section 7.
NOTE: Short titles cannot be accepted and will result in the CRS having to submit a revised DAIDS IoR Form which will delay protocol registration.
CRSs should not include the DAIDS protocol version number, and/or protocol date in Section 7.

Sections 8, 9, and 10:
The IoR should read Section 8, sign Section 9 and date Section 10. The complete legal handwritten signature of the IoR should be included in Section 9 and should correspond with the name in Section 1 of the DAIDS IoR Form.
NOTE: If more than one IoR is listed in section 1 of the DAIDS IoR Form, both IoR's must sign and date this section.

NOTE: If a CRS updates their DAIDS IoR Form, the IoR(s) is responsible for signing and dating the new document even if the change(s) only affect page 1. NOTE: An updated DAIDS IoR Form that is dated the same as the original or previous version will not be accepted.

C. CURRICULUM VITAE (CV)

REQUIRED FOR ALL INITIAL REGISTRATIONS AND WHEN THERE IS ANY MAJOR CHANGE TO THE CURRENT CV ON FILE WITH THE DAIDS PRO.

The Investigator of Record (IoR) overseeing DAIDS-supported and/or sponsored clinical research must provide evidence of qualifications (experience, training and education) to assume responsibility for the conduct of clinical trials. CRSs must submit to the DAIDS PRO, a CV for the IoR for all initial protocol registrations. All CVs must provide sufficient documentation for DAIDS to verify the IoR(s) qualifications to conduct a clinical trial.

All investigators must sign and date their CV prior to submission to the DAIDS PRO. All IoRs are required to submit an updated, newly signed and dated CV when there is ANY major change to the current CV on file with the DAIDS PRO or at a minimum of every 2 years.

In addition, if the IoR is a physician, a copy of the IoR's current medical license documentation or equivalent (i.e., documentation of good standing in the country where they are practicing) must be submitted with all CVs.

NOTE: Examples of major changes to the IoR CV include but are not limited to:

- *Change in contact information*
- *Change in education*
- *Change in experience*
- *New trainings*
- *New publications*

U.S. federal regulations require that the IoR's CV be submitted to the U.S. FDA for all studies being conducted under an IND. DAIDS, as the IND sponsor, submits the IoR CV to the U.S. FDA. Sub-investigators are not required to submit CVs to the DAIDS PRO. However, sites should keep a copy of all sub-investigator CVs in the regulatory files at the site.

DAIDS accepts a NIH Bio-Sketch formatted CV that includes education/training, current employment, past relevant employment, licensures/memberships, and any relevant publications.

The NIH Bio-Sketch formatted CV template is available here.

D. DOCUMENTATION OF INSTITUTIONAL REVIEW BOARD/ ETHICS COMMITTEE (IRB/EC) & OTHER REGULATORY ENTITY (RE)/APPROVING ENTITY APPROVALS

REQUIRED FOR ALL INITIAL, AMENDMENT and LoA REGISTRATIONS, CONTINUING/ ANNUAL REVIEW SUBMISSIONS, SITE INITIATED REVISIONS TO SITE- SPECIFIC ICFs, ADMINSTRATIVE REGISTRATIONS, AND SUBMISSION OF REVISED SITE ICF(s) IN RESPONSE TO A DISAPPROVAL NOTIFICATION

i. IRB/EC Approvals

CRSs are required to submit the current version and all subsequent versions of NIAID (DAIDS)-supported and/or sponsored clinical trials and observational studies, including the DAIDS-approved sample informed consent (SIC) and site-specific ICFs, to their IRB/EC and other applicable REs/Approving Entity(ies) for review and approval. CRSs must submit a copy of ALL appropriate documentation to and from the IRB/EC/RE/Approving Entity along with a copy of all the final approval letter(s) to the DAIDS PRO as part of the protocol registration submission. Original documents should be kept in the regulatory files at the CRS. The IRB/EC/RE/Approving Entity approval letter(s) accompanying all initial, amendment, and LoA registrations must be a final approval not requiring any modifications to the site-specific ICF(s).

NOTE: Appropriate documentation includes but is not limited to:

- the submission letter from the site to the IRB/EC
- the letter(s) from the IRB/EC documenting queries and changes required to the site-specific ICFs
- site response to the queries
- final approval letter(s)

All IRB/EC/RE/Approving Entity approval letter(s) must be able to be linked to the current DAIDS-approved version of the protocol. If an IRB/EC/RE/Approving Entity does not include the DAIDS required identifying information in their approval letters, CRSs can submit a memo with their IRB/EC/RE/Approving Entity submission that includes: identifying information corresponding to the protocol, lists all the documents submitted for IRB/EC/RE/Approving Entity review as well as the date of submission to the IRB/EC/RE/Approving Entity. The required identifying information is:

- Complete Protocol Title for the current DAIDS-approved version of the protocol. The DAIDS PRO will accept a long or short title for those protocols which include both on the DAIDS-approved SIC.
- DAIDS ES and/or Network Protocol ID Number
- DAIDS Protocol Version Number from the final version of the protocol approved by DAIDS *AND/OR* the final version date of the protocol document approved by DAIDS.

The CRS's memo can be used to document that the IRB/EC/RE/Approving entity received the correct version of the protocol and may be included with the IRB/EC/RE/Approving entity approval letters that are submitted to the DAIDS PRO.

NOTE: The CRS's memo to the IRB/EC/RE/Approving entity requesting review must pre-date the date on the final IRB/EC/RE/Approving entity approval letter(s).

NOTE: Sites are strongly advised to document the date the CRS receives each final IRB/EC/RE/Approving Entity approval letter to ensure compliance with the DAIDS protocol registration policy regarding submission of amendment and LoA registration materials to the DAIDS PRO within 14 calendar days of receipt of all final IRB/EC/RE approval letters. This documentation should be kept in the site's regulatory files for verification by monitors.

NOTE: If any of the IRB/EC/RE/Approving Entity approval letter(s) or CRS's memo do not contain enough information to be linked to the most current DAIDS- approved version of the protocol, designated site personnel (i.e., CRS coordinator, IoR) and/or additional personnel listed in the DPRS will be sent a Requested Materials notice that details the missing and/or corrected information/materials that must be submitted to the DAIDS PRO for registration processing to continue. The review process will not continue until the requested materials are received at the DAIDS PRO. For information on how to submit requested materials refer to Section VII, Sub Section D. i.- "Requested Materials" of this manual.

ii. Other RE/Approving Entity Approvals

When other approvals are required in addition to the local IRB/EC at a CRS prior to implementation at a CRS, copies of those approval letters and any other appropriate correspondence (as noted in Section i above) must be submitted to the DAIDS PRO with registration materials.

NOTE: If a given RE/Approving Entity requires review/approval of initial versions of protocols but does not review and approve full version amendments and LoAs, the CRS Leader or IoR should document this fact in the comments section of the IRB/EC/RE approval field in the DPRS or with a memo to the DAIDS PRO when submitting registration materials.

NOTE: DAIDS requires that each site participating in DAIDS supported and/or sponsored clinical trials, list all entities that must review and approve a clinical trial prior to implementation at a CRS on their Form FDA 1572 and/or DAIDs IoR Form. For information on completing the Form FDA 1572 and/or DAIDS IoR Form, refer to Section IV, Sub Sections A and B –"Section 5 - Institutional Review Board (IRB)/Ethics Committee (EC) and All Other Regulatory Entity(ies)

(RE)/Approving Entity (ies) and Institutional Biosafety Committees (IBCs)" of this manual.

iii. Documentation of Pediatric Risk/Benefit Category

Per the DAIDS Policy for Enrolling Children (including Adolescents) in NIAID (DAIDS)-supported and/or -sponsored Human Subject Clinical Research, for research studies including children or adolescents, DAIDS requires documentation of the IRB/EC designation of the pediatric risk/benefit category from the U.S. Federal regulations, 45 CFR 46.404-407 & 21 CFR 50.51-54 and IRB/EC approval for involvement of children based on the determination specified by that category. This requirement applies to the initial and continuing/annual reviews of research protocols and to any subsequent reviews of full version protocol amendments and LoAs involving potential study risks or benefits. The documentation may be in the IRB/EC approval letter(s) or in other official correspondence from the IRB/EC to the site Investigator.

NOTE: Failure to submit documentation of the IRB/EC designation of the pediatric risk/benefit category or documentation that the CRS will not enroll children or adolescents at the time of registration submission to the DAIDS PRO will result in delays in protocol registration.

iv. Institutional Biosafety Committee (IBC) Approval

REQUIRED FOR ALL INITIAL REGISTRATIONS FOR RESEARCH THAT INVOLVES RECOMBINANT DNA

Research supported by NIH funding that involves recombinant DNA is subject to special regulatory oversight by an IBC. In addition, clinical trials testing products containing recombinant DNA must be submitted to the NIH Office for Biotechnology Activities (OBA) for review by the NIH Recombinant DNA Advisory Committee (RAC). Detailed information regarding the requirements for NIAID (DAIDS) -sponsored and/or -supported research involving recombinant DNA is available on the RSC website under the "Protocol Registration" section.

Once IBC approval is received, a copy of the final approval letter and any other appropriate correspondence (as noted in section i above) must be submitted to the DAIDS PRO with the initial registration submission. Failure to submit documentation of IBC approval at the time of initial registration submission to the DAIDS PRO will result in delays in protocol registration.

If an IBC must review and approve all full version protocol amendments and LoAs prior to the implementation at a CRS, documentation of the IBC approval should be submitted to the DAIDS PRO at the time of amendment or LoA registration.

All IBC approval letter(s) must be able to be linked to the current DAIDS- approved version of the protocol at the time of initial protocol registration. Since not all IBCs include the DAIDS-required identifying information in their approval letters, a CRS can submit a memo with their IBC submission which lists identifying information corresponding to the protocol, all the documents submitted for review as well as the date of submission to the IBC. The required identifying information is:

- Complete Protocol Title for the current DAIDS-approved version of the protocol. The DAIDS PRO will accept a long or short title for those protocols which include both on the DAIDS sample informed consent forms.
- DAIDS ES and/or Network Protocol ID Number
- DAIDS Protocol Version Number from the final version of the protocol approved by DAIDS *AND/OR* the final version date of the protocol document approved by DAIDS.

The CRS's memo can be used to document that the IBC received the correct version of the protocol and may be included with the IBC approval letter that is submitted to DAIDS PRO.

