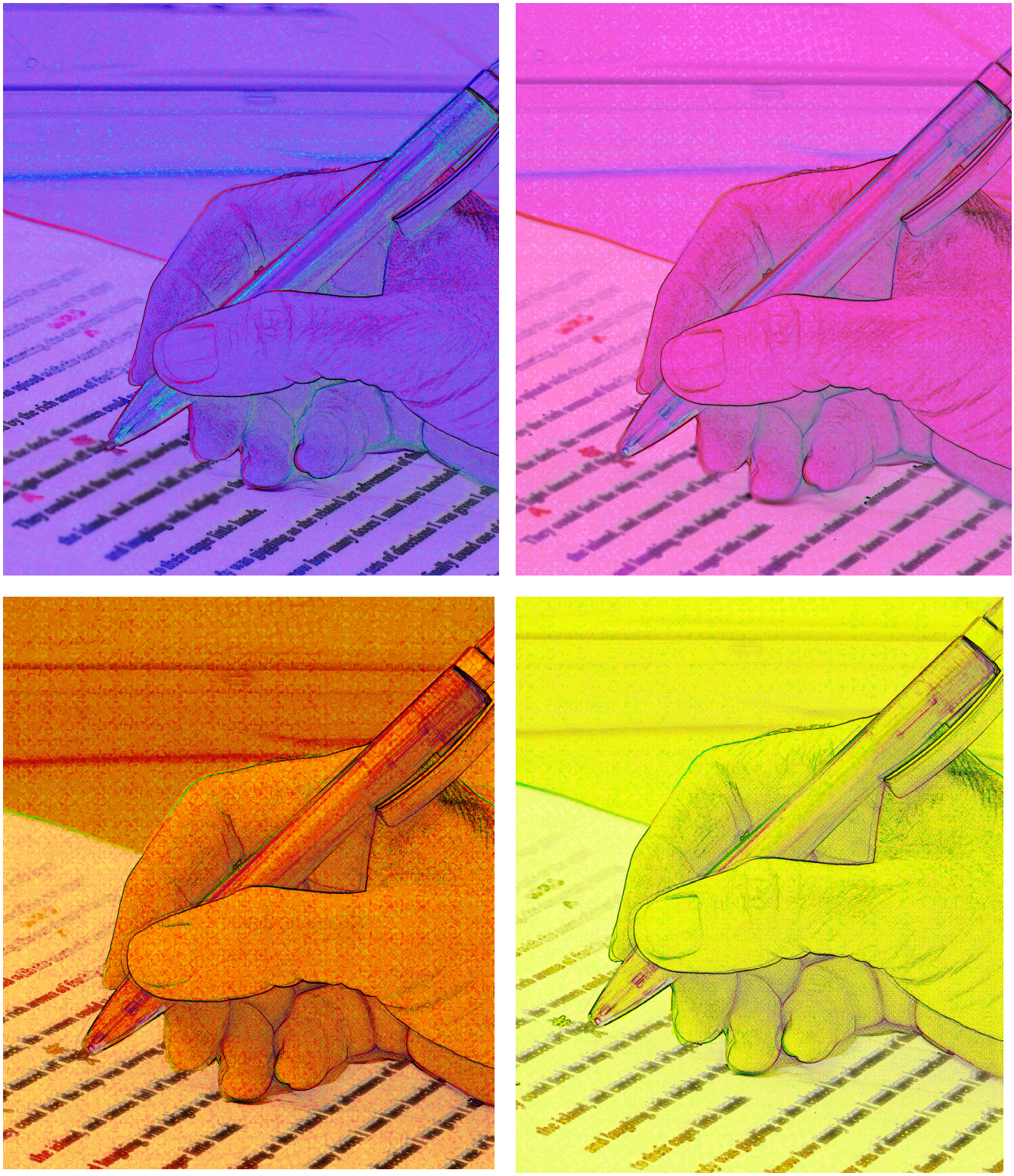
AN ACTIVIST'S

Protocol Review Toolkit



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TAG
Treatment Action Group

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ABOUT CRAG

The CRAG is an international, community-based advisory body that works to ensure the meaningful participation and engagement of affected communities in research conducted by the U.S. Centers for Disease Control and Prevention's Tuberculosis Trials Consortium (TBTC). This group of research-literate activists supports a robust and innovative TBTC research agenda, which reflects both community needs and scientific priorities.

