Consultations in LMICs for The Good Clinical Trials Collaborative Guidance

Final Report August 2021

good clinical trials

QUICKSAND

Contents

About the Project

The Good Clinical Trials Collaborative (GCTC) aims to put forth new guidance to support a more effective regulatory environment for randomised clinical trials (RCTs). Thereby enabling more informative, ethical and efficient trials to improve patient care. The GCTC was launched in June 2020, and is supported by Wellcome, the Gates Foundation and the African Academy of Sciences.

Quicksand, a design-thinking and innovation practice based in India, was commissioned by the Good Clinical Trials Collaborative (GCTC) to conduct Human-Centred Design or HCD-led consultations with RCT teams and participants in Low and Middle-Income Countries (LMICs). The goal of these consultations was to gather insights from diverse RCT types and settings, and provide the GCTC with these perspectives while the universal guidance and principles were being drafted.

Consultations were conducted with people who have interacted closely with RCTs, as initiators, implementers, or participants. Depending on the country's context, consultations were held virtually, in-person, or telephonically. Discussion with experts (Principal Investigators, trial managers, social scientists, community engagement practitioners) explored experiences with RCT protocols, community engagement, recruitment and follow ups. Discussions with participants explored perceptions of RCTs and experiences with RCTs that impact decision-making, trust, integrity, adherence and withdrawal.

Quicksand, supported by project partners in each country, reached out to advocacy groups, trial teams and participants. A fascinating and diverse range of experiences across India, South Africa, Nigeria, Thailand, Brazil, Sierra Leone and Kenya were captured through ensuing discussions; many of which warrant in-depth research projects of their own.

The project scope was not limited to any particular area or kind of RCT so as to provide a range of input into the GCTC guidance that seeks to be applicable to regulators, RCT teams, RCT reviewers, participant groups and quality management personnel.

The following report hopes to bring to the fore people's needs and motivations when interacting with RCTs and provide actionable recommendations for the guidance content, and more broadly, for the practice of ethical and efficient RCTs in the Global South.

Report Summary

The final report of the project pulls together what was learned through the enquiry in seven LMICs on RCTs; in consultation with experts and participants. It begins with the section on project methodology; which illustrates the approach of Human-Centred Design (HCD), a few challenges and limitations of the project, and a description of how the project was designed.

The next section provides an overview of the consultation sample; defining the types and domains of RCTs, characteristics of RCT participants, and expert domains that were covered through the project. Following this is an account of how these consultations were conducted in each country. The next section titled "LMIC Consultations and the GCTC Guidance" describes key reflections and suggestions for the GCTC guidance. This section is followed by "Key Learnings," segregated into three themes that cover insights and supporting evidence from the project. The report concludes with a set of broader recommendations for RCT sponsors, advocates and teams to further the practice of efficient, informative and ethical RCTs in LMICs. The annex of the report contains takeaways from the seven direct feedback sessions with Global South experts on the GCTC guidance draft. Further details on "LMIC Consultations and GCTC Guidance" and "Key Learnings" are captured below:

LMIC Consultations and the GCTC Guidance

This section highlights direct links between key learnings gathered through the consultations and statements in the GCTC guidance on the "Principles of Good Randomised Clinical Trials", "key messages" and "why this is important". These links highlight which statements and principles have strong resonance and alignment with project key learnings and suggest where the guidance can provide more nuanced content, examples and best practices to maximise its relevance in LMICs.

Key Learnings Theme 1: Conducting an RCT in the Global South

This theme contains insights on RCT sites and systems of approval in LMICs that are drawn from discussions on RCT protocols particularly; protocol approval and review, protocol adaptation and implementation during RCT conduct.

Key Learnings Theme 2: The Importance of Community Engagement in RCTs

This theme aims to highlight the value-add and purpose of community engagement towards the success of an RCT. Community engagement has been referred to as the "zeitgeist"[1] of today's scientific research. To those for whom the role of community engagement is clear, it is amply evident that no research can be successful without emphasis on it. However, there isn't a clear, shared understanding of community engagement amongst researchers and RCT participants. Community engagement can be extremely contextual and complex, and at times there isn't a focussed intent to facilitate its two-pronged purpose of 1) ensuring the success of both instrumental/scientific goals of an RCT and 2) upholding intrinsic/ethical goals of an RCT.

Key Learnings Theme 3: RCT Integrity from a Participant's Point of View

The University of Edinburgh highlights that research integrity means conducting research in a way that "allows others to have confidence and trust in the methods and the findings of the research. It relates both to the scientific integrity of conducted research and to the professional integrity of researchers."[2] The section highlights insights linked to integrity from a participant's point of view that relate to both these factors. Attention is given to the nuances of individual and community characteristics like socioeconomic status, gender identity, community type and professional background and how these relate to participant motivations, experiences and needs.

1. Lindsey Reynolds & Salla Sariola (2018) The ethics and politics of community engagement in global health research, Critical Public Health, 28:3, 257-268, DOI: 10.1080/09581596.2018.1449598
2.The University of Edinburgh has adopted the UK Research Integrity Office's (UKRIO) Code of Practice for Research and the Universities UK (UUK) Concordat to Support Research Integrity. LINK: https://www.ed.ac.uk/research-office/research-integrity/what-is-research-integrity

Key Learnings Theme 1:
Conducting an RCT in the Global South

Key Learnings Theme 2:
The Importance of Community Engagement in RCTs

Key Learnings Theme 3:
RCT Integrity from a Participant's Point of View

Methodology

Human-Centred Design (HCD) Consultations

Methods of Human-Centred Design are inspired and influenced by research disciplines like ethnography and social science. The core ethos of the approach is to allow people's stories, experiences and opinions to be expressed as openly and in as much detail as time allows. It therefore prioritises depth in discussions with individuals or small groups, rather than quantity in terms of numbers of people included in these consultations. However, the project attempted breadth with the types of people consulted; Quicksand and partners identified people from varying professional backgrounds, geographical locations, and socioeconomic contexts.

Usually, the approach favours in-situ immersion into the daily lives and experiences of people, as well as collaborative co-design and co-creation sessions. For this project, sessions were structured between 90-120 minutes, and discussion topics were supported by visual tools and activities. These tools aided in mapping out expert and participant experiences and preferences. Project partners used their own judgement and experience to conduct sessions tailored to the situation of the pandemic in their countries and suited to respondent needs.

Discussion topics were culled out based on GCTC guidance requirements, supporting secondary research on RCTs, and expert feedback. The session flow and activity design was decided upon collaboratively between the GCTC team and Quicksand. Topics are detailed in the next section.

At a Glance

Human-Centred Design led consultations from March - June 2021 in 7 LMICs

Quicksand worked with facilitation partners in Nigeria (Professor Morenike and team), Thailand (DSIL Global), Brazil (Flutter Innovation) and South Africa (Matchboxology)

Quicksand team led consultations with experts in India and Kenya, as well as with a trial team and participants in Sierra Leone

Project respondents included ex and current RCT participants, and experts with experience designing, reviewing, managing and conducting RCTs.

Discussions were around themes collaboratively chosen by the GCTC team and Quicksand, and were supported by visual tools for co-creation and live-analysis

Project Design

The project was designed to take place in two rounds.

Round 1: The primary purpose of Round 1 was to pilot themes for discussion with RCT teams in India, and seek feedback from experts on the appropriateness and relevance of chosen topics. In India, a group termed the "Red Team," consisting of five experts in community engagement during RCTs, and RCT quality management, provided feedback on the session flow and topics. Additionally, three global experts in research engagement and RCT conduct (especially in community-based settings and epidemic situations) were engaged to provide feedback on consultation topics from a global perspective.

Round 1 sessions were conducted in India by Quicksand with Principal Investigators and trial teams. These sessions explored the theme of randomisation in RCTs. Topics within this theme included; stages in protocol design, feasibility of good practice in recruitment and follow ups, typical informed consent process, clinical trial "equipoise", participant preferences, and factors influencing trust in an RCT. Key learnings have been detailed out in the Round 1 report shared with the GCTC team.

Round 2: Consultation sessions in this round took place in all project geographies, with RCT participants as well as experts. Quicksand designed supporting visual tools to facilitate discussion. Partners tailored discussions according to their context; choosing to use the online collaborative platform "Miro", physical print-outs of the tools, or conduct sessions completely verbally.

Project Limitations

As this project took place during the ongoing COVID-19 pandemic, reaching out to RCT participants in India was put on hold due to the fraught nature of the second wave in the country. In Kenya, sessions with participants did not take place as the project partner did not follow up with Quicksand on potential sessions.