NOTE: The CRS's memo to the IBC requesting review must pre-date the date on the final IRB/EC approval letter(s).

NOTE: If the IBC approval letter or CRS's memo does not contain enough information to be linked to the most current DAIDS-approved version of the protocol, designated site personnel (i.e., CRS coordinator, IoR) and/or additional personnel listed in the DPRS will be sent a Materials Request notice that details the missing and/or corrected information/materials that must be submitted to the DAIDS PRO for registration processing to continue. The review process will not continue until the requested materials are received at the DAIDS PRO. For information on how to submit requested materials refer to Section VI, Sub Section D. i. - "Requested Materials" of this manual.

v. Suspension or Termination of IRB/EC Approval

Per U.S. federal regulations, 45 CFR 46.113 the IRB/EC has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's/EC's requirements or that has been associated with unexpected serious harms to participants. The regulations mandate that when the reviewing IRB/EC suspends or terminates its approval of research, this information be reported to, among others, the investigator and sponsor.

Per the DAIDS Critical Events Manual, for any studies that are protocol registered through the DAIDS PRO, the CRS must submit documentation of the suspension or termination of IRB/EC approval to DAIDS as soon as possible, but in no later than 3 reporting days through the DPRS. If a study is not registered through the DAIDS PRO, the CRS must notify the appropriate DAIDS Program Officer (PO) or Contracting Officer Representative (COR) of the IRB/EC actions to suspend or terminate IRB/EC approval.

SITE-SPECIFIC INFORMED CONSENT FORMS (ICFs) REQUIRED FOR ALL INITIAL, AMENDMENT & LoA REGISTRATIONS IF THERE WAS A CHANGE TO THE SITE-SPECIFIC ICFs, CONTINUING /ANNUAL REVIEW SUBMISSIONS IF THERE WAS A CHANGE TO THE SITE-SPECIFIC ICFs, SITE-INITIATED REVISIONS TO SITE-SPECIFIC ICFs, & SUBMISSION OF REVISED SITE ICFs IN RESPONSE TO A DISAPPROVAL NOTIFICATION

Site-specific ICF(s) must contain all information necessary to comply with U.S. federal regulations, local laws and regulations, and DAIDS policies. This includes all the basic and additional elements, as appropriate, as outlined in U.S. federal regulations, 45 CFR 46.116 & 21 CFR 50.25 . It is recommended that sites develop their own site-specific ICF(s). To assist sites with developing their site-specific ICF(s), DAIDS works with the Protocol Teams to create sample informed consents (SIC) that contain all the specific elements required by the U.S. federal regulations, 45 CFR 46.116 & 21 CFR 50.25.

A CRS must submit to the DAIDS PRO a copy of all site-specific ICF(s) that will be used during the consent process at the site after review and approval by the IRB/EC and other applicable REs/Approving Entity (ies), and retain the original(s) on file at the site.

If some SIC forms provided with the protocol will *not* be needed at a CRS, (i.e., if a pregnancy ICF is not needed because pregnant women will not be enrolled), the CRS should document this either in the comments section of the ICF field of the DPRS or with a memo to the DAIDS PRO with the registration submission.

When an IRB/EC/RE/Approving Entity approves a site-specific ICF and the site contact information is left blank, the CRS must include a memo with their registration submission explaining that the CRS will insert the site-specific contact information prior to consenting participants.

If an IRB/EC/RE requires language in a site-specific ICF specific to the institution or based on local regulations/requirements, the site should include that information in the site-specific ICF and must provide documentation from IRB/EC/RE regarding the required language in the site-specific ICF. However, even though an IRB/EC/RE requires language in site-specific ICF, none of the basic and additional elements found in the Sample IC (SIC) should be removed. Refer to the Frequently Asked Questions on the DAIDS RSC website for additional information regarding the development of site-specific ICFs

If a CRS deletes or makes any substantive change to basic and/or additional elements as presented in the DAIDS-approved SIC, the IoR or designee for the clinical trial must provide written documentation to explain the deletions/change(s) at the time of registration submission to the DAIDS PRO.

All site-specific ICF(s) must be able to be linked to the current DAIDS approved version of the protocol. The DAIDS-required identifying information is:

- Complete Protocol Title for the current DAIDS-approved version of the protocol. The DAIDS PRO will accept a long or short title for those protocols which include both on the DAIDS-approved SIC forms.
- DAIDS ES and/or Network Protocol ID Number
- DAIDS Protocol Version Number from the final version of the protocol approved by DAIDS *AND/OR* the final version date of the protocol document approved by DAIDS.

NOTE: For version tracking purposes at the CRS (i.e., at the request of an IRB/EC and other applicable REs/approving entity (ies)), CRSs can specify the site (local) version number or version date of the site-specific ICF(s) in the header or footer of their site-specific ICF(s). However, the DAIDS protocol version number and/or the final version date of the DAIDS-approved protocol should remain on all site-specific ICFs as well.

NOTE: If any of the site-specific ICF(s) do not contain enough information to be linked to the most current DAIDS-approved version of the protocol, designated site personnel (i.e., CRS coordinator, IoR) and/or additional personnel listed in the DPRS will be sent a Materials Request notice that details the missing and/or corrected information/materials that must be submitted to the DAIDS PRO for registration processing to continue. The review process will not continue until the requested materials are received at the DAIDS PRO. For information on how to submit requested materials refer to Section VII, Sub Section D. i. - "Requested Materials" of this manual.

i. Types of ICFs and Protocol Registration requirements

Main ICF: The Main ICF issued for enrollment of participants into the protocol. The Main ICF should include all of the basic and appropriate additional elements as outlined in U.S. federal regulations, 45 CFR 46.116 & 21 CFR 50.25. The link to OHRP's guidance on informed consent form required elements can be found

here.

Screening and Stored Specimen ICFs: The following are DAIDS requirements regarding generic screening and stored specimen consent forms and protocol-specific screening consent forms:

Generic screening and stored specimen ICF: A generic screening and/or stored specimen ICF is an ICF that is developed by a CRS for its own purposes and not related to any DAIDS requirement and should NOT be submitted to the DAIDS PRO. The DAIDS PRO will NOT review or approve any such generic screening and/or stored specimen ICFs if they are submitted with registration materials.

Protocol-specific screening and stored specimen ICF: A protocol-specific screening and/or stored specimen ICF is an ICF developed for a specific protocol that is approved by DAIDS and is included as part of the final protocol and DAIDS-approved SICs. If the DAIDS-approved Main ICF includes screening procedures and stored specimen information and a CRS chooses to develop a separate protocol-specific screening and/or stored specimen ICF to be used at the site, then the screening and eligibility and/or stored specimen information can be removed from the site-specific main ICF. In this instance the CRS must submit *BOTH* the protocol-specific screening and/or stored specimen ICF and the site-specific main ICF to the DAIDS PRO for review and approval.

Short ICFs: If a CRS elects to use a short ICF in addition to the main ICF, the CRS must have a main ICF *OR* written summary that includes all of the required basic and appropriate additional elements which have been approved by the IRB/EC and has been submitted to the DAIDS PRO for registration. A CRS must receive a Registration Notification from the DAIDS PRO for all short form ICFs prior to implementation.

Sub-study ICFs: If a NIAID (DAIDS)-supported and/or-sponsored protocol includes a separate DAIDS-approved SIC for a sub-study that is part of the main protocol and the CRS anticipates participating in the sub-study, the CRS must include the sub-study site-specific ICF in their protocol registration submission. A CRS must receive a Registration Notification from the DAIDS PRO for all sub-study ICFs prior to implementation.

Pregnancy ICF: If a DAIDS-supported and/or sponsored protocol includes a DAIDS-approved SIC for women who become pregnant while on study and the CRS anticipates that some pregnant women may be included or followed on the study, the CRS must submit the site-specific pregnancy ICF to the DAIDS PRO.

Sites have the flexibility to combine the pregnancy ICF and the main ICF into one ICF, as long as the required information is still present and this approach is approved by the IRB/EC. If one or more ICFs are combined, there should be a

note to the DAIDS PRO documenting why one of the original consents is not included in the registration submission.

If the site will not follow or enroll pregnant women, the pregnancy ICF does not need to be submitted, and the site should document the plan not to include pregnant women with a note to the DAIDS PRO. A CRS must receive a Registration Notification from the DAIDS PRO for any pregnancy ICF prior to implementation.

Assents: The IRB/EC must determine that adequate provisions are made for soliciting the assent of children and/or adolescents when in the judgment of the IRB/EC the children and/or adolescents are capable of providing it, 45 CFR 46.408. The IRB/EC is responsible for determining the age of assent and for determining whether the use of an assent form is appropriate. A CRS must receive a Registration
Notification from the DAIDS PRO for all assents prior to implementation.

ii. Health Insurance Portability and Accountability Act (HIPAA) – Privacy Rule

The Privacy Rule is a U.S. federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information.

The DAIDS PRO does not review site-specific ICFs for information related to HIPAA. If the site-specific ICF(s) contains language pertaining to HIPAA authorization, the DAIDS PRO will NOT assess this language for Privacy Rule compliance. In addition, it is very important that confidentiality language included in the DAIDS-approved sample informed consent remain in the site-specific ICF even if this information is included in a separate HIPAA authorization form.

NOTE: The HIPAA regulations do not apply to non-U.S. CRSs.

Information related to the Privacy Rule can be found at the following HHS website.

V.CLINICALTRIALS.GOV INFORMED CONSENT REQUIREMENTS

ClinicalTrials.gov is the clinical trial registry databank maintained by the NIH National Library of Medicine (NLM) which was created by statute outlined in the Food and Drug Administration Amendments Act of 2007 (FDAAA). Through FDAAA, the U.S. Food & Drug Administration (FDA) amended current informed consent regulations (21 CFR 50.25) to now require that all informed consent documents for applicable drug (including biological products) and device clinical trials include a specific statement that clinical trial information will be entered into ClinicalTrials.gov.

As of December 1, 2011, for new protocols, the following language MUST be included in the DAIDS-approved sample informed consent (SIC) ONLY for applicable trials:

"A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

The DAIDS PRO will review site-specific ICFs for information related to clinicaltrials.gov. If the DAIDS-approved SIC contains the clinicaltrials.gov language, then the language MUST be in all site-specific informed consents for that study. Failure to include this language in applicable site-specific informed consents will result in a required corrections notification.

