AN ACTIVIST'S PROTOCOL REVIEW TOOLKIT

TAG
Treatment Action Group

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Clinical trials form the heart of clinical research and look at new ways to prevent, detect, or treat disease. They might evaluate new drugs or new combinations of drugs, new diagnostics, new vaccines, or new ways to use existing health technologies. They can also look at other aspects of care, such as improving the quality of life for people during and after treatment and for people with chronic illnesses. Clinical research can take different forms, including **operational or programmatic research**. However, the primary focus of this toolkit is **randomized controlled clinical trials**. People participate in clinical trials to help others, but for those with a particular illness or disease, clinical trials may also offer the possibility of receiving the newest prevention, diagnostic, or treatment options and the benefit of additional care and attention given by clinical trial staff. Clinical trials offer hope for many people and provide an opportunity for researchers to develop better technologies and interventions to improve health outcomes for others in the future.

Operational or programmatic research: early implementation of new health technologies in programmatic settings to generate data on practical implementation and to inform plans for broader roll-out and routine use by country programs.

Randomized controlled clinical trials: a study design that randomly assigns participants into an experimental group (receiving the intervention that is being tested) or a control group (receiving an alternative intervention, no intervention, or the standard of care).

The design and conduct of clinical trials are often informed by community advisory boards (CABs), which are groups of research-literate community members and advocates who represent the interests of the populations among whom, or the communities in which, research is conducted. CABs help define research questions; co-design trials; educate and inform communities about ongoing or planned studies; and communicate the interests, needs, and concerns of communities to research teams. One important way CABs achieve these objectives is by reviewing clinical trial **protocols**. By getting involved in protocol development, CABs offer investigators a way to solicit input from the communities that stand to benefit from research, and, in turn, offer communities a way to ensure that research is responsive to local and regional needs and priorities.

Protocol: a plan that states the specifics of a clinical trial, such as the trial design and objectives, rationale, hypothesis to be tested, drugs, diagnostics, or other investigational products to be used, procedures or methods of administration, endpoints, reference standards, eligibility criteria, and risks and benefits.

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TABLE OF CONTENTS

1. AN ACTIVIST'S PROTOCOL REVIEW TOOLKIT

This Protocol Review Toolkit for Activists, developed in consultation with members of two existing CABs — the Global Tuberculosis Community Advisory Board (TB CAB) and the Community Research Advisors Group (CRAG) — includes tools designed to facilitate community participation in the development of clinical trials protocols. These tools have proven useful for the CRAG in its role advising the Tuberculosis Trials Consortium (TBTC) and for the TB CAB in its engagement with independent investigators and research and product sponsors. We hope this document can help support other CABs to engage in research by reviewing and providing feedback on clinical trials protocols. The toolkit is made up of four key resources: **a protocol review companion, a protocol input questionnaire, a feedback letter template, and a trial impact assessment.**

Figure 1: How to use An Activist's Protocol Review Toolkit

1. STIMULATE YOUR THINKING

Protocol Review Companion

Refer to the questions in this document as you read protocols to guide your review of different aspects of the proposed study. Use it as a checklist or as a thinking aid.

2. ORGANIZE YOUR FEEDBACK

Protocol Input Questionnaire & Feedback Letter Template

Fill this out to provide feedback to researchers on the protocol. Note any concerns or aspects of the study that you would like to see changed.

3. EVALUATE YOUR IMPACT

Trial Impact Assessment

Use this to keep track of any changes made to the protocol based on your review and feedback and to compile any points of follow-up for the investigators.

2. PROTOCOL REVIEW COMPANION

*Download a Word version of the Protocol Review Companion **here***

Protocol Description and Background

1. Does the protocol provide the purpose, relevance, and scientific justification for the current study?
2. What are the specific data the researchers plan to collect, and have they explained how these data and the participants selected will help to answer the research question(s)?
3. Does the protocol provide enough background information or details from past trials to support this study?
4. Based on the answers above, are the researchers in true **equipoise** about conducting the study?
5. Are there enough resources available for the completion of the trial?