ABOUT TB CAB

The TB CAB is a group of strong, research-literate community activists from HIV and TB networks around the world. The TB CAB works in an advisory capacity to researchers and product developers conducting trials of new TB drugs and diagnostic technologies, and provides input on study designs, early access, regulatory approval, post-marketing, and implementation strategies. Visit the TB CAB online at tbonline.info.

ABOUT TAG

Treatment Action Group (TAG) is an independent, activist and community-based research and policy think tank fighting for better treatment, prevention, a vaccine, and a cure for HIV, tuberculosis, and hepatitis C virus. TAG works to ensure that all people with HIV, TB, or HCV receive lifesaving treatment, care, and information. We are science-based treatment activists working to expand and accelerate vital research and effective community engagement with research and policy institutions. TAG catalyzes open collective action by all affected communities, scientists, and policy makers to end HIV, TB, and HCV.

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AN ACTIVIST'S PROTOCOL REVIEW TOOLKIT

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TABLE OF CONTENTS

1. AN ACTIVIST'S PROTOCOL REVIEW TOOLKIT

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 surgical procedures or devices, or new ways to use existing treatments. They can also look at other aspects of care, such as improving the quality of life for people with chronic illnesses. People participate in clinical trials to help others, but for those with a particular illness or disease, clinical trials also offer the possibility of receiving the newest treatment options and the benefit of additional care and attention given by clinical trial staff. They offer hope for many people and provide an opportunity for researchers to find better treatments for others in the future.

The design and conduct of clinical trials are often informed by community advisory boards (CABs), which are groups of nonscientists who represent the interests of the patient populations in whom, or the communities in which, research is conducted. CABs help define research questions, 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 their needs.

Protocol:
a plan that states the specifics of a clinical trial, such as the hypothesis to be tested, drugs to be used, methods of administration, trial length, endpoints, and eligibility criteria.

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 product developers. 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 three key documents: a **protocol review companion**, a **protocol input questionnaire**, and a **trial rating rubric**.

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.

Stimulate your thinking

Protocol Input Questionnaire

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

Organize your feedback

Trial Rating Rubric

Use this to keep track of any changes made to the protocol based on your review and feedback. CABs can use this internally to measure and evaluate the impact of their work.

Evaluate your impact

2. PROTOCOL REVIEW COMPANION

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 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?
6. What is the study design (e.g., quantitative, qualitative, mixed methods, quasi-experimental, randomized controlled study)?
7. Will the study have a control group (a group of people who will not be receiving the treatment or intervention being studied, for a basis of comparison)? Have the principal investigators explained the procedures and purpose of using a control group?
8. If the control group is made up of patients with a disease or condition, will they be receiving, at minimum, the standard treatment that they would be receiving from their doctors if they were not part of the study?

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 and drug regimens be tested in their countries before approval.)
2. Will study drugs be made available in these countries after the trial ends? How will access to study drugs continue after the trial (e.g., **compassionate use**, **expanded access** programs)?

Requirements of Study Participants

3. 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 of the trial.)

Equipoise:
a guiding principle of ethical medical research that requires that genuine uncertainty exist 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).

Compassionate use:
a mechanism for accessing a drug before its review and approval by a regulatory authority that requires physicians to request access on a named-patient basis, usually directly from the drug sponsor. The drug sponsor evaluates and approves requests on a case-by-case basis, but does not use or collect data on outcomes for patients granted access via compassionate use. The applying physician is responsible for ensuring that the drug is imported in accordance with national regulations.

Expanded access:
a mechanism for accessing a drug before its review and approval by a regulatory authority that requires patients to enroll in a trial. The drug sponsor initiates an open-label trial and collects safety and outcomes data on participants. Unlike a regular clinical trial, there is no control arm, randomization, or blinding. Still, expanded access programs must be registered as clinical trials with local regulatory authorities.