NOTE: Per U.S. federal regulations, this language cannot be modified.

NOTE: Participants do not need to be re-consented for existing or ongoing studies unless the IRB/EC determines otherwise.

NOTE: The required language can be translated into local language.

NOTE: If the inclusion of the ClinicalTrials.gov language is mandated by the IRB/EC/RE (for non-applicable trial), documentation from the IRB mandating the statement inclusion must be provided.

Information related to the informed consent requirement for clinicaltrials.gov can be found on the following HHS website.

VI. TRANSLATION REQUIREMENTS

For all documents that require translation to a language other than Spanish, a CRS must submit to the DAIDS PRO a copy of the DAIDS Protocol Registration Translation Confirmation Document, attesting that the translation is a true and accurate reflection of the local language documents that have been reviewed and approved by the IRB/EC and other REs/Approving Entity.

NOTE: Only one DAIDS Protocol Registration Translation Confirmation Document that attests to the accuracy of the translation of each language for all of the protocol registration documents listed below is required with each protocol registration submission.

NOTE: CRSs ARE NOT required to complete the DAIDS Protocol Registration Translation Confirmation Document for any protocol registration documents in Spanish.

An electronic copy of the DAIDS Translation Confirmation Document can be found on the DAIDS RSC web site under the "Protocol Registration" section.

i. Form FDA 1572, IoR Form, CVs, and Medical Licenses

All Form FDA 1572s, DAIDS IoR Forms, CVs and Medical Licenses must be prepared in English. Non-English versions of these documents will not be accepted by the DAIDS PRO.

ii. IRB/EC, other RE/Approving Entity, and IBC approval letters

All non-English IRB/EC, other applicable RE/Approving Entity, and IBC approval letter(s) must be translated into English, with the exception of Spanish. CRSs must submit copies of both the local language and translated English approval letter(s) to the DAIDS PRO.

NOTE: CRSs should provide an English translation of any other appropriate IRB/EC/RE/IBC documentation that explains changes/deletions in the site specific ICFs or that could assist the DAIDS PRO when reviewing registration materials.

iii. Site-specific ICFs

CRSs must prepare site-specific ICFs in all languages in which they will conduct informed consent discussions for each study. If CRSs elect to use short ICFs in addition to the Main ICF, the short ICF must also be prepared in all languages in which the informed consent discussions will be conducted. After approval by all applicable IRBs/ECs and REs, copies of the approved site-specific ICFs must be submitted to the DAIDS PRO.

If informed consent discussions will be conducted in English and another local language, including Spanish, the site-specific English and local language ICFs must be submitted to the DAIDS PRO. No back-translations are required by DAIDS.

If informed consent discussions will be conducted in a local language other than English or Spanish, site-specific local language ICFs must be submitted to the DAIDS PRO. Back-translations (into English) of the site-specific local language ICFs for which discussion will be conducted also must be submitted to the DAIDS PRO.

NOTE: If a DAIDS Clinical Trials Network has specific requirements regarding translation of site-specific ICFs, the CRS should follow those requirements as well as any applicable translation and back-translation requirements specified in institutional policies, the study protocol, and/or the network Manual of Operations.

NOTE: Site specific ICFs in languages that were not submitted with the original initial registration should be submitted as additional ICF language type within DPRS and will be considered initial registration in the newly submitted language type.

VII. PROTOCOL REGISTRATION SUBMISSIONS

Prior to implementing a protocol and enrolling participants, a CRS must receive final approval for the site-specific ICFs from the IRB/EC and other applicable REs/Approving Entity(ies). In addition, the CRS must successfully complete the DAIDS initial protocol registration process. However, successfully completing the DAIDS initial protocol registration process *does not* authorize a CRS to begin enrollment of participants. CRSs will be notified by the appropriate DAIDS scientific program (i.e., Program Officer), Operations Center or Data Management Center when enrollment may begin for a protocol.

Each CRS will complete the protocol registration process for all clinical research supported and/or sponsored by DAIDS that is reviewed by DAIDS Scientific Review Committees, namely the Prevention Sciences Review Committee (PSRC) and the Clinical Sciences Review Committee (CSRC) and if it is determined protocol Registration is required. Upon receiving final IRB/EC and other applicable RE/Approving Entity approval(s), the CRS will submit all required registration documents to the DAIDS PRO via the DAIDS DPRS.

Upon making *ANY* submission to the DAIDS PRO, a CRS will receive a Confirmation of Submission notice that indicates successful submission of materials to the DAIDS PRO. If a CRS does not receive a Confirmation of Submission notice within 24 - 48 hours of submitting materials, the CRS should contact the DAIDS PRO.

The CRS must place a copy of all final Protocol Registration notifications from the DAIDS PRO in the site's regulatory files. Refer to Section II - Definitions of this manual for a list of final registration notifications.

A. INITIAL REGISTRATION

A CRS that has *NOT PREVIOUSLY* received a Registration Notification from the DAIDS PRO for any version of the protocol must complete the initial protocol registration process.

If a CRS has previously received a DAIDS PRO Registration Notification for one language (i.e., English) and later submits registration documents for a new language (i.e., Spanish), the new language should be submitted as an Additional IC Language submission type but will be considered an initial registration as this is the first time the specific language has been submitted to the DAIDS PRO for review.

If a CRS has previously received a Registration Notification from the DAIDS PRO for one informed consent type (i.e., main, pregnancy) and later submits registration documents for a new informed consent type (i.e., stored specimen, short form), the new informed consent type should be submitted as an Additional IC Type but is considered an initial registration as this is the first time the informed consent form has been submitted to the DAIDS PRO for review.

NOTE: If a CRS has previously received a Registration Notification from the DAIDS PRO and is only submitting an additional language or informed consent type, the site is NOT required to resubmit the Form FDA 1572/DAIDS IoR Form and the IoR CV with the protocol registration submission.

The following documents must be submitted to the DAIDS PRO for all initial registration submissions:

- A copy of the Form FDA 1572 signed and dated by the IoR (for studies conducted under an IND) OR a copy of the DAIDS IoR Form signed and dated by the IoR (for non-IND studies)
- Investigator of Record CV and other required documentation (current medical license or equivalent)
- A copy of the CRS's IRB/EC and other applicable RE/Approving Entity approval letter(s) and any other appropriate documentation from the IRB/EC and other applicable REs/Approving Entity(ies). *NOTE: For examples of other appropriate IRB/EC/RE/Approving Entity documentation refer to section D, sub-section i - "IRB/EC/RE/Approving Entity approvals" of this manual.*
- A copy of the IRB/EC and other applicable RE/Approving Entity approved site-specific ICFs (all languages including English translations, if applicable).Refer to section V, "Translation Requirements" of this manual.
- A copy of the CRS's IBC approval letter, if applicable

NOTE: If an initial registration submission is missing any required documents or is incomplete, designated site personnel (i.e., CRS coordinator, IoR) and/or additional personnel listed in the DPRS will be sent a Requested Materials notice that details the missing and/or corrected information/materials that must be submitted to the DAIDS

PRO for registration processing to continue. The review process will not continue until the requested materials are received at the DAIDS PRO. For information on how to submit requested materials refer to Section VII, Sub Section D. i. "Requested Materials" of this manual.

When all required documents have been received and reviewed, a CRS will receive a Registration Notification from the DAIDS PRO that will include all languages and informed consent types that have been submitted. The Registration Notification from the DAIDS PRO indicates successful completion of the initial protocol registration process.

If a CRS receives a Registration with Required Corrections Notification, a CRS must make the required corrections and submit them to their IRB/EC for review and approval *OR* must submit justification for why the required correction(s) will not be made to the DAIDS PRO within 120 calendar days of the date the Registration with Required Corrections Notification was issued. For information on how to submit required corrections refer to Section VII, Subsection D. iii. -"Registrations with Required Corrections" of this manual.

NOTE: The 120 calendar days is for submission of IRB/EC approved corrections OR justifications for why the corrections will not be made to the DAIDS PRO.

Upon successful completion of the DAIDS PRO initial registration process, indicated when a CRS receives a Registration Notification or a Registration with Required Corrections Notification, a CRS will begin receiving safety information for the protocol (i.e., safety reports, safety memos, investigator's brochures, etc.) from the DAIDS RSC Safety Information Center.

If a site-specific ICF(s) does not include all the required basic and appropriate additional elements to comply with U.S. Federal Regulations and DAIDS policies, designated CRS personnel (i.e., CRS Coordinator, IoR) will be notified via a Disapproval Notification from the DAIDS PRO regarding the deficiencies. The Disapproval Notification will outline the deficiencies in the site-specific ICF(s) that must be revised/corrected before a final Registration Notification can be issued.

NOTE: A Disapproval Notification is not a final notification and DOES NOT indicate successful completion of the protocol registration process.

For information on the options a CRS has upon receipt of a Disapproval Notification from the DAIDS PRO, refer to Section VII, Sub Section .D. ii.- "Disapprovals" of this manual.

B. AMENDMENT REGISTRATIONS

i. Full Version Protocol Amendment Registration

A full version "Protocol Amendment" is a revision to a protocol made by the Protocol Team/Chair/Awardee that requires DAIDS review and final approval/sign-off before implementation. The changes to the protocol are incorporated into the protocol document and will result in a change to the DAIDS protocol version number (i.e., 2.0, 3.0, etc.). Sites should refer to the protocol document for information on the protocol registration process for full version protocol amendments.

CRSs should submit the amended protocol, DAIDS-approved SIC(s), and the amended site-specific ICF(s) to their IRBs/ECs and other applicable REs/Approving Entity(ies) for review and approval as soon as possible. Per the DAIDS Protocol Registration policy, submission to the local IRB/EC must take place within 45 calendar days for U.S. sites and 75 calendar days for non-U.S. sites of the date the amendment was approved by DAIDS and distributed to the sites.

NOTE: The 45 or 75 calendar day requirement for submission of full version protocol amendment registration materials is for local IRB/EC only.

Amendments including any revised site-specific ICF(s) must be implemented immediately upon CRS receipt of all required IRB/EC and RE approvals unless the amendment specifies otherwise. A CRS can implement the IRB approved revised ICF(s) immediately and DAIDS PRO approval notification is not required for amendments unless specified in the amendment.