Equipoise: a guiding principle of ethical medical research that requires that genuine uncertainty exists in the expert medical community about whether an intervention under study will be beneficial or better than the control (no intervention or standard of care).

6. What is the study design (e.g., quantitative, qualitative, mixed methods, **quasi-experimental**, randomized controlled)?

7. What are the primary and secondary **endpoints** or **objectives** of the trial and do these adequately represent the potential clinical benefit (e.g., efficacy and safety) of the prevention, diagnostic, or treatment intervention under study? Will data be collected according to a timeframe that best supports determination of whether these endpoints or objectives have been reached? Are there any endpoints or objectives of interest to affected communities that are not captured in the study design (e.g., acceptability, tolerability, feasibility, improvements to quality of life)?

8. Will the study have a control group (a group of people who will not be receiving the intervention being studied, for a basis of comparison)? Have the principal investigators explained the procedures and purpose of using a control group?

9. If the control group is made up of participants with a disease or condition, will they be receiving, at minimum, the standard of care they would be receiving from their health providers if they were not part of the study?

10. What is the comparator treatment or regimen against which the investigational treatment(s) or regimen(s) will be compared? For TB prevention or vaccines studies, is there a **standard of prevention** against which the investigational preventive therapy or vaccine will be compared? For TB diagnostics studies, what is the **reference standard** that will be used to evaluate test performance? Are these the best choices to demonstrate performance, considering the participant populations and **use case**?

Locations Where Research Will Be Performed

1. Do study sites include countries or regions where the disease is prevalent or has a high health, economic, or societal impact? (Note: many regulatory authorities require that drugs, drug regimens, vaccines, and diagnostics be tested in their countries before approval.)

2. Will the investigational products (drugs, diagnostics, vaccines, etc.) be made available in these countries after the trial ends? How will access to the investigational products be made available and continue after the trial (e.g., **pre-approval access, post-trial access**, operational research)?

Requirements of Study Participants

1. How many participants will be enrolled in the study and do the investigators provide an explanation of how they determined the number of participants? (Note: this is important to ensure that the results are not misinterpreted, that the studies are large enough to generate statistically valid results, and that the results will be generalizable to the larger patient population outside the trial.)

Quasi-experimental: studies that aim to evaluate interventions but that do not use randomization.

Endpoint: targeted outcome(s) of a clinical trial (e.g., survival, relapse-free cure, tolerability of side effects) that is statistically analyzed to help determine the clinical benefit of the intervention being studied.

Objective: specific aim(s) of a diagnostics study detailing what the study will measure and evaluate, which may include quantitative measures of test accuracy or diagnostic yield and/or qualitative characteristics such as usability or acceptability of tests.

Standard of prevention: the best available drugs or vaccines for prevention of disease against which novel preventive interventions are compared to determine efficacy and safety, as well as other qualities such as ease of administration and adherence.

Reference standard: the most accurate diagnostic or combination of diagnostics and methods against which the performance of novel screening and diagnostic tools is measured and evaluated.

Use case: specific purposes, settings, and populations for which interventions are intended and evaluated (e.g., disease prevention among child contacts, confirmatory diagnosis in primary care facilities, treatment of pregnant people, etc.).

Pre-approval access: a mechanism for accessing a drug before its approval by a regulatory authority. Pre-approval access programs can take several forms, including: 1) individual access on a named-patient basis; 2) group access through participating research centers via bulk importation; or 3) single-arm clinical trials in which people with limited therapeutic options are offered the medications as part of clinical cohort studies.

Post-trial access: initiatives to bridge the gap between when a study closes and stringent regulatory approval and/or World Health Organization endorsement of a drug or diagnostic and its local registration, inclusion in guidelines, and availability through national TB programs.