4. What activities are the participants expected to engage in by participating (e.g., surveys, focus groups, interviews, diagnostic procedures, blood draws, medication adherence requirements)?
5. 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)?
6. How long will researchers follow participants? Is this information clearly described in the consent forms and supporting materials?
7. Where will data collection take place (e.g., waiting room, exam room, research office, other location)?
8. Will participants be paid for their participation through financial or other forms of compensation? (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.)
9. If participants will be receiving payment after their participation in the trial ends, how will research staff link their names/contact information confidentially to their compensation?
10. Will the study collect any private or sensitive information from participants? How will this information be protected? Is this information discussed in consent forms?
11. 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?
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?
4. Does the study protocol articulate processes for ensuring that a distressed participant gets the help he or she needs? In the event that 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?
5. 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 leave out important groups of people affected by the disease (e.g., adolescents and children, women, pregnant or postpartum women, people with HIV, people with HIV on antiretroviral medication, incarcerated populations, people who use drugs, people who use alcohol)?
4. 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?
5. Are any classes of subjects excluded from early-stage (phases I and II) versus late-stage (phase III) trials? If certain populations are excluded, are there plans to include them in later stages of research?
6. 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 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 subjects be recruited (e.g., flyers, announcements, word of mouth, "snowballing," clinic-based recruitment)?
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)?

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?
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?

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.

5. Are the risks posed to participants by the trial clearly and comprehensively described in the informed consent materials?
6. Are alternative treatments or procedures described clearly to all participants? (Note: it is important for study participants to be made aware of all of their options for receiving care, including those available outside of the trial setting, before consenting to participate.)
7. If the trial intervention offers no direct benefits to participants, has the study protocol stated this in the informed consent form?

Results Dissemination

8. 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)?
9. 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 (http://www.who.int/ictrp/en/)?
10. Are there plans for a community engagement structure to vet results dissemination materials?
11. Is there a post-trial communication plan in place that has been shared with community representatives?
12. Does the protocol include any plans for substudies 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

13. Do the investigators have any financial interests in any non-site sponsors? Does the study have any non-site and/or corporate funding sources?
14. Is the research being conducted in partnership with a privately or publically funded entity? In either case, does the protocol detail who is accountable for ensuring access to investigational products post-trial? (Note: where public funds have been used to help advance the development of new drugs, the price needs to be fair and accessible so that the public can benefit from the investment of its tax dollars.)

Ethics Reviews

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

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 on 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 and Treatment Action Group. Available from: http://www.treatmentactiongroup.org/sites/g/files/g450272/f/201305/RFA FINAL.pdf.

Clinical Trials: A Community Guide to HIV Research. Developed by: HIV i-Base. Available from: http://i-base.info/wp-content/uploads/2009/07/8-clinical-trials-mar09.pdf.

Basic Scientific Literacy Training Module. Developed by: HANC HIV/AIDS Network Coordination. Available from: https://www.hanc.info/cp/resources/Pages/BSL-Training-Module.aspx.

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3. PROTOCOL INPUT QUESTIONNAIRE*

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 is appropriate? (Note: relevant issues to think about here might include use of either placebo or standard of care for the control arm.)	☐	☐	☐
Brief comment:			

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

Protocol Description and Background	Yes	No	Unknown
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 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:			

Requirements of Study Participants	Yes	No	Unknown
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, 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 populations?	☐	☐	☐
Brief comment:			
Is there anything in this study that would discourage the enrollment of a specific group or groups (e.g., women, men, adolescents, children, people with HIV, people with diabetes, drug users, pregnant or lactating women, people over age 50, etc.)?	☐	☐	☐
Brief comment:			

Eligibility Criteria	Yes	No	Unknown
Do you agree with that discouragement?	☐	☐	☐
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 specify plans for maintaining the confidentiality of participants?	☐	☐	☐
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 substudies 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:			

4. TRIAL RATING RUBRIC

PROTOCOL TITLE _____

Did your feedback result in any changes to the reviewed protocol?

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: