HIV/AIDS Network Coordination

JUNE 6, 2023

HOW TO CRITICALLY (AND QUICKLY) READ A PROTOCOL

NOW WITH AN HIV CURE RESEARCH APPENDIX

ORIGINALLY PREPARED BY DR. JEFFREY SCHOUTEN

LAST UPDATED: JUNE 6, 2023, BY COMMUNITY PARTNERS

Table of Contents

Introduction

This document was initially developed in 1997 for the AIDS Clinical Trials Group (ACTG) to help CAB members review a treatment protocol. However, this document has evolved and continues to be updated as needed. The general approach for reviewing a protocol is the same for CAB members working with treatment, cure, and/or prevention networks, though each protocol is unique and may have additional questions to consider.

It is important for CAB members to critically review protocols from a community perspective. Some of the key questions to consider when reviewing a protocol are outlined below to help CAB members focus their review on the most critical areas of the protocol. Each of the sections/topics listed below is addressed in protocols across all the NIAID-funded networks though they may be labeled differently or listed in a different order.

Cover Sheet and Protocol Team Membership

The protocol cover sheet notes which Network Committee developed the protocol and is typically followed by a list of the members of the protocol team, which should always include the CAB representative/s.

Study Objectives

Study objectives are typically provided early in the protocol, possibly after the background and rationale for the study. The objectives often include a list of sub-studies.

Quickly review the number of sub-studies, and ask if it is feasible to try to do so many studies under one main study? What conversations have taken place to make sure that community members are involved in the review process where the study is being developed and conducted? If the study is being conducted by more than one network, consider whether all the communities have been consulted.

Protocol Summary

Schema

The schema is a general outline of the study including randomization (if any), number of participants, treatment arms, criteria for treatment response or efficacy and/or failure, and secondary steps, etc. The schema will give you a good idea of the study design and target population, including eligibility criteria, which you should review carefully to determine how inclusive the study is and how clearly and accurately the study population is described. Is the rationale for the control group included? There may be times when a study is prematurely terminated, and it's important to know under what circumstances that could happen.

Study Design

What are the main research questions? Are these questions a high priority in the community? Will the study provide information that will impact future research even if the results are not immediately useful?

Duration of Study

How long will the study participant be involved? When will study results be available to participants? What information will be available to the participant during the trial? What information will be available to the participant at the end of the study? Does the study address access to the study product(s) when the trial is complete?

Study Procedures and Clinic Visits (Schedule of Evaluations/Events)

What is included in each clinic visit? How long does each clinic visit take? Are the descriptions of procedures clear? Will the participant also have to provide information to the clinic by phone or electronically? Are the visits, telephone reports, etc., too complicated? How are they explained to the participant? Think about the various tests that are being done and if there are too many or too few. For example, are there too many blood tests? Are there enough viral load assessments? Look for information about whether study participants will get their test results in "real time". Will the test results be available immediately, or will the test results of participants be "batched" together with results coming later, and often not shared with the participant?

Study Population

Who will be recruited for this study? How many individuals is the study seeking to recruit? Are there specific targets for certain populations? What language is used to describe the study population—is it inclusive, accurate, and non-stigmatizing? Is the study population described correctly in terms of gender identity and sex assigned at birth?

Eligibility Criteria

The eligibility criteria are important to review because they dictate who can and cannot participate in the study. If the eligibility criteria are based on sex assigned at birth or gender identity, it is important that there is a valid scientific reason. Also, if specific populations are included, it is important it be very clear that they are eligible to participate. Do the eligibility criteria make sense? Do they serve the purpose of the study? Are any groups of people excluded unnecessarily? Do the criteria create barriers that would make it difficult to enroll participants? To help ensure that the study is as inclusive as possible, ask if there are scientific justifications for exclusions and reference the Representative Studies Rubric and ask the protocol team to discuss and complete it.

Informed Consent

Does the informed consent explain the study in simple, clear language? Are all the medical terms explained? Is there a plan for publication? How and when will participants be informed of the results? Are all the major risks and benefits explained? How is participant confidentiality maintained? Are participants adequately compensated for participation? How will research-related harm be compensated? Is emergency contact information included? Will participants understand their legal rights after reading the informed consent?