The CRS may delay implementing an amendment when the IRB/EC/RE/Approving Entity approved amendment states the protocol changes will be implemented once specific operational issues (i.e., training on new procedures added in the amendment) are addressed. The IRB/EC/RE/Approving Entity documentation must be kept in the site's regulatory files for verification by monitors.

When the IRB/EC/RE/Approving Entity approved amendment and revised site-specific ICFs are not implemented immediately after final IRB/EC/RE/Approving Entity approval, sites may continue conducting protocol related interactions and interventions with already enrolled study participants under the previously approved version as long as the IoR has determined that this is in the participant's best interest. After receiving final IRB/EC/RE/Approving Entity approval and while operational issues are being addressed, new participants may only be enrolled under the previously approved version of the site-specific ICFs when the IRB/EC/RE/Approving Entity has determined this is acceptable. The IRB/EC/RE/Approving Entity determination should be documented in writing and filed in the site's regulatory files.

A CRS must submit full version protocol amendment registration documents to the DAIDS PRO within 14 calendar days of the CRS's receipt of all the required final written IRB/EC approval documentation for the amendment. The submitted documents must include documentation of the date the amended protocol and any revised site-specific

ICF(s) were submitted to the local IRB/EC. The DAIDS PRO will not review any revised site-specific ICF(s) unless otherwise noted in the protocol.

NOTE: Sites are strongly advised to document the date the CRS receives each final IRB/EC/RE/Approving Entity approval letter. Documenting this information supports the CRS's action to comply with the DAIDS protocol registration policy regarding submission of amendment and LoA registration materials to the DAIDS PRO within 14 calendar days of receipt of all final IRB/EC/RE/Approving Entity approval letters. This documentation should be kept in the site's regulatory files for verification by monitors.

If a CRS has received a Registration Notification from the DAIDS PRO for an earlier version of the protocol including all informed consent types and specific language(s), then the registration to a new version of the protocol would be a full version protocol amendment. A CRS that has never received a Registration Notification from the DAIDS PRO for any version of the protocol, language or informed consent type must follow the instructions for Initial Protocol Registration detailed in Section VI, sub-section A of this manual.

NOTE: If a CRS has submitted a registration packet for a previous version of a protocol prior to a new version being approved by DAIDS and distribution to the sites, the DAIDS PRO will continue to process the registration for the earlier version.

The following documentation must be submitted to the DAIDS PRO for all full version protocol amendment registration submissions:

- A copy of the site's IRB/EC and other applicable RE/*Approving Entity* approval letter(s) and any other appropriate documentation from the IRB/EC and other applicable REs*/Approving Entity(ies) listed on the FDA Form 1572/DAIDs IoR Form*. *NOTE: For examples of other appropriate IRB/EC/RE documentation refer to section D, sub-section i - "IRB/EC/RE/Approving Entity approvals" of this manual.*
- Documentation of the date the amended protocol and any revised site- specific ICF(s) were submitted to the local IRB/EC
- A copy of the IRB/EC and other applicable RE/*Approving Entity* approved site ICF(s) (all languages including English translations, if applicable).Refer to section V, "Translation Requirements" of this manual.
- A copy of the CRS's IBC approval letter, if applicable

NOTE: Examples of appropriate documentation of the date the amended protocol and any revised site-specific ICF(s) were submitted to the local IRB/EC includes but is not limited to:

- *the submission letter from the site to the IRB/EC a memo from the IoR or designee specifying the date of submission to the IRB/EC*

NOTE: If the IRB/EC determines that a full version protocol amendment does not require changes to the site-specific ICF(s), the CRS should document this either in the comments section of the ICF field of the DPRS or with a memo to the DAIDS PRO with

the full version protocol amendment registration submission. Otherwise, all previously registered ICF types must be submitted with the amended version or Justification for the omission of ICF type must be provided.

NOTE: Re-consenting participants as a result of amendment (Change or new information that may affect subject participation) is the decision of the CRS's IRB/EC. CRSs should follow their IRB/EC/RE/Approving Entity instructions for re- consenting participants as a result of the amendment.

NOTE: If a full version protocol amendment registration submission is missing any required documents or is incomplete, designated site personnel (i.e., CRS coordinator, IoR) and/or additional personnel listed in the DPRS will be sent a Requested Materials notice that details the missing and/or corrected information/materials that must be submitted to the DAIDS PRO. For information on how to submit requested materials refer to Section VII, Sub Section D. i. - "Requested Materials" of this manual.

When all required documents have been received and approved, a CRS will receive a Registration Notification from the DAIDS PRO that will include all languages and informed consent types that have been submitted. The Registration Notification from the DAIDS PRO indicates successful completion of the full version protocol amendment registration process.

NOTE - A Registration Notification from the DAIDS PRO is NOT required prior to implementing a full version protocol amendment at a CRS.

NOTE: Once a new version of a protocol is approved by DAIDS and has been distributed to the sites, a CRS will no longer be able to register for a previous version.

ii. Letter of Amendment (LoA) Registration

CRSs should submit the LoA and any amended site-specific ICF(s) to their IRBs/ECs and other applicable REs/Approving Entity(ies) for review and approval as soon as possible. Per the DAIDS Protocol Registration policy, submission to the local IRB/EC must take place within 45 calendar days for U.S. sites and 75 calendar days for non-U.S. sites of the date the LoA was approved by DAIDS and distributed to the sites.

NOTE: The 45 or 75 calendar day requirement for submission of LoA materials is for local IRB/EC only.

NOTE: Protocol revisions resulting from LoAs DO NOT affect the DAIDS protocol version. For version tracking purposes at the CRS (i.e., at the request of an IRB/EC and other applicable REs/Approving Entity(ies)), CRSs can specify the site (local version number or version date of the site-specific ICF(s) in the header or footer of their site-specific ICF(s). However, the DAIDS protocol version number and/or the final version date of the DAIDS-approved protocol should remain on all site-specific ICFs as well.

LoAs including any revised site-specific ICF(s) must be implemented immediately upon CRS receipt of all required IRB/EC and RE/Approving Entity approvals unless the LoA specifies otherwise and DAIDS PRO approval notification is not required for LoA unless specified in the LoA.

The CRS may delay implementing a LoA when the IRB/EC/RE/Approving Entity approved LoA states the protocol changes will be implemented once specific operational issues (i.e., training on new procedures added in the LoA) are addressed. The IRB/EC/RE documentation must be kept in the site's regulatory files for verification by monitors.

When the IRB/EC/RE/Approving Entity approved LoA and revised site-specific ICFs are not implemented immediately after final IRB/EC/RE approval, sites may continue conducting protocol related interactions and interventions with already enrolled study participants under the previously approved version as long as the IoR has determined that this is in the participant's best interest. After receiving final IRB/EC/RE/Approving Entity approval and while operational issues are being addressed, new participants may only be enrolled under the previously approved version of the site-specific ICFs when the IRB/EC/RE has determined this is acceptable. The IRB/EC/RE/Approving Entity determination should be documented in writing and filed in the site's regulatory files.

A CRS must submit LoA registration documents to the DAIDS PRO within 14 calendar days of the CRS's receipt of all the required final written IRB/EC approval documentation for the LoA. The submitted documents must include documentation of the date the LoA and any revised site-specific ICF(s) were submitted to the local IRB/EC. The DAIDS PRO will not review any revised site-specific ICF(s) unless otherwise noted in the protocol.

NOTE: Sites are strongly advised to document the date the CRS receives each final IRB/EC/RE approval letter. Documenting this information supports the CRS's action to comply with the DAIDS protocol registration policy regarding submission of amendment and LoA registration materials to the DAIDS PRO within 14 calendar days of receipt of all final IRB/EC/RE/Approving Entity approval letters. This documentation should be kept in the site's regulatory files for verification by monitors.

The following documentation must be submitted to the DAIDS PRO for all LoA registration submissions:

- A copy of the site's IRB/EC and other applicable RE*/approving entity* approval letter(s) and any other appropriate documentation from the IRB/EC and other applicable REs*/Approving Entity(ies) listed on the FDA Form 1572/DAIDs IoR Form*. *NOTE: For examples of other appropriate IRB/EC/RE documentation refer to section D, sub-section i. - "IRB/EC/RE/Approving Entity approvals" of this manual.* Documentation of the date the LoA and any revised site-specific ICF(s) were submitted to the local IRB/EC

- A copy of the IRB/EC and other applicable RE/Approving Entity approved site ICF(s) (all languages including English translations, if applicable). Refer to section v, “Translation Requirements” of this manual.
- A copy of the CRS's IBC approval letter, if applicable.

NOTE: Examples of appropriate documentation of the date the LoA and any revised site-specific ICF(s) were submitted to the local IRB/EC includes but is not limited to:

- *the submission letter from the site to the IRB/EC*
- *a memo from the IoR or designee specifying the date of submission to the IRB/EC*

NOTE: Re-consenting participants as a result of LoA (Change or new information that may affect subject participation) is the decision of the CRS’s IRB/EC. CRSs should follow their IRB/EC/RE/Approving Entity instructions for re- consenting participants as a result of the LoA.

NOTE: If a LoA registration submission is missing any required documents or is incomplete, designated site personnel (i.e., CRS coordinator, IoR) and/or additional personnel listed in the DPRS will be sent a Requested Materials notice that details the missing and/or corrected information/materials that must be submitted to the DAIDS PRO. For information on how to submit requested materials refer to Section VII, Sub Section D. i. - “Requested Materials” of this manual.

When all required document have been received, a CRS will receive a Registration Notification from the DAIDS PRO for each LoA registration submission. The Registration Notification from the DAIDS PRO indicates successful completion of the LoA registration process.

NOTE: LoAs are considered individual amendments to a protocol. Thus, sites must protocol register to all LoAs independent of initial and amendment registrations. If a site elects to include a LoA as part of another submission to the IRB/EC/RE/Approving Entity (i.e., continuing review, amendment review, and initial review) the site must clearly document all the materials that are being submitted to the IRB/EC/RE/Approving Entity for review and approval. It is a CRS’s responsibility to inform the DAIDS PRO regarding all registrations (i.e., LoA, amendment, initial, continuing review) the site is requesting at the time of submission. Failure to register to a LoA may result in a CRS being out of compliance with DAIDS policies and may result in delays in implementing operational changes triggered by LoA registrations.

NOTE: All submission types (Initial, Amendment, LoA) must be submitted independently.