2. What activities are the participants expected to engage in by participating (e.g., surveys, focus groups, interviews, diagnostic procedures, blood draws, medication adherence requirements)?
3. What is the duration of the activity, the number of times the activity will occur, and the total time period of active participation per participant (e.g., days, weeks, months, years)?
4. How long will researchers follow participants and is the follow-up period well justified? Is this information clearly described in the consent forms and supporting materials?
5. Where will data collection take place (e.g., waiting room, exam room, research office, other location)?
6. Will participants be compensated for their participation through financial or other forms of support? (Note: common forms of payment include reimbursement for transportation to and from the research site, compensation for time off from work, or a small incentive awarded for participation or completion of all study visits.)
7. If participants will be receiving compensation after their participation in the trial ends, how will research staff link their names/contact information confidentially to their compensation?
8. Will the study collect any private or sensitive information from participants? How will this information be protected and where will it be stored? Is this information discussed and explained in consent forms?
9. Does the study use interpreters, and if so, what are the procedures for recruiting interpreters and ensuring their cultural competence (awareness of and ability to understand and appropriately respond to cultural differences when providing care to patients with diverse values, beliefs, behaviors, and needs)? Will study materials be translated into local languages?

Description of Research Risks and Benefits

1. What are the risks, if any (physical, psychological, social, legal, or other), to the participants and their families or other close contacts?
2. What is the likelihood of these risks occurring, and/or how serious are they?
3. How have the investigators worked to minimize these risks, and are these risks made clear in informed consent materials?
4. Is there a compensation plan for unanticipated severe risks or adverse events resulting from the intervention under study (e.g., clinical trials insurance)?
5. Are the study approaches adequate to maximize safety and minimize potential adverse events?
6. How will potential drug-drug interactions (especially for people living with HIV on antiretroviral therapy, people taking hormone-based therapies, and people taking opioid substitution therapies) be prevented, monitored, or mitigated if they occur?
7. In diagnostic, TB preventive treatment, and vaccine studies where a proportion of participants are expected to develop active disease during the study, how will the investigators ensure participants receive the best quality of care?
8. Are the study procedures and follow-up schedule designed to maximize the health and well-being of the participants during the study and after study completion, especially in studies where participants may develop active disease or be at risk of relapse?
9. Where the study intervention may result in health risks for pregnant people or fetuses, does the study provide adequate options for contraception and birth control and promote gender parity in preventing health risks related to pregnancy?

10. Does the study protocol articulate processes for ensuring that a distressed participant gets the help they need? If a participant experiences negative physical or psychological effects, are there referral procedures in place to ensure that the participant is linked to appropriate psychological and/or physical treatment or assistance?

11. What are the potential benefits to the participants of this study (e.g., access to nutritional support, drugs, diagnostics, evaluations, screening, counseling, medical referrals, training, additional screening, and monitoring at no cost to the participants)?

Eligibility Criteria

1. Does the study include **vulnerable populations**?

2. Does the study exclude any classes of participants (e.g., by gender, class, race, age)?

3. Does the study use inclusive language that recognizes transgender and non-binary people?

4. Does the study leave out important groups of people affected by the disease (e.g., adolescents and children, women, pregnant or lactating people, people living with HIV, people living with HIV on antiretroviral therapy, people with other comorbidities such as diabetes, incarcerated populations, sex workers, people who use drugs, people who use alcohol)?

5. If the study purposely excludes any class of participants or important groups of people affected by the disease, do the investigators present an adequate justification for this exclusion?

6. Are any classes of participants excluded from early-stage (phases I and II / analytical validation) versus late-stage (phase III / clinical performance verification and demonstration) trials? If certain populations are excluded, are there plans to include them in later stages of research?

7. Are the populations that are either included in or excluded from the trial represented in community advisory structures, like a CAB? (Note: particularly for those who are excluded, this can help them advocate for inclusion either in the current trial or in future trials of the same drug or other intervention.)

Vulnerable populations: groups of people who are not well integrated into health care systems because of ethical, cultural, economic, geographic, or other forms of discrimination and marginalization. Vulnerable populations face a greater risk of poor health status and health care access. In addition, some vulnerable populations might lack the capacity to provide consent freely (e.g., because they are in prison) or to fully understand what they are agreeing to (e.g., because of age, maturity level, or mental ability). These persons should be given additional protections by investigators and review committees.

Description of Recruitment and Procedures

1. Does the study describe the methods used to recruit participants?

2. How and from where will participants be recruited (e.g., flyers, public announcements, word of mouth, digital recruitment campaigns, clinic-based recruitment, patient advocacy network engagement)?