Keep in mind that the informed consent is only a "template"; each individual institution's Institutional Review Board (IRB) or Ethics Committee has their own requirements for the content and format of the informed consent.

Barriers to Participation

Are there aspects of this trial that will make it difficult to participate in? What could be done to minimize the barriers?

Review for Stigmatizing language

Is non-stigmatizing language being used throughout the protocol and all study related documents? Is the NIAID HIV Language Guide being used as a reference to check for stigmatizing language?

HIV Cure Research Appendix

Analytical Treatment Interruptions

Risks and benefits of being in cure research with analytic treatment interruptions (ATI): ”Cure research” refers to studies that in general have the long-term goal of allowing people living with HIV to live healthy lives without the need to take antiviral medications- either pills or injections). These studies evaluate the impact of interventions on the latent HIV reservoir (the source of HIV viral rebound when medications are stopped). The goal is to either allow for enhanced immune function to control HIV (a functional cure) or, more challenging, to remove replication-competent HIV from the body (a sterilizing cure). Currently, the measure of the impact of the intervention can be assessed only by stopping antiretroviral therapy and measuring how quickly HIV viral rebound occurs. This is referred to as an analytic treatment interruption. As HIV viral rebound can pose health risks to the participant, close frequent monitoring of HIV viral levels is conducted. Also, with HIV viral rebound the chance of HIV transmission increases. Thus, important aspects of cure research studies include the ATI duration and HIV viral RNA monitoring during the ATI, and the restart criteria for antiviral therapy based on increasing HIV viral load levels. An important consideration includes reduction of risk of HIV transmission to partners during and after the ATI. Another factor to consider is any chance of resistance upon restarting an antiretroviral regimen.

Monitoring for viral rebound: How frequently am I being monitored for viral rebound? What are the restart criteria? When will antiviral therapy restart and what options do participants have? These are all critically important aspects in the design of cure research studies. There are no current uniform criteria when to restart antiretroviral therapy. In part, this is because different interventions may target different levels of HIV viral rebound to observe the desired effect- a decrease in the HIV viral reservoir and delayed viral rebound. The informed consent process should clearly delineate when ART will be restarted, and the options participants have available should they decide to restart ART *sooner or later* than defined in the protocol.

Proof of concept studies:

Proof of concept studies are typically small studies that are conducted to provide evidence that an intervention, drug, etc. has some of the intended effects and may be a candidate to move into further trials. This is the current stage of cure research studies.

False expectations of being in a cure research proof of study concept: Future cure research studies will likely involve combinations of therapies, as one intervention is unlikely to achieve a functional cure. The informed consent process for cure research studies should be very explicit that proof of concept studies provide no benefit to the individual participants. The ATI possesses risks without benefitting the participant.

Study preclusion

Some of these studies preclude you from being in a study if you've been in a prior cure study. Due to the various proof of concept studies in the cure research field, some studies will not allow participants who have been in certain other studies. This is because of the potential impacts from a previous intervention on the interventions in the current study. The informed consent process should clearly address this issue, as well as limitations on enrolling in other studies *during* the current study, and the potential limitations on *future* trial participation, if someone enrolls in the current study under consideration.

Leukapheresis:

Does the study include leukapheresis? Leukapheresis is a procedure performed to selectively remove many white blood cells from your blood. This is done by removing blood from your arm via two large intravenous tubes and processing it through a special machine to separate the white blood cells from the red blood cells, plasma, and platelets in your blood. The red blood cells, plasma, and platelets are then returned to your bloodstream via another vein. Usually, a person undergoing leukapheresis has an intravenous tube in each arm while sitting back in a chair in a special lab. The procedure may take a couple of hours.

The intravenous tubes used for leukapheresis are larger than for a normal blood draw and may be somewhat uncomfortable. Rarely, a person may feel faint during or after leukapheresis. During the procedure, participants will receive a compound called ACD-A (citrate), which prevents blood from clotting. Citrate may cause chills, nausea, and heartburn. In addition, citrate may use up some of the calcium in the bloodstream, causing the blood calcium level to go down. Low calcium can cause numbness and tingling, especially in the hands and feet and around the mouth. Citrate can also sometimes cause muscle spasms. A large volume blood draw from a vein into ~10 tubes may be used in place of leukapheresis in some studies. The amount of blood drawn for clinical research purposes must pose only minimal risk to the participant and must be approved by the Institutional Review Board with oversight of the clinical trial.

The protocol consent should clearly state the details of the leukapheresis procedure and detail if it is a required or optional procedure, as well as the participant compensation.

PrEP and U=U

PrEP, U=U, and becoming transmissible again: Due to the increased risk of HIV transmission as HIV viral load increases, cure research studies should address this risk. It can be minimized by offering *pre*-exposure prophylaxis (PrEP) to participant's partners during the course of the ATI or providing *post*-exposure prophylaxis (PEP) to partners in the event of a possible HIV exposure. Participants should be aware of and counseled about this risk. The protocol should address how PrEP and/or PEP will be provided if requested.

Study participant compensation:

As cure research studies involve risk to participants without any benefit, compensation for participants is a very important consideration for participants, local CABs, IRBs and protocol teams. The informed consent process should clearly discuss and include in detail the compensation offered participants for each aspect of the study. Also, cure research studies may include sampling of lymph nodes, genital secretions, intestinal biopsies, or other special tissue collections. For some studies some of these will be optional, some may be required for participation.

Criminalization:

This is an important consideration for all people living with HIV due to the very different local, regional, national, and international rules and regulations about the possible criminalization of HIV transmission. Laws range from possible criminal charges for non-disclosure of HIV status, even if someone has an *undetectable* HIV viral level, to possible criminalization only when someone is actually able to possibly transmit HIV sexually- i.e. has a *detectable* HIV viral load level. Since cure research studies, by design, allow HIV levels to increase to detectable levels in participants during ATIs, participants should be made aware of these implications in their jurisdiction or areas where they may plan to travel.

Resources

There are a number or resources to support CABs available on the Office of HIV/AIDS Network Coordination public portal. Under Coordination Areas, go to Community and then Community Partners and then Resources for a listing of available resources.

Training materials are available to support your knowledge of clinical research and protocol development on the DAIDS Learning Portal (DLP), including ***Understanding Clinical Research*** and ***Research Ethics and Informed Consent.***

These e-learning modules can be found on the Resources Page of the DLP under Community Engagement, along with other resources, publications, and training tools that may be valuable to you and your CABs. Please feel free to share this broadly with your communities.

The DLP is available to staff, stakeholders, and others working with the Division of AIDS. If you do not already have an account, click on "request an account" to get access; you will need your site number to complete the request form. If you are affiliated with a site, you can simply ask the study coordinator or site PI for the site ID. However, even if you're not affiliated with a site, you can request an account by using 99999 as your site ID. You will receive an automated email with instructions on how to create a password. If you have any problems accessing the materials, please contact support- daidslearningportal@niaid.nih.gov/.

Additional online resources

CUREiculum Webinar Series (AVAC)

Language for HIV Cure

US Dept. of Health and Human Resources Informed Consent FAQs

Glossary

ATI: is an acronym for Analytic Treatment Interruption. ATI is a temporary pause in standard HIV treatment of antiretroviral therapy.

CAB: A Community Advisory Board is an advisory group of community members and organization members that provide community input and feedback for clinical trials.

IRB: Institutional Review Boards review research studies to ensure they comply with applicable regulations and policies, meet ethical standards, and protect participants.

PBMC: PMBC is an acronym for Peripheral Mononuclear Blood Cells. These cells allow the isolation of T-cells, B-cells, and mononuclear cells used for basic research. They can assist in making immunotherapies. Once the blood is drawn and PBMCs collected, they are purified and quickly frozen before use.

PEP: is an acronym for Post-Exposure Prophylaxis. PEP is taken after a possible exposure to HIV.

PrEP: is an acronym for Pre-Exposure Prophylaxis. PrEP is medicine that reduces your chances of getting HIV through injection drug use or sex.

U=U: is an acronym for Undetectable = Untransmittable.