NOTE: A Registration Notification from the DAIDS PRO is NOT required prior to implementing a LoA at a CRS.

C. SUB-STUDY REGISTRATION

A CRS must protocol register to all sub-studies that have a protocol number and/or DAIDS protocol identification number if a site anticipates enrolling participants. A CRS will receive a registration notification for each sub-study that is submitted for protocol registration. CRSs must register to embedded sub-studies as part of the main study registrations. Registration for embedded sub-studies is required for all versions of the main study unless the site informs the DAIDS PRO that they are no longer participating in the embedded sub-study and request deregistration. CRSs should register to stand alone sub-studies as separate registrations and can be done independently from the main study registration. A CRS registering to a stand-alone sub-study is required to submit all required documents (i.e., IRB/EC approval letter(s), site-specific consent(s), Form FDA 1572 and/or DAIDS IoR Form, and IoR CV) when registering to a stand- alone sub-study.

NOTE: For an explanation of embedded and stand-alone sub-studies refer to Section II, "Definitions" of this manual.

D. OTHER SUBMISSIONS

Other submissions are *ANY* submissions made to the DAIDS PRO that are not Initial, Amendment or LoA registrations. Below is detailed information on requirements related to "other submissions" a CRS may submit to the DAIDS PRO.

i. Requested Materials

Requested materials are additional and/or corrected materials requested by the DAIDS PRO as a result of an incomplete submission to the DAIDS PRO. If any required documents are missing, incomplete, or are inaccurate, the DAIDS PRO will issue a Requested Materials notice to designated CRS personnel (i.e. CRS Coordinator, IoR). This request *will* stop the registration review process.

NOTE: The Protocol Registration review process will not continue until all Requested Materials have been received by the DAIDS PRO.

The following documentation must be submitted to the DAIDS PRO in response to a Materials Request Notification as a "materials Request" type submission

- A copy of the requested materials

A CRS will receive a Confirmation of Submission notice once the requested materials have been received by the DAIDS PRO.

ii. Disapprovals

If it is determined during the DAIDS PRO review process that a site-specific ICF(s) does not include all the required basic and appropriate additional elements to comply with U.S. Federal Regulations and DAIDS policies, designated CRS personnel (i.e., CRS Coordinator, IoR) will be notified via a Disapproval Notification from the DAIDS PRO regarding the deficiencies. The disapproval notification will outline the deficiencies in the site-specific ICF(s) that must be revised or corrected before a final Registration Notification can be issued.

Upon receipt of a Disapproval Notification from the DAIDS PRO a CRS has two options:

1. Make the necessary revisions/corrections and submit the revised document(s) to their IRB/EC and other applicable RE approval(s) for review and approval. Upon receiving final IRB/EC/RE approval for the revised document(s) the CRS must make a "Corrected Materials" submission to the DAIDS PRO.

   OR

2. Submit justification for the omission/changes to the DAIDS PRO via a request for Disapproval Reversal

Under Option 1 - The following documentation must be submitted to the DAIDS PRO as “Corrected Materials” once a CRS receives final IRB/EC and other applicable RE/Approving Entity approval for the revised document(s):

- A copy of the site’s IRB/EC and other applicable RE approval letter(s) and any other appropriate documentation from the IRB/EC other applicable REs/Approving Entity(ies). *NOTE: For examples of other appropriate IRB/EC/RE documentation refer to section D, sub-section i. “IRB/EC approvals” of this manual.*
- A copy of the IRB/EC and other applicable RE/Approving Entity approved revised site-specific ICF(s)

When ALL required documents have been received and it is confirmed that the required corrections have been made, the DAIDS PRO will issue a Registration Notification.

Under Option 2 - If a CRS believes that a Disapproval Notification has been issued in error, the CRS can submit a request for Disapproval Reversal. A CRS must provide justification and/or documentation explaining why the disapproval should be reversed.

The following documentation must be submitted to the DAIDS PRO to request a disapproval reversal:

- Written justification and/or a copy of any documentation supporting the CRS's request for the disapproval reversal

A CRS will be notified within 4 business working days as to whether or not the disapproval will be reversed via e-mail from the DAIDS PRO.

iii. Registrations with Required Corrections

If a CRS receives a Registration with Required Corrections Notification, a CRS must make the required corrections and submit them to their IRB/EC/RE/Approving Entity for review and approval *OR* must submit justification for why the required corrections will not be made within 120 calendar days of the date the Registration with Required Corrections Notification was issued.

A Registration with Required Corrections Notification indicates that a CRS may begin using the site-specific ICFs after protocol activation by the appropriate Operations Center, Data Management/Statistical Center or DAIDS Program.

Upon receipt of a Registration with Required Correction Notification from the DAIDS PRO a CRS has two options:

1. Make the necessary required corrections and submit them to their IRB/EC for review and approval. Upon receiving final IRB/EC and other applicable RE/Approving Entity approval for the corrected document(s) the CRS must make a "Corrected Materials" submission to the DAIDS PRO.

   OR

2. Submit justification for the omission/changes via a "Corrected Materials" submission to the DAIDS PRO.

Under Option 1 - The following documentation must be submitted to the DAIDS PRO as "Corrected Materials", once a CRS receives final IRB/EC and other applicable RE approval for the corrected document(s):

- A copy of the site's IRB/EC and other applicable RE/Approving Entity approval letter(s) and any other appropriate documentation from the IRB/EC other applicable REs/Approving Entity(ies).
- A copy of the IRB/EC and other applicable RE/Approving Entity approved revised/corrected site-specific ICF(s)

NOTE: For examples of other appropriate IRB/EC/RE/Approving Entity documentation refer to section D, sub-section i "IRB/EC approvals" of this manual.

Under Option 2 - If a CRS has believes that a Registration with Required Corrections Notification has been issued in error, the CRS can submit justification and /or documentation explaining why the Registration with Required Corrections Notification should be reversed.

The following documentation must be submitted to the DAIDS PRO as "Corrected Materials":

- Written justification and/or a copy of any documentation supporting the CRS's request for the Registration with Required Corrections reversal.

For Option 1 and 2, a CRS will receive an Approval of Required Corrections Notification from the DAIDS PRO when all the required corrections has been reviewed and approved. The official registration date will remain the date the Registration with Required Correction Notification was issued.

iv. Administrative Registration

Administrative registrations should occur when a site is not recruiting participants in a NIAID (DAIDS)-supported and/or -sponsored clinical trial but has administrative functions only. Protocol/Grant PI/Protocol Chair/Co-Chair's routinely make substantial study interventions (decisions and interpretations) that affect study participants even though participants may not be enrolled or seen at the Protocol/Grant PI/Protocol Chair/Co-Chair's CRS. As a result, the Protocol/Grant PI/ Protocol Chair/Co-Chair's institutions are considered engaged with the research and must assure compliance with applicable Department of Health and Human Services (DHHS) regulations. For more information on engagement refer to the OHRP guidance document.

Based on U.S. federal regulation 45 CFR 46.103(a), "each institution engaged" in human subject research that is supported and/or sponsored by the DHHS must provide the OHRP with a satisfactory Assurance of Compliance with the regulations, unless the research is exempt under U.S. federal regulation 45 CFR 46.101(b).

For all administrative registrations, DAIDS requires that that the Protocol/Grant PI/Protocol Chair/Co-Chair consults with their IRB/EC and receive documentation in writing of the IRB/EC's decision concerning their protocol review and approval. At least two different kinds of decisions can be made:

1) IRB/EC wants to be involved in reviewing and approving the protocol.
2) IRB/EC does not want to be involved in reviewing and approving the protocol and will rely on another IRB/EC, designated on the Federal Wide Assurance (FWA), for review and approval.

DAIDS will honor the decision of the IRB/EC. The Protocol/Grant PI/ Protocol Chair/Co-Chair (s) need to consult with their IRB/EC and obtain written documentation of the IRB/EC's decision regarding their review and approval of the protocol in order to comply with U.S. federal regulations.

Upon receipt of final approval and/or documentation from the IRB/EC, an administrative registration submission should be made to the DAIDS PRO.

The following documentation must be submitted to the DAIDS PRO for all Administrative Registrations:

- A copy of the IRB/EC approval letter *AND* any other appropriate documentation from the IRB/EC including the IRB/EC decision regarding protocol review and approval. *NOTE: For examples of other appropriate IRB/EC/RE/Approving Entity documentation refer to section D, sub-section i "IRB/EC approvals" of this manual.*
- A copy of the Form FDA 1572 signed and dated by the Protocol/Grant PI/Protocol Chair/Co-Chair (for studies conducted under an IND) *OR* a copy of the DAIDS IoR Form signed and dated by the Protocol Protocol/Grant PI/ Protocol Chair/Co-Chair (for non-IND studies)
- A copy of the Protocol/Grant PI/Protocol Chair/Co-Chair CV and corresponding Medical license/equivalent

A CRS will receive a Registration Notification from the DAIDS PRO for each administrative registration submission when all required documents have been received. The Registration Notification from the DAIDS PRO indicates successful completion of the administrative registration process.

v. Change of Investigator of Record (IoR)

When there is a change in the IoR listed in Section 1 on the Form FDA 1572 or DAIDS IoR Form, a CRS should submit a copy of the revised Form FDA 1572 or the revised DAIDS IoR Form to the DAIDS PRO. To officially change the IoR for a protocol(s), the CRS must submit the documentation within 30 calendar days of the CRS's notification that the current IoR will no longer serve as the IoR for the study.

The following documentation should be submitted to the DAIDS PRO for all Change of IoR requests:

- Memo requesting a change of IoR
- A copy of the new Form FDA 1572 signed and dated by the new IoR (for studies conducted under an IND) *OR* a copy of the new DAIDS IoR Form signed and dated by the new IoR (for non-IND studies)
- CV for the new IoR and other required documentation (current medical license or equivalent)

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

NOTE: The Change of IoR is NOT official until the CRS receives a Change of IoR Approval Notification from the DAIDS PRO.

NOTE: A CRS must notify their DAIDS Office for Clinical Site Oversight (OCSO) representative and/or DAIDS Program Officer when there is a change in CRS Leader or other key CRS site personnel and/or contact information.

vi. Continuing/Annual Review

The DHHS regulations, 45 CFR 46.109(e) require that all DHHS supported research undergo continuing IRB/EC review at intervals appropriate to the degree of risk, but NOT LESS than once per year. Continuing review must be performed prior to the expiration date specified on the IRB/EC approval letter(s) and/or site-specific ICFs. The frequency of ongoing reviews should be documented in IRB/EC policies and procedures and may be protocol/study specific. CRSs can visit the OHRP website for additional guidance related to continuing review.

CRSs participating in NIAID (DAIDS)-supported and/or -sponsored clinical trials, reviewed by the DAIDS Scientific Review Committees and are protocol registered are required to submit documentation of IRB/EC Continuing/Annual review approval to the DAIDS PRO. Continuing/Annual review documentation must be submitted to the DAIDS PRO within 14 days of the CRS receiving final written documentation of IRB/EC Continuing/Annual review approval. The IRB/EC approval of continuing review must be a final approval and not require any modifications or further input by the CRS.

The following documents must be submitted to the DAIDS PRO for all continuing/annual review submissions:

- A copy of the IRB/EC Continuing/Annual review approval letter *AND* any other appropriate documentation from the IRB/EC. *NOTE: For examples of other appropriate IRB/EC/RE/Approving Entity documentation refer to section D, sub-section i "IRB/EC approvals" of this manual.*
- A copy of the IRB/EC approved site-specific ICF(s) if revised at the time of Continuing/Annual review

NOTE: All IRB/EC approval letters for Continuing/Annual review must state that the approval is for continuing review (i.e., similar terminology is acceptable: yearly review, annual review)

NOTE: Documentation of IRB/EC receipt of continuing review request alone does not satisfy the DHHS requirement regarding documentation of Continuing/Annual review and approval by the IRB/EC.

NOTE: The DAIDS PRO will not review any revised site-specific ICF(s) submitted with the continuing/annual review registration submission.

CRSs will only be sent a Confirmation of Submission notice that indicates continuing/annual review materials have been received by the DAIDS PRO. CRSs will *NOT* receive any additional notifications from the DAIDS PRO for Continuing/Annual review documentation unless there is a problem with the documentation submitted (i.e., incomplete packet or inappropriate review by the IRB/EC). If problems are noted, the DAIDs PRO will follow-up via e-mail to inform the CRS about the deficiencies and to request corrected continuing/annual review documentation.

If a CRS's IRB/EC procedures for expedited review deviate from those as specified in OHRP guidance (i.e., specific pre-approved country procedures), then the CRS must provide documentation of the IRB/EC procedures to the DAIDS PRO at the same time the CRS submits their IRB/EC Continuing/Annual review approval documents. In addition, documentation of any change in timing of the IRB/EC review procedure for Continuing /Annual reviews for the CRS must be submitted to the DAIDS PRO along with the final IRB/EC Continuing/Annual review approval letter(s).

Lapses in Continuing Review

Per the DHHS regulations 45 CFR 46.103(b) & 46.109(e) and OHRP guidance on continuing review, if there is a lapse in continuing review (i.e., If an investigator has failed to provide continuing review information to their IRB/EC or the IRB/EC has not reviewed and approved a research study by the Continuing/Annual review date specified by the IRB/EC), the research at the CRS must stop, unless the IRB/EC finds that it is in the best interest of individual participants to continue participating in the research interventions or interaction. Enrollment of new participants cannot occur after the expiration of IRB/EC approval(s).

CRSs should contact their DAIDS Office for Clinical Site Oversight (OCSO) representative and/or DAIDS Program Officer when there is any lapse and for additional guidance and information.

CRSs should submit IRB/EC lapse documentation (i.e., the site's documentation of the lapse to the IRB/EC and the IRB/EC's response) to the DAIDS PRO.

vii. Site Initiated Revisions to Site Informed Consent Forms (ICFs)

Modifications to a CRS's site-specific ICFs are considered site initiated when the changes are made as a result of new information or at the request of the IRB/EC and other applicable REs/Approving Entity(ies).

Revisions to a CRS's site-specific ICFs are only considered site-initiated when revisions have been made after the CRS has received a Registration Notification from the DAIDS PRO for the most current DAIDS-approved protocol version. Any changes made to a CRS's ICF(s) prior to receiving a Registration Notification from the DAIDS will be considered part of the CRS's initial or amendment registration. For additional information on initial and amendment registration submissions refer to Section VI, Sub-Sections A - "Initial Registration" and B - "Amendment Registration" of this manual.

Site-initiated revisions *DO NOT* affect the final DAIDS protocol version number and CRSs must be sure that the correct DAIDS protocol version number, remains on all site ICF(s). For version tracking purposes at the CRS, CRSs can specify the site (local) version number or version date of the site-specific ICF(s) in the header or footer of their site-specific ICF(s). However, the final DAIDS protocol version number and/or final version date of the protocol document approved by DAIDS should remain on all site-specific ICFs as well.

The following documentation must be submitted to the DAIDS PRO for all site-initiated revised ICFs:

- A copy of the site-initiated revised ICF(s)
- A copy of the site's IRB/EC and other applicable RE/Approving Entity approval letter(s) and any other appropriate documentation from the IRB/EC other applicable REs/Approving Entity(ies).

NOTE: For examples of other appropriate IRB/EC/RE/Approving Entity documentation refer to section D, sub-section i "IRB/EC approvals" of this manual.

NOTE: If a site initiated revised ICF submission is missing any required documents or is incomplete, designated site personnel (i.e., CRS coordinator, IoR) and/or additional personnel listed in the DPRS will be sent a Requested Materials notice that details the missing and/or corrected information/materials that must be submitted to the DAIDS PRO. For information on how to submit requested materials refer to Section VII, Sub Section D .i. - "Requested Materials" of this manual.

Once the CRS receives approval from their IRB/EC and other applicable REs/Approving Entity(ies), the CRS may implement the revised site-specific ICFs immediately. The DAIDS PRO will not review the site initiated revisions to CRS's ICFs.

CRSs will be sent a Confirmation of Submission notice that indicates materials have been received by the DAIDS PRO. CRSs will *NOT* receive any additional notifications from the DAIDS PRO for site initiated revisions to site-specific ICFs.

viii. Updated Form FDA 1572 or DAIDS IoR Form

When there is *ANY* major change to the information listed on the Form FDA 1572/DAIDS IoR Form submitted to the DAIDS PRO, a CRS should submit an updated Form FDA 1572 (IND studies) or DAIDS IoR Form (Non-IND studies) to the DAIDS PRO within 30 calendar days.

The following documentation should be submitted to the DAIDS PRO for all Updated Form FDA 1572s/DAIDS IoR Forms:

- A copy of the updated Form FDA 1572 signed and dated by the IoR (for studies conducted under an IND)

OR

- A copy of the updated DAIDS IoR Form signed and dated by the IoR (for non-IND studies)

NOTE: If there is a Change of IoR (listed in Section 1 of either form), refer to Section VI, Sub-Section D. v - "Change of Investigator of Record" of this manual.

NOTE: CRSs should submit a copy of the signed and dated Form FDA 1572/DAIDS IoR Form to the DAIDS PRO and retain the original version in their regulatory files at the site.

CRSs will be sent a Confirmation of Submission notice that indicates materials have been received by the DAIDS PRO. CRSs will *NOT* receive any additional notifications from the DAIDS PRO for updated Form FDA 1572s or DAIDS IoR Form unless the updated document(s) results in a Change of IoR at the CRS.

ix. Deregistration

Any CRS that has completed the DAIDS protocol registration process for a protocol (main or sub-study), must complete the DAIDS deregistration process for each protocol to which it is registered.

NOTE: Deregistration is NOT automatic when a study is completed.

Deregistration can occur when:

- The CRS no longer has participants on study (all follow-up has been completed) and does not plan to enroll additional subjects
- If no participants were ever enrolled at the CRS and the study has closed to accrual.

The DAIDS deregistration process is independent of a CRS's closure/termination of a study at their IRB/EC. The IRB/EC's determination to close or terminate a study is *NOT* required for a CRS to deregister with DAIDS. Completion of the DAIDS deregistration process indicates that a CRS's participation in a study is complete but does not reflect the closure of a multi-center study at all CRSs participating in the study.

If a CRS plans to complete the DAIDS deregistration process for a study but will not be closing/terminating the study at their IRB/EC, the CRS should consult its IRB/EC to confirm any requirements and/or standard operating procedures that must be met prior to deregistration. A CRS's IRB/EC may require the continued submission of safety information and/or other data for the study. In this case, deregistration with DAIDS PRO should *NOT* be done until the study has been completed at all participating sites.

In addition, a CRS should contact their DAIDS Clinical Trials Network or DAIDS Program Officer to confirm any protocol, network and/or DAIDS specific requirements prior to deregistering with the DAIDS PRO and/or closing/terminating the study with the IRB/EC.

The following documentation must be submitted to the DAIDS PRO for all deregistration requests:

- Memo stating that the CRS no longer intends to participate in the protocol(s)

AND/OR

- A Copy of the IRB/EC closure/termination letter for the protocol if the protocol has been closed with the IRB/EC at the time of deregistration

A CRS will receive a Deregistration Notification from the DAIDS PRO when deregistration has been reviewed and approved by the DAIDS PRO.

NOTE: A CRS is not considered deregistered until a Deregistration Notification has been issued by the DAIDS PRO.

Once a CRS receives a Deregistration Notification for a protocol, the CRS is no longer required to submit any additional protocol registration documents to the DAIDS PRO if the protocol amends. A CRS must continue to follow their IRB/EC requirements for submission of documents if the protocol has not been closed/terminated with the IRB/EC.

Upon completion of the DAIDS deregistration process, a CRS will no longer receive safety information (i.e., safety reports, safety memos, investigator's brochures) from the DAIDS RSC Safety Information Center.

Additional guidance is available regarding the DAIDS registration process along with a summary of site responsibilities once deregistration is complete. This information is located on the RSC web site under the "Protocol Registration" section.

VIII. APPENDIX A - INSTRUCTIONS ON HOW TO ACCESS & SUBMIT PROTOCOL REGISTRATION MATERIALS THROUGH THE DAIDS PROTOCOL REGISTRATION SYSTEM (DPRS)

How do I gain access to DPRS?

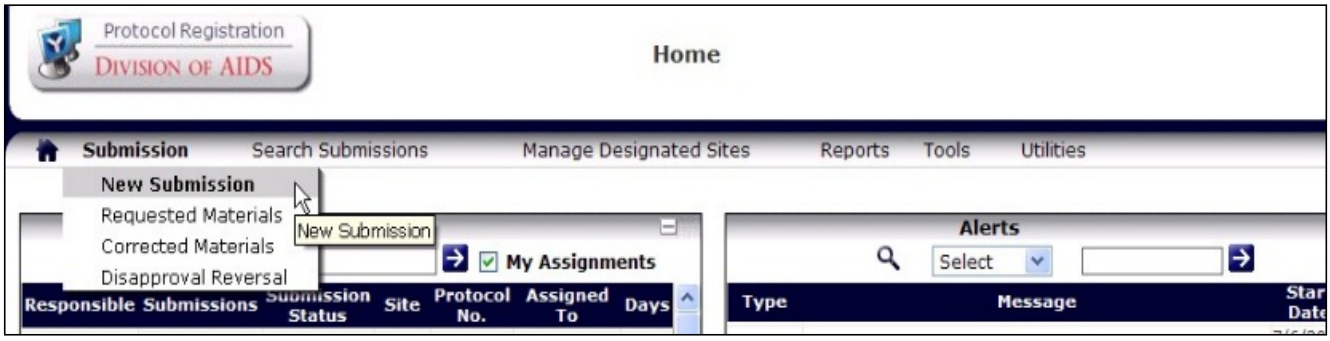
1. DPRS can be accessed via the DAIDS Learning Portal. DPRS Training completion is required to gain DPRS access. Log into the DAIDS Learning Management System (LMS) with your user name and password. Then enter DPRS into the search field, and select the DPRS training course. If you do not have a DAIDS LMS account click here to request account access.
2. Once the DPRS training has been completed, DPRS user log-in and password will be sent to the trainee. If the training has been completed, but have not received DPRS login details yet, contact DAIDS-ES Support at DAIDS-ESSupport@niaid.nih.gov.

How do I access the New Submission screen?

1. Go to the DAIDS Protocol Registration Page. Enter your user name and password and click Login.

2. From the Home Page, click Submission on the main navigation bar and then click New Submission from the drop-down menu, which takes you to the New Submission page.

Figure 1: New Submission Option



How do I complete the Site Submission process?

1. **Enter the Submission Details**: Enter the appropriate information under the **Site & Protocol details** heading. Click the LOV icon to select the Site, IoR and Protocol No. Click the list of values to select the version/LOA.

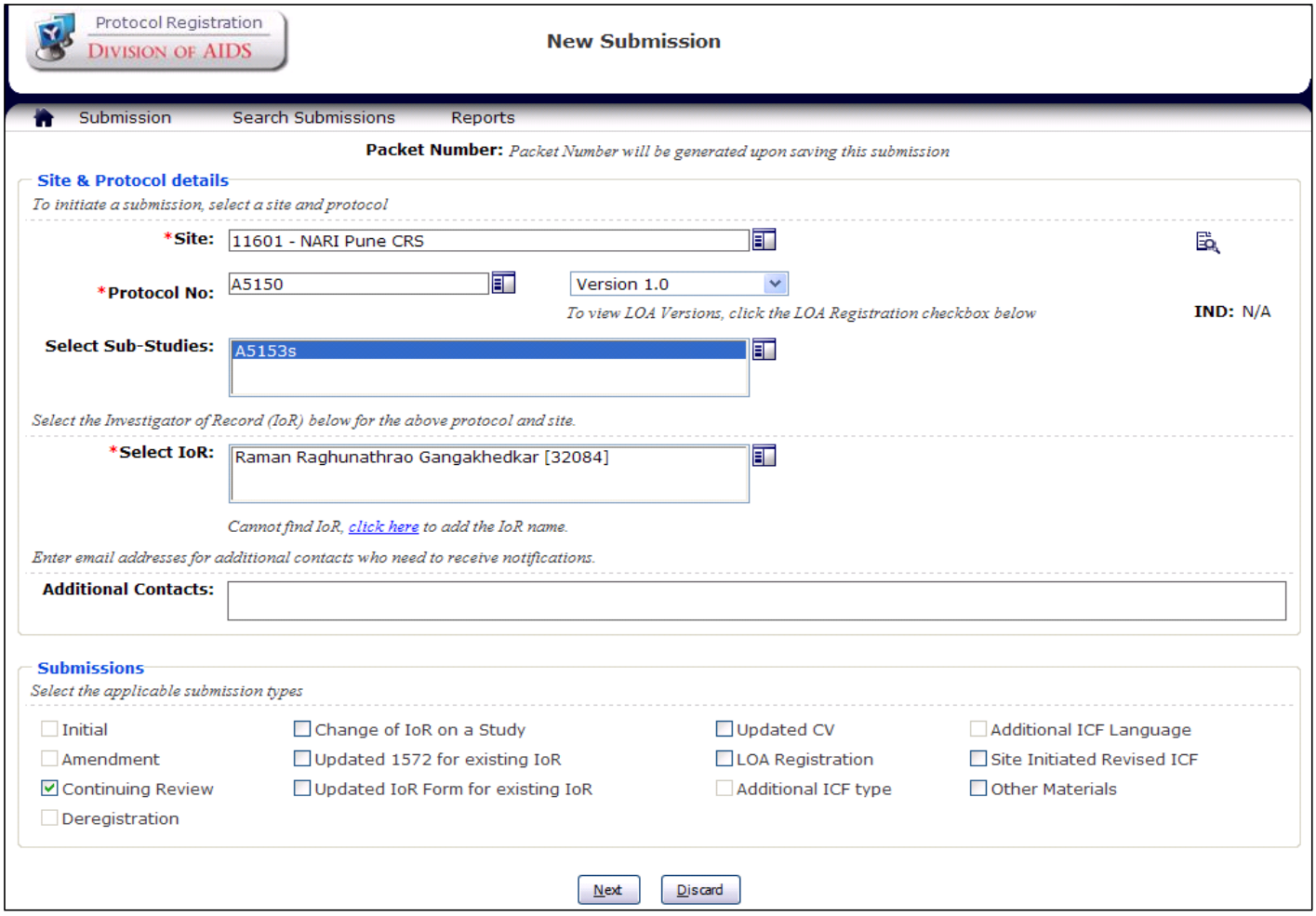
2. **Select Sub-Studies:** This list of values displays all sub-studies associated with the study. Select a sub-study displayed to submit materials for the sub-study along with the study. The packet will be created when the main study is submitted.

3. **Submissions:** Select the appropriate checkboxes under the Submissions heading.

Note: The system selects the same submission type for the sub-study as on the main study.

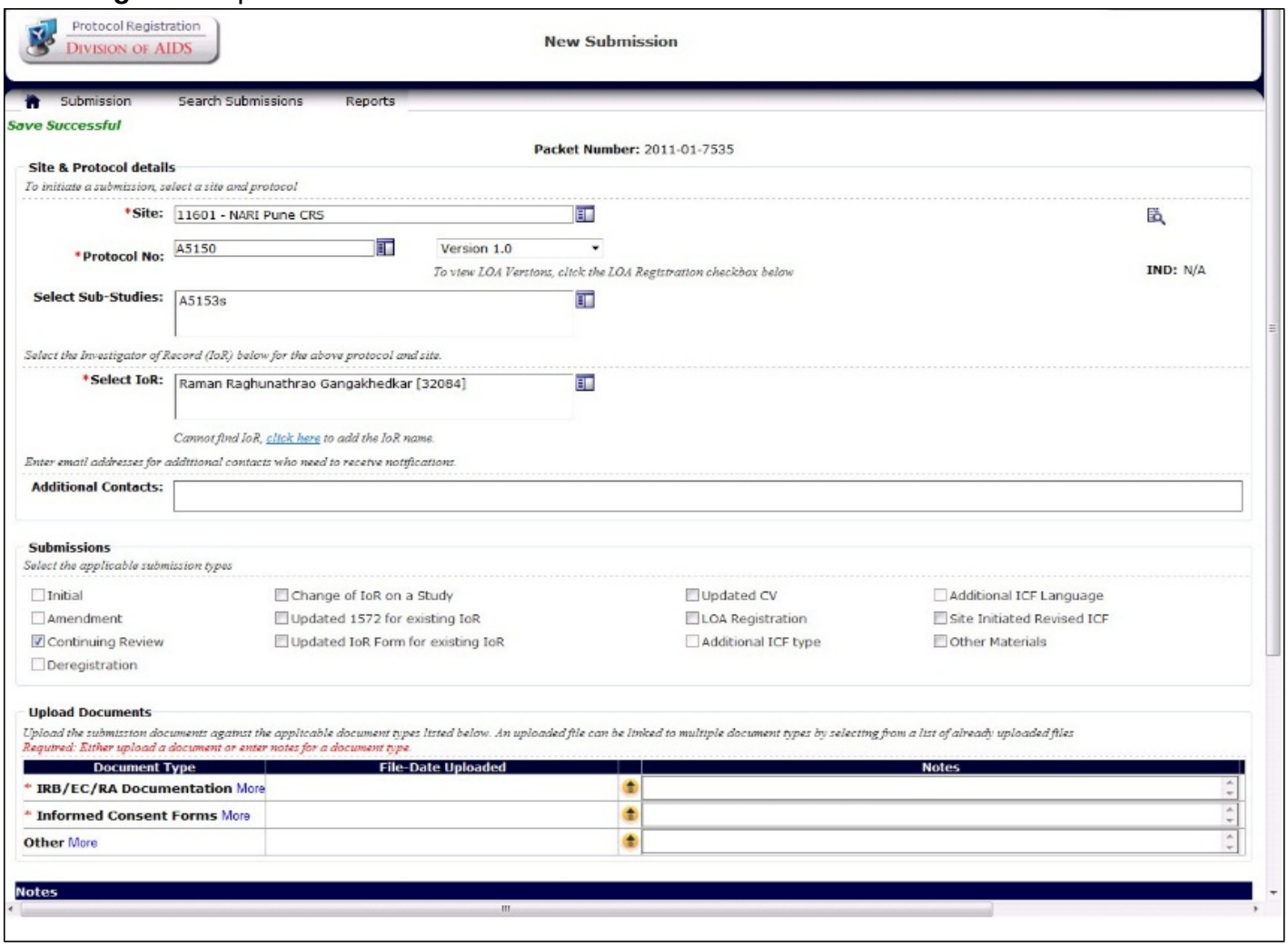
4. **Next:** Click Next. If the save is successful, the Upload Documents heading appears in the lower half of the screen.