3. Are there existing, site-specific community engagement structures in place? If not, are there plans to create them? How will these community engagement mechanisms be structured (e.g., site CABs, a consortium-level CAB with site representation, a combination of the two)?

4. Will budget be allocated to support community engagement structures and activities?

5. How will investigators protect the identity and personal information of participants (e.g., codes, pseudonyms, masking of information) during and after clinical trials, including for any biological specimens collected for storage in biorepositories for future evaluation of diagnostics?

Procedures for Obtaining Free and Informed Consent

1. What is the procedure for obtaining a participant's free and **informed consent** to enter the trial?

2. Is the consent process in a language that likely participants can understand? Are there supporting materials to ensure that people understand the consent process for participation in the trial and, where applicable, for the collection of biological specimens to be stored in biorepositories?

3. Does the consent process give people enough time to read, understand, and ask questions about the trial and to make a choice free of coercion and undue influence?

4. Does the consent process include the names and contact information of the researchers and/or community members in a position to address potential questions about the trial?

5. Are the risks posed to participants by the trial clearly and comprehensively described in the informed consent materials, including potential adverse events resulting from the investigative products under study?

6. Are method of administration, dosing intervals, pill burden, and any adherence requirements clearly explained along with any systems for adherence support during the trial?

7. Does the consent process describe what is offered to people who choose not to participate or who withdraw from the study?

8. Are alternative treatments, procedures, or other interventions described clearly to all participants? (Note: it is important for study participants to be made aware of all their options for receiving care, including those available outside of the trial setting, before consenting to participate.)

9. If the trial intervention offers no direct benefits to participants, has the study protocol stated this in the informed consent form?

10. What communication technologies or platforms will be used to contact the participants and, if applicable, to perform virtual visits?

Informed consent: a process designed to protect study participants in research. Before entering a study, participants must sign a form stating that they have been given and understand important information about the study and voluntarily agree to take part.

Results Dissemination

1. Does the protocol include a post-trial communication plan that will be informed by community representatives?

2. Does the protocol include draft materials for sharing study results with participants and their communities or outline other means to do so (e.g., a findings letter addressed to individual participants or site-specific dissemination plans)?

3. Are there plans for community groups to review and provide input on results dissemination materials?

4. Before recruitment begins, will the trial be registered in a publicly accessible location, such as clinicaltrials.gov or the World Health Organization's International Clinical Trials Registry Platform (https://www.who.int/clinical-trials-registry-platform)?

5. Does the protocol include any plans for sub-studies or evaluations that will address pragmatic concerns about implementing the intervention in a real-world setting (e.g., qualitative studies of patient experiences, cost comparisons between the intervention and the control, evaluations of adherence strategies, etc.)?

Financial Conflicts of Interest

1. Do the investigators have any financial conflicts of interest with any of the research or product sponsor(s)? Does the study have any corporate funding sources?

2. Is the protocol transparent about funding sources? Is the research being conducted in partnership with a privately or publicly funded entity? Where public funding is being leveraged, are there any access conditions or other safeguards in place to promote access to investigational products post-trial? (Note: pricing of new drugs, diagnostics, or vaccines should always be fair and accessible to ensure that all people benefit from scientific progress and its applications, and access conditions or other safeguards should always be in place wherever public funds have been used to help advance the development of these technologies.)

Ethics Reviews

1. Will the trial be reviewed by one or more **institutional review boards (IRBs)**, independent ethics committees, or any other applicable regulatory entity? (Note: this should be a basic requirement for all research involving human participants.)

2. If the trial is multinational or multisited, will national or local level IRBs or ethics committees also review the protocol?

Institutional Review Board (IRB): a committee made up of medical or scientific professionals and nonmedical or nonscientific members whose responsibility is to ensure the protection of the rights, safety, and well-being of human participants involved in a clinical trial and to provide public assurance of that protection.

Additional Resources

Many of the concepts in this document are elaborated in guides that have been developed to help activists and community representatives understand the fundamentals of clinical research. For more information, we recommend consulting:

Research Fundamentals for Activists, developed by Consortium to Respond Effectively to the AIDS and TB Epidemic (CREATE) and Treatment Action Group. Available from: https://www.treatmentactiongroup.org/wp-content/uploads/2013/05/RFA-FINAL.pdf

Clinical Trials: A Community Guide to HIV Research, developed by HIV i-Base. Available from: https://i-base.info/wp-content/uploads/2015/12/MANUAL-trials-mar09-EN-FINAL-NO-graphic.pdf

Good Participatory Practice (GPP) Guidelines, developed by AIDS Vaccine Advocacy Coalition (AVAC). Available from: https://www.avac.org/good-participatory-practice

Basic Scientific Literacy Training Module, developed by HIV/AIDS Network Coordination (HANC). Available from: https://www.hanc.info/resources/training/bsl-training.html

How to Critically (and Quickly) Read a Protocol, developed by HANC. Available from: https://www.hanc.info/content/dam/hanc/documents/community/How%20to%20Read%20Protocol(short)%20HANC%20-FINAL%208-19-21_English.pdf

Recommendations for Community Engagement in HIV/AIDS Research: A Guide for Communities and Researchers, developed by HANC, Community Partners, and the United States National Institutes of Health (NIH) Division of AIDS (DAIDS). Available from: https://www.hanc.info/content/dam/hanc/documents/community/Recommendations-for-Community-Engagement-v3.0-Nov2020-English.pdf

The Representative Studies Rubric: A Tool to Enhance the Representativeness of Study Populations in Clinical Research, developed by HANC. Available from: https://www.hanc.info/content/dam/hanc/resources/RSR-HANC-Website.pdf

Bill of Rights and Responsibilities for HIV Research, developed by HANC. Available from: https://www.hanc.info/content/dam/hanc/documents/community/Bill-of-Rights-and-Responsibilities-FINAL-10-1-19.docx

Glossary of Terms: Community Engagement in TB Research & Development, developed by Moldova National Association of Tuberculosis Patients (SMIT). Available from: https://drive.google.com/file/d/1qMsz-ZhQNWcov4ZkY9OVlbEOaxYl8ZaD/view

Words Matter: Suggested Language and Usage for Tuberculosis Communications, developed by Stop TB Partnership. Available from: https://www.stoptb.org/news/tb-language-guide-20-launched-stop-tb-partnership-board-meeting

3. PROTOCOL INPUT QUESTIONNAIRE*

Download a Word version of the Protocol Input Questionnaire **here**

PROTOCOL TITLE: _____ DATE: _____

REVIEWER NAME: _____

Protocol Description and Background	Yes	No	Unknown
Does the protocol, as written, include enough information and supporting material to allow full understanding of the study purpose, relevance, justification, and design?			
Brief comment:			
Do you agree with the justification for the proposed intervention?			
Brief comment:			
Do you think the study's choice regarding a control arm, standard of prevention or care, or reference standard is appropriate? (Note: relevant issues to think about here might include use of placebo for the control arm or whether the standard of prevention or care or the reference standard is the right comparator.)			
Brief comment:			
Do you think the study seeks to answer an important question that will benefit the community?			
Brief comment:			

Locations Where Research Will Be Performed	Yes	No	Unknown
Does the protocol include any information about plans for post-trial access to study drugs, diagnostics, or other investigational products in countries where the research is being conducted?			
Brief comment:			
Do you think people at your site would participate?			
Brief comment:			

Requirements of Study Participants	Yes	No	Unknown
Are expectations of participants, including the length of participation, clear and fair?			
Brief comment:			
Does the protocol include information on forms of support participants will receive outside of the intervention under study (e.g., enablers such as transportation reimbursements, nutritional support, medical referrals, compensation for time off work, etc.)?			
Brief comment:			

Description of Research Risks and Benefits	Yes	No	Unknown
Does the protocol adequately describe potential risks and benefits of the research?			
Brief comment:			

Eligibility Criteria	Yes	No	Unknown
Does the protocol allow for the safe inclusion of vulnerable and/or most-affected or high-risk populations?			
Brief comment:			
Is there anything in this study that would discourage or exclude the enrollment of a specific group or groups (e.g., women, men, adolescents, children, people living with HIV, people with diabetes, drug users, pregnant or lactating people, people over age 50, etc.)?			
Brief comment:			
Do you agree with that discouragement or exclusion and is it well justified?			
Brief comment:			
If you met the eligibility criteria, would you participate in this study?			
Brief comment:			

Description of Recruitment and Procedures	Yes	No	Unknown
Does the protocol include and provide details on plans for engaging communities throughout the duration of the trial?			
Brief comment:			
Does the protocol include information on forms of support participants will receive outside of the intervention under study (e.g., enablers such as transportation reimbursements, nutritional support, medical referrals, compensation for time off work, etc.)?			
Brief comment:			

Procedures for Obtaining Free and Informed Consent	Yes	No	Unknown
Are consent forms and study educational materials designed in a way that will be understandable and acceptable to participants?			
Brief comment:			

Results Dissemination	Yes	No	Unknown
Does the protocol specify plans for dissemination of results to study participants and their communities?			
Brief comment:			

Other Impressions and Input	Yes	No	Unknown
Does the protocol include any plans for sub-studies or evaluations that will address pragmatic concerns about implementing the intervention in a real-world setting (e.g., qualitative studies of patient experiences, cost comparisons between the intervention and the control, evaluations of adherence strategies, etc.)?			
Brief comment:			
Do you have any other suggested changes to the protocol?			
Brief comment:			

**Adapted from the Protocol Input Questionnaire of the AIDS Clinical Trials Network (ACTG) Community Advisory Board (CAB).*

4. PROTOCOL FEEDBACK LETTER TEMPLATE

Download a Word version of the Protocol Feedback Letter Template **here**

To: [Trial sponsors or investigators]
Cc: [Other trial partners]

Subject: [CAB name] feedback and questions regarding [Trial name]

[Date]

Dear [Trial sponsors or investigators],

Thank you very much for sharing the [Trial name] protocol and consent form with the [CAB name]. As research-literate activists committed to supporting the development of new technologies capable of improving [Disease] diagnosis, prevention, and treatment, the [CAB name] greatly appreciates your engagement and the opportunity to provide feedback and ask questions about the proposed study to [Purpose of trial].

[Paragraph summarizing compiled CAB member feedback on the trial protocol and stating that detailed feedback is included below the signature]

[Paragraph requesting responses to feedback and questions and describing any other requested next steps]

We look forward to your continued engagement and response, which can be directed to the chair of the [CAB name], [Individual name and email address].

Respectfully submitted,

On behalf of the [CAB name]

[Issue 1 (e.g., **Study design and rationale**)]

- [Detailed feedback point 1]
- [Detailed feedback point 2, etc.]

[Issue 2 (e.g., **Eligibility criteria**)]

- [Detailed feedback point 1]
- [Detailed feedback point 2, etc.]

[Issue 3 (e.g., **Informed consent**)]

- [Detailed feedback point 1]
- [Detailed feedback point 2, etc.]

[Issue 4 (e.g., **Results dissemination**), etc.]

- [Detailed feedback point 1]
- [Detailed feedback point 2, etc.]

Questions and other comments

- [Question or comment 1]
- [Question or comment 2, etc.]

5. TRIAL IMPACT ASSESSMENT

Download a Word version of the Trial Impact Assessment **here**

PROTOCOL TITLE: _____

Did your feedback result in any changes to the reviewed protocol and what do you see as the significance or impact of these changes?

If yes, please explain here (e.g., investigators agreed to expand inclusion criteria to participants ≤ 15 years old):

How likely is it that this change would have happened without your influence?

☐ *Unlikely*

☐ *Somewhat likely*

☐ *Very likely*

Did any aspects of your feedback not result in a change to the reviewed protocol?

If so, did the investigators provide a rationale for not changing the protocol per your suggestion?

Are there any points of follow-up with the investigators?

If yes, please explain here:

Are there any lessons to note from this protocol review?

If yes, please explain here:

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