Figure 2: Enter details in the New Submission screen



5. **Upload Documents:** Click the upload icon to upload the appropriate documents. Enter notes to provide additional clarification. Click **Save**.

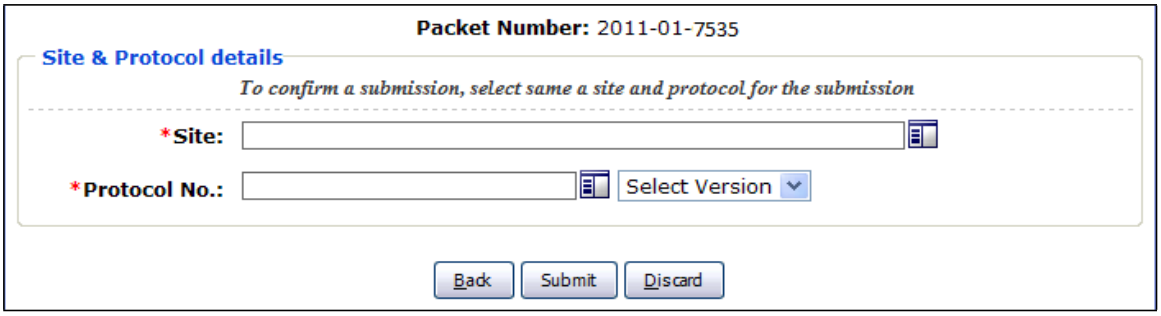
Figure 3: Upload documents in the New Submission screen and add notes



6. **Confirm Submission Details:** When finished, click **Submit**. At the pop-up confirmation window, confirm the Site, IoR Name and Protocol No. Select the version and again click **Submit**.

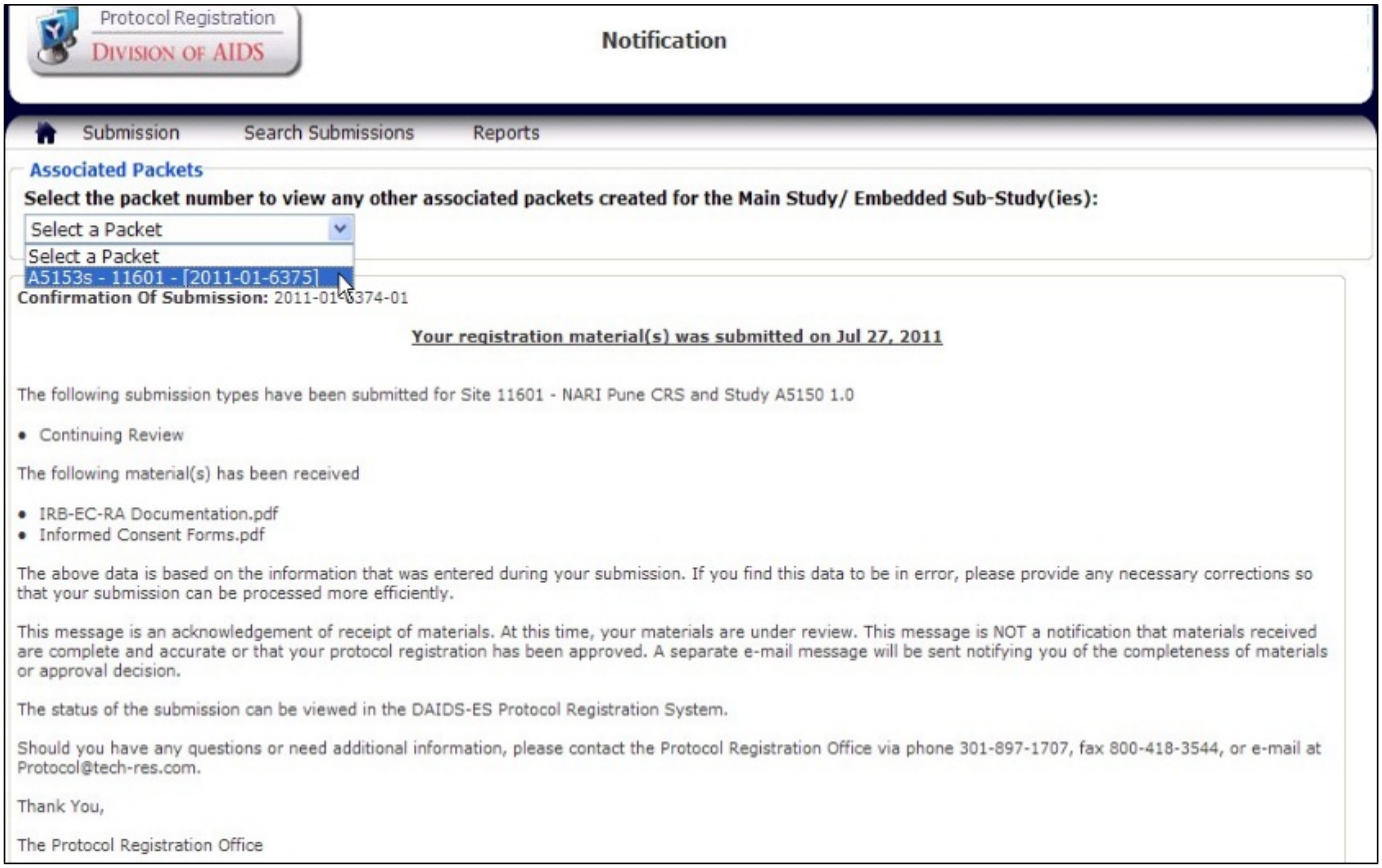
The system confirms whether the submission was successful.

Figure 4: Confirm Submission Details



7. **Optional:** System will provide option to submit sub-study packets that have not yet been submitted by selecting a packet number at the top of the Notification screen.

Figure 5: Navigate to associated packets yet to be submitted



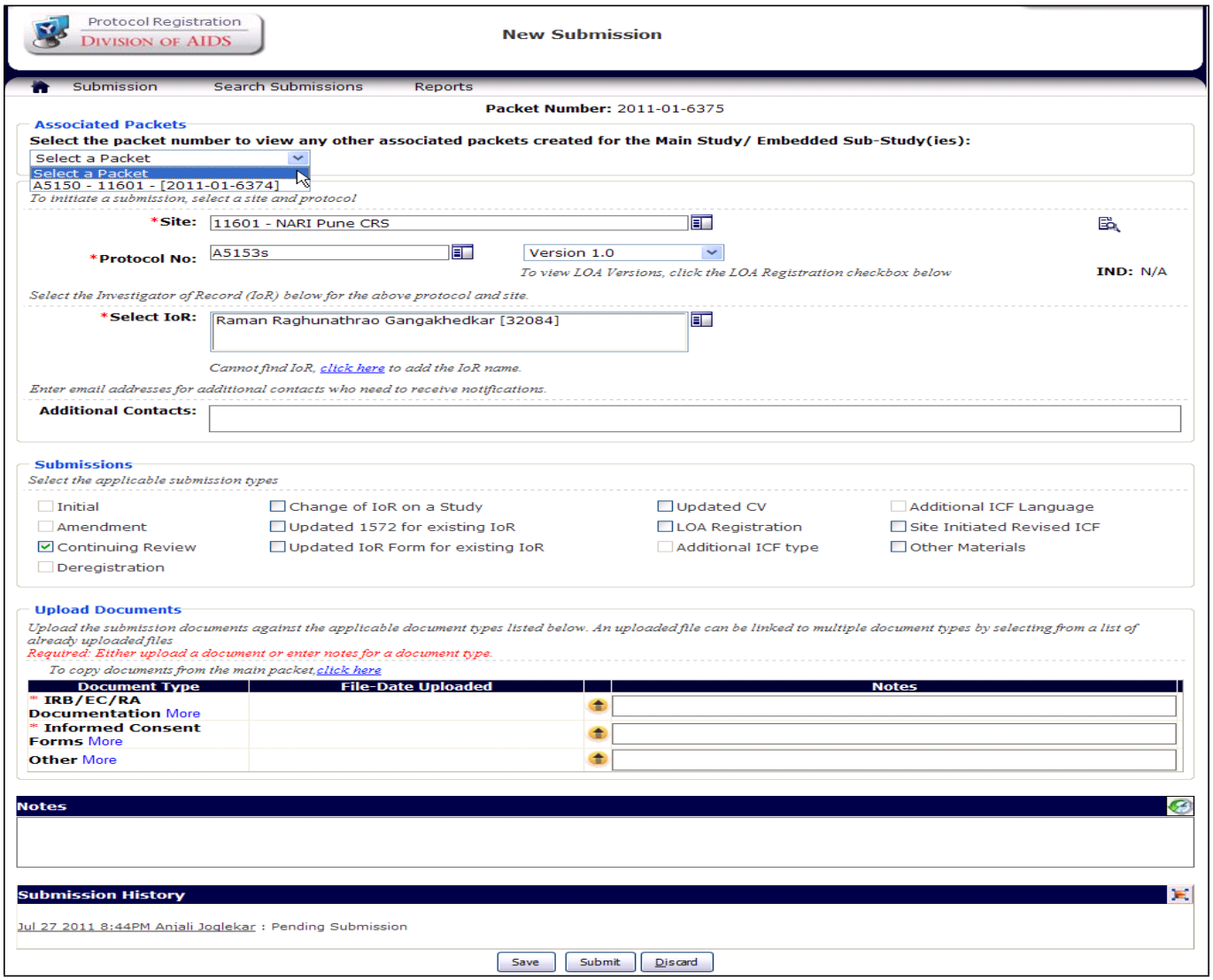
How do I view the sub-study packet?

1. Select a packet number at the top of the screen to view any other associated packets for this study. The Sub-Study screen appears similar to the main submission except the Protocol Number is changed to the sub-study number. The submission type remains the same.

   Note: You can use this feature to toggle between the sub-study packets. You also can copy person information to sub- study packets.

2. Click the Upload Documents hyperlink in the associated packets to copy documents from the main packet.

Figure 6: Viewing the sub-study packet



Still Have Questions?
Email: DAIDS ESSupport@NIAID.NIH.gov
Phone: 1 866 DES 1605 (866 337 1605) Fax: 1 866 DES 1606 (866 337 1606)