Consultations did not take place with stakeholders from the level of funding and approval of RCTs in the Global South, as this was not considered in the project plan. On reflection, engagement with these stakeholders could have brought key learnings especially relevant to guidance uptake.

Topics explored with experts

The aim of sessions with experts was to understand challenges and experiences related to RCT protocols and community engagement. Therefore, the following was discussed;

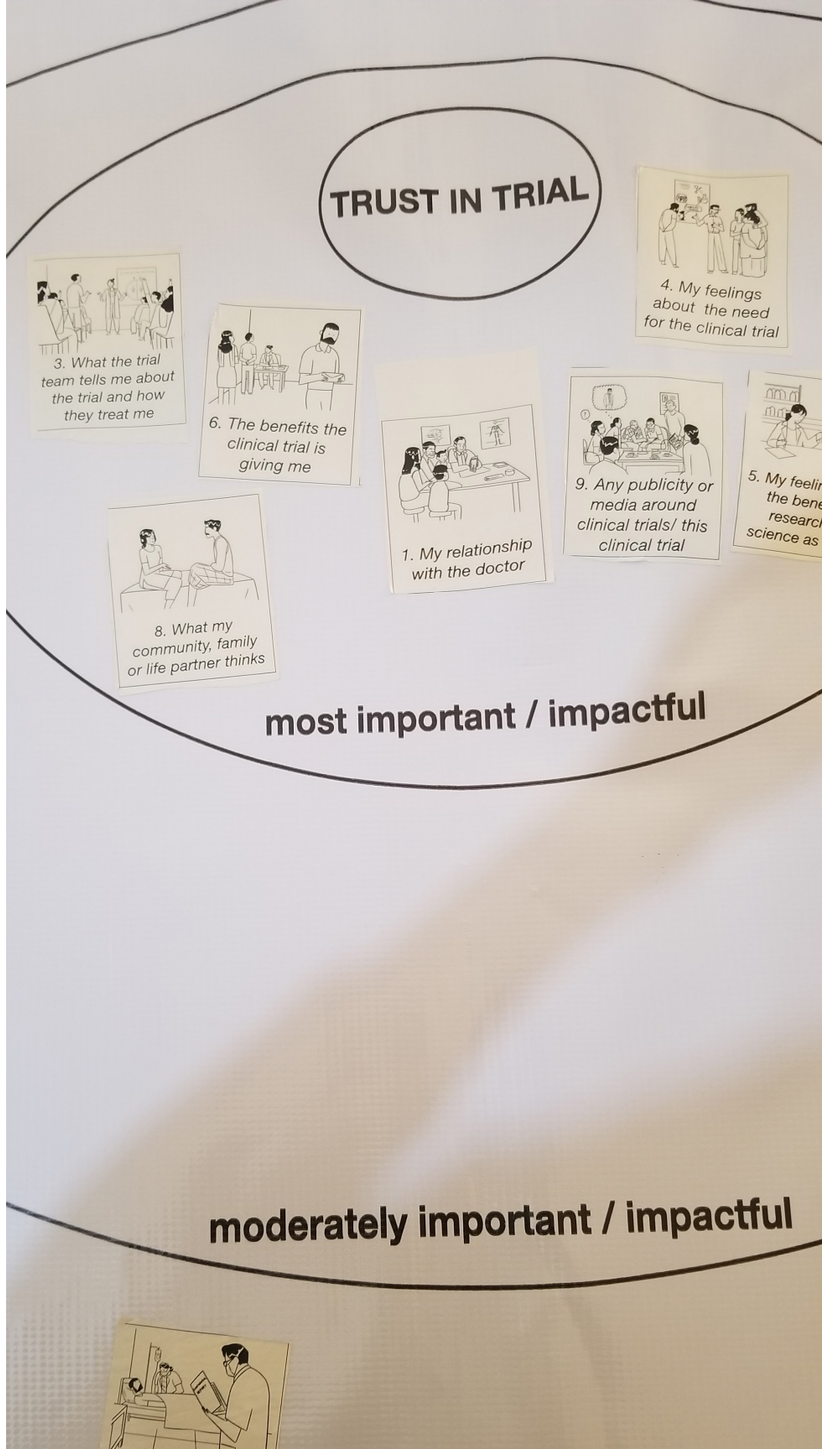
- Challenges and mitigation strategies in protocol design and implementation linked to 1) Site specific or community and 2) Approvals and regulations
- Community engagement in an RCT through the view of a clinical trial journey; looking at pre-trial, during the trial, post-trial stages

---

Topics explored with RCT participants

The aim of sessions with participants was to understand and gain context for individual, community-related and societal factors that can increase or decrease trial integrity for participants. Therefore, the following was discussed;

- The role and purpose of RCTs
- Factors that influence trust and breach of trust in an RCT
- Experiences of involvement before the trial, experiences of informed consent, experiences of participation during the trial, and experiences after the trial was complete
- Five “non-negotiables” for a good clinical trial



Consultation Sample Overview

49 Experts
47 Participants

Below is an overview of the types of participants, experts, RCTs and areas covered:

Sierra Leone

Participants: Community members
Experts: Trial manager, community liaison officers
RCT types: Vaccine
RCT areas: Ebola

Thailand

Participants: Sex workers, MSM, drug-users, transgender community
Experts: Protocol reviewers, director of a research network, PIs, research site manager
RCT types: Public health intervention, drug, vaccine, prevention tools
RCT areas: Maltreatment of children, HIV, Gonorrhea, Hep C

South Africa

Participants: Community members
Experts: Social and community scientist, CAB Member, study coordinator, and Community Liaison Officer
RCT types: Prevention tools and methods, vaccines
RCT areas: HIV, COVID-19

Kenya

Participants experience (through an expert): Community engagement, post-trial access and advocacy
Experts: Advocate for improving health outcomes
RCT types: HIV prevention/ treatment

Brazil

Participants: Health workers, mothers with children living with Zika attached to advocacy and support groups
Experts: Scientist, recruiter, human genomics scientist & bioethicist, RCT coordinators
RCT types: Genetic studies (genomic medication, microbiome), emergency vaccines
RCT areas: COVID-19, Zika, HIV, dengue, miscegenation, triplets

Nigeria

Participants: MSM community, patients
Experts: RCT ethicists, PI
RCT types: Drug, intervention, treatment,
RCT areas: Malaria, tuberculosis, anxiety (due to extraction of lower molar), surgical site infections , HIV treatment

India

Participants experience (through an expert): Cluster randomised trials, hospital-based trials, community-based trials
Experts: PIs, recruitment teams, RCT doctors, quality managers, research site coordinators
RCT types: Public health intervention, drug, vaccine, rare diseases
RCT areas: Mental health, Kangaroo Mother Care, COVID-19, childhood pneumonia, MDR TB, pneumococcal disease

Consultation Process

Partners in each country were responsible for a) recruitment of RCT experts and participants for the consultations and b) conduct of sessions. Each partner had past work experience in public health, clinical trials, human-centred design and research ethics, as well as established networks for recruitment. Considerations around biomedical research confidentiality and Ethics Committee approvals for Human-Centred Design projects were challenges to RCT participant recruitment. Highlights of each partner's approach is given below:

Thailand: DSIL Global engaged professional networks in Thailand drawing on contacts across United Nation agencies, Thai research institutions, treatment and community advocacy groups and corporate contacts (Janssen Pharmaceuticals). Expert interviewees were approached to support introductions to trial participants, Thai language information was disseminated in LINE groups and via email to aid in the recruitment of participants. Sessions with trial participants were tailored to participants needs, at least two of the sessions occurred with participants outside of Bangkok (Pattaya and Udon Thani respectively).

Brazil: Flutter Innovation has partnered with Quicksand previously on a Wellcome-commissioned project titled "envisioning human-centred approaches in clinical trials" and had built good connections with researchers in public universities in Brazil and with community-based support groups for women and children affected by the Zika epidemic and microcephaly. The team utilised a recruiting agency. Recruitment took place through public universities, research centres, emergency care units and hospitals. Flutter learned that most clinical trials for COVID took place in two urban research centres in Sao Paulo and Rio de Janeiro. In Brazil, COVID vaccine RCT participants consulted primarily were from medical communities.

South Africa: Matchboxology (MBX) has partnered with Quicksand previously on a Wellcome-commissioned project titled "envisioning human-centred approaches in clinical trials" and had built good connections with a Community Advisory Board (CAB) member and community representative. Recruitment took place via enquiries with CAB networks in South Africa. Given sensitivities around clinical trials during the pandemic, MBX faced some challenges with experts based in academic institutions as they insisted on ethics approvals for this project before making commitments. Consultations were conducted at a community-based research site. The CAB and research team there reviewed the project protocol and discussion guides.

Nigeria: Prof. Morenike Folayan was introduced to Quicksand by a representative of the African Academy of Sciences (connected via the GCTC team). Prof. Morenike Folayan is a Paediatric Dentist and academic, and has published extensively on ethics of clinical trials and research design and implementation. As Prof Morenike Folayan is attached to a research institute, the ethics approval for this project was obtained within a short timeline via the IRB. Recruitment initially was focused on randomised clinical trials outside of Prof Morenike Folayan's institute, but PIs of these RCTs were slow to respond. A decision was taken to look for a diversity of types of RCTs from the research institute. Discussions took place with respondents who are from low-literacy and high-literacy backgrounds.

India: In Round 1, Quicksand engaged clinical trial experts and trial teams. Quicksand was unable to conduct further interviews with RCT participants in India for Round 2 due to the second wave of COVID-19.

Sierra Leone and Kenya: Through the African Academy of Science, the GCTC, and past project engagements, Quicksand was able to conduct consultations with researchers, RCT participants and advocates based in Sierra Leone and Kenya.

LMIC Consultations and the GCTC Guidance

The GCTC guidance delineates seven principles of good randomized clinical trials. Each principle is substantiated by key messages and a paragraph that calls out the importance of each key message. The introduction to this document gives context into why the GCTC and guidance exists; provides a brief summary of the characteristics of this guidance and its objectives; a description of the wide range of individuals and organisations this guidance seeks to support who are involved in planning, conduct, analysis, oversight, interpretation, funding, and oversight of trials with any design, any health intervention, any purpose, any setting, and as any role.

Consultations gathered ground-level insights on RCTs and took place in seven LMICs. This section makes recommendations for the guidance based on key learnings from the consultations.

GCTC Principles of Good Randomized Clinical Trials

Good RCTs should be designed to produce scientifically sound answers to relevant questions

Good RCTs must respect the rights and well-being of participants

Good RCTs should be collaborative and transparent

Good RCTs should be designed to be feasible for their context

Good RCTs manage quality effectively

Good RCTs have appropriate trial governance

A good RCT uses a proportionate approach to safety assessment and reporting

Implications of consultation key learnings on "trust" in the guidance

The guidance conveys descriptions of trust and trustworthiness in the introduction (linked to the effects of lacking useful information from RCTs), principle 1 (linked statistical analysis of main outcomes) principle 2 (at a more ethical and philosophical level), and in principle 3 (linked to actionable phases like result-sharing, trial registration). From theme 3 key learnings on participant experiences, trust in an RCT was built and sustained by factors like trial team behaviours (friendly, respectful, accessible), and attitudes (professional, non-judgmental, open to feedback); the sharing of good quality information and open communication during the trial; and meaningful feedback mechanisms and redressal of feedback. Especially for participants with no prior scientific knowledge, it isn't easy to differentiate and evaluate types of research. Therefore, to create a complete understanding of how trust in RCTs is built and sustained before, throughout, and after the trial there is room to link appropriate guidance sections to these factors.

Key Learnings for Principle 2 / Good RCTs must respect the rights and well-being of participants

General feedback on the principle:

To further strengthen the lens of participant experiences (theme 3 key learnings) in the guidance, the principle can elaborate further on how "meaningfulness" and "relevance" of decisions, outcomes, participant wellbeing and safety is discovered and maintained in clinical trials. For instance the guidance could call out community, stakeholder and participant engagement mechanisms (theme 2 key learnings) as tools to respect the rights and well-being of participants. There is a need for this principle to cohesively speak to three key stakeholder needs - trial managers, participants, communities - addressing these needs would support this principle in RCT practice.

Specific suggestions:

Respecting the **"well-being"** of participants requires significant effort and investment in supportive systems like like good quality mental health counselling, round-the-clock care from RCT doctors, and provisions to maintain confidentiality. This principle can elaborate more on systems that can enhance well-being and how RCTs can look after participant's needs in this regard. RCT participation can be stressful, especially in trials with placebos, the unblinding phase can have significant psychological impact. Participation can also be tedious and time-consuming within the context of daily lives and routines. RCTs can also take place in the midst of epidemics, or with communities that are already marginalised and vulnerable.

The key message **"working in partnership with people and communities"** as this section rightly points out, is key and valuable for contributions to the design, execution, and interpretation of RCTs. As this is crucial, we believe that there is room to be more descriptive of other key stakeholders and their roles in this partnership like; health advocates, patient advocates, community representatives and community based organisations. The use of the term community engagement, along with patient and public involvement, can highlight the importance of "community" in LMICs. As the practice of this key message requires detailed planning and sustained actions, the guidance can reference existing good practice guidance.

In the key message **"appropriate participant communication"** the importance of providing timely and relevant information is extremely important not only for ethical reasons but also to prevent dissatisfaction in participants that might impact

retention. Excessive detail, especially if presented in written formats, is not ideal. Additionally dialogue - time to ask questions and weigh options - as much transparency around the RCT goals and expectations, and a friendly demeanor of informed consent staff is extremely key to communication. The guidance should encourage trial team members who frequently engage with participants to communicate on what an RCT is, and how its conduct is monitored and regulated from the point of view of participant safety, wellbeing and rights.

In the key message on **"relevant consent"**, the guidance highlights the importance of tailoring information to the needs and and expectations of the participant, and highlights "models and methods" for obtaining and maintaining consent. Consultations highlighted that trial team members (their communication skills, training) and also their effort to consistently engage with RCT participants is key to the consent process. The guidance could highlight the role of these people.

In the key message on **"modifying consent"** the guidance mentions the following, "if the reasons for withdrawal are not properly explored, and the 'withdrawal' is interpreted with prejudice to mean complete removal from the study, trial participants may be unnecessarily and inadvertently lost to full or partial follow-up." This rings true to the key learnings from this project. Consultations revealed that participant withdrawal from an RCT isn't addressed just by probing around possible misunderstandings; as in some cases withdrawal is an intentional act by the RCT participant. Guidance therefore needs to speak to the prevention and redressal of these cases as well (i.e. when it is an intended act). Examples of bad experiences and lack of satisfaction with the trial product and/or the quality of trial conduct prompted participants to withdraw suddenly and without intimation. The guidance can address this by highlighting the role of the following; training of individuals who conduct informed consent and recruitment to communicate around potential risks, discomforts and consequences of withdrawal, training of trial staff/ monitors to observe participant behaviours, and the need to set up appropriate mechanisms to engage with participant discomfort or negative experiences during the trial. The key learnings from consultations relevant to this key message is also linked to guidance principle 5 on quality management of RCTs.

In the section on **"implications of changing consent"** it would be appropriate to also mention clear communication and transparency with participants from the trial team in the event their right to withdraw consent for data already collected is not applicable to the particular RCT.

Key Learnings for Principle 3 / Good RCTs should be collaborative and transparent

General feedback:

The project highlighted how the RCT ecosystem in LMICs is not just about key players, researchers and participants. RCT stakeholders are numerous, and this section provides the opportunity to be more descriptive about the types of stakeholders and their roles in the endeavour.

Specific suggestions:

The key message **"collaboration between organisations"** is extremely relevant to the context of the Global South. PIs mentioned the power imbalance and infrastructure asymmetry between resource rich and resource poor settings. While the principle captures this effectively, to bring this to life the use of actionable terms like "trusting local partners" "community stakeholder engagement" and "listening to local partners" can be considered.

The key message titled **"transparency and trust"** could also provide clarity in this title of its relation to result-sharing with communities/participants and dissemination to wider stakeholders (termed as RCT beneficiaries in the stakeholder map from this project). If relevant, the

section may also highlight the following to sustain trust and confidence; RCT benefits for advocacy and policy-influence, the importance of returning first to participants/participating communities and ensuring that promises related to post-trial access and follow-ups are followed through. The guidance can also suggest the following beyond result-sharing; the consideration of prioritised access to approved drugs to RCT participants/communities following successful RCT interventions; extended follow-ups beyond the trial, and access to medication depending on the trial population needs. This can go a long way in appreciating the efforts of RCT participants and can prolong support for RCTs in communities.

Key Learnings for Principle 4 / Good RCTs should be designed to be feasible for their context

General feedback:

This principle is extremely relevant for LMICs and resonates with the feedback received from Global South RCT designers, implementers and reviewers. The key messages may need to be more tailored to Global South contextual realities, for example, around weak health systems, developing/absent RCT infrastructure, the need to build skills and capacity of researchers and approval bodies for efficient and ethical RCT conduct and RCT initiation.

Specific suggestions:

The key message **"setting and context"** provides guidance on the need for RCTs to be shaped by the setting and participant health needs, preferences, and awareness. This resonates well with project key learnings. As observed earlier, "public and patient involvement" does not encompass the role that "engagement", and qualitative research like "community mapping" plays in identifying setting and participant needs. The guidance can be more direct about the purposes of these tools/approaches. For example, engagement covers a spectrum; informing, consulting, collaborating, involving and empowering[3] which are brought to life by engagement "activities." Qualitative and social science research through its use of observation over time and active listening and mapping can be effective in identifying a multiplicity of factors related to setting and context that has already been included in the text of this key message. Community mapping before the trial can ensure disease burden and population specific needs are adequately assessed. RCT protocol designers can then devise and weigh options to mitigate these (in a proportionate and rational manner aligned to the core messages of the entire guidance). This assessment and consequent mitigation will impact principles on safety, quality, scientific soundness, and participant rights positively.

The statements in the paragraph on **"setting and context - why this is important"** highlights the instrumental purposes of the key message well. This statement should be substantiated further with intrinsic/ethical purposes as this will likely lend itself to increasing the value of the key message. The key message is also important because it lends itself to- reducing the risk of exploitation, reducing risks of participation from the point of view of vulnerability, and addressing complex issues like therapeutic misconception, power dynamics and information asymmetry.

In the section on **"the use of existing resources"**, differences between resource-poor and resource-rich settings become stark. Rather than a "waste" of resources, the deficit of resources, infrastructure and skills were highlighted. This deficit or lack had a clear impact on the kinds of sites that were a) selected for RCTs b) on exclusion of considered sites after feasibility checks.

3. IAP2 Spectrum of Public Participation (https://cdn.ymaws.com/www.iap2.org/resource/resmgr/pillars/Spectrum_8.5x11_Print.pdf)

Key Learnings for Principle 5 / Good RCTs manage quality effectively

General feedback:

This principle provides actionability and recommendations to support guidance messages that might be perceived as abstract (like those in principle 2 and principle 3). Therefore, there is ample opportunity to provide examples in this principle from these consultations and others, and references to existing good practice videos and documents.

Specific suggestions:

The key message on **critical-to-quality factors** adequately captures key issues around quality that are linked significantly to participant well-being and safety. The assessment considerations can be supplemented with more examples from the project that are aligned to participant experiences and community engagement needs. More details follow. Examples of factors associated with the intervention can also call out the known and potential characteristics of the trial product/intervention. Examples of factors associated with evaluations required to answer the study objective that would not be expected in usual care can highlight not only invasive investigations, but also trial procedures like frequent data collection and questions (as this might impact psychological wellbeing). Examples of resource implications can also include indication for additional community engagement resources as needed, or training/upskilling of the trial team as required.

The guidance can reference case studies of RCTs and examples from community involvement and engagement to describe/ illustrate how key issues can be identified and how these issues can be minimised, mitigated or monitored.

The key message on **rational monitoring** provides guidance on how monitoring should be proportionate, be seen as an opportunity to further improve quality and provides examples that align with key learnings in theme 1 around how protocols need to have room for modification when the RCT enters the stage of implementation. The guidance could highlight that this key message is relevant to stakeholders like funders, ethics committees and regulators who are responsible for RCT oversight, auditing or inspection. Besides these stakeholders, community engagement personnel and feedback mechanisms more intertwined with RCT conduct, are also important to identify problems and issues that may remain hidden/unknown to the trial management.

In the paragraph on **“rational monitoring- why this is important”** the social and ethical value of rational monitoring can be highlighted. This can be an opportunity to monitor participant vulnerabilities (for example, low research literacy that impacts understanding on the importance of adherence or voluntariness and heightens the risk of exploitation) which can be important for good adherence, and prevent lost-to-follow ups and withdrawals.

Key Learnings for Principles 1, 6 and 7

Overall, these sections were observed to be more relevant to readers from trial teams and those responsible for RCT design and implementation. The addition of cues on participant experiences (what motivates their participation and what causes atypical behaviours that can impact trial integrity) and community/stakeholder/participant engagement can be valuable to bolster the value and actionability of these principles.

The following statements in the guidance have good resonance and alignment with participant needs in LMICs:

Principle 1 / Good RCTs should be designed to produce scientifically sound answers to relevant question: "Disproportionate data collection wastes time and resources and detracts from the objective of the RCT" : Participant experiences detailed how the need/frequency of invasive procedures were deliberated upon when prospective participants were involved in protocol related decision-making. Participants need to see clear links to the value of these procedures for RCTs through communication, and researchers must put participant needs first in these cases.

Principle 1 / Good RCTs should be designed to produce scientifically sound answers to relevant question :"Extended follow-up after the scheduled closure of an RCT can allow for detection of both persistent or enhanced beneficial or harmful effects following cessation of study treatment (i.e. a legacy effect)": Participant experiences highlighted the importance of post-trial follow-ups beyond the trial in making them feel safe and valued. Consultations also highlighted that follow-ups be endeavored with all participants, even those who dropped out voluntarily or involuntarily (on account of exclusion criteria).

Principle 7 / A good RCT uses a proportionate approach to safety assessment and reporting: The content of this principle resonates well with best practices and non-negotiables of Good Clinical Trials as defined by RCT participants. The key messages around safety delineated in this principle become extremely important in epidemic situations that are filled with anxiety, misinformation, and unknowns, and significantly threaten life and quality of life. The guidance could include this as a caveat or consideration to boost its prioritisation in these situations.

Specific suggestions:

Principle 1 / Good RCTs should be designed to produce scientifically sound answers to relevant questions: "Subgroup analyses should be interpreted cautiously, especially if they are not pre-specified or multiple in number (whether pre-specified or not)." : Experts from Thailand and India provided examples based on their experience, on the value of unplanned subgroup analyses. Subgroup analyses that reveal insights into causes of high-risk behaviour, barriers to treatment uptake, barriers to prevention etc. can identify future research priorities that can be beneficial for populations living with HIV, or with the increased risk of HIV.

Principle 1 / Good RCTs should be designed to produce scientifically sound answers to relevant questions
"Efforts should be made to optimize adherence to the allocated intervention(s)" is the key message related to optimal adherence to the allocated intervention. The next key message around blinding and masking highlights that non-adherence related participant behaviours "can be avoided through use of placebo medications or dummy interventions or by ensuring that those individuals or systems responsible for assessing participant outcomes are unaware of the treatment allocation."

From consultations, it was learned that non-adherence was also impacted by factors like; bad experiences during the trial (related to dissatisfaction with the nature of the product and RCT, trial team behaviour), long RCT timelines, and when participants perceived that risks and discomfort outweighed benefits. Case studies of RCTs with placebo controls, gathered through consultations, revealed instances of participants considering and practicing non-adherence. Optimal adherence behaviours are linked to the quality of the trial (principle 5) and respect for participant rights and wellbeing (principle 2). Guidance could suggest the following to optimise adherence- effective communication before the trial about its purpose, risks and procedures; simple reassurances and reminders during the trial; careful assessment of participant preferences, needs and pain-points before and during the trial; and feedback loops between participants and trial teams. Consultations also revealed that RCT quality of care and access to health check-ups can positively influence adherence behaviours especially in lower-resourced settings.

Principle 6 / Good RCTs have appropriate trial governance:"The need for a member or a component of the governance structure (e.g. the Data Monitoring Committee) to have independence from trial sponsorship and management should be determined in advance, by assessing the risk that advice could be materially influenced by the relationship." This principle adequately captures the need for diverse strengths and capabilities, a balanced approach to monitoring, and the need for independent bodies to review RCTs. This resonates well with all governance related challenges and plans that RCT stakeholders highlighted. This principle can also be made more actionable by cross-linking to best practice guidance on governance mechanisms, for example; "Good Participatory Practice by AVAC". The role of the partnership between trial community engagement teams and RCT participant advisory groups / community advisory boards in monitoring an RCT can be another best practice example to support the practicability of this principle.

Principle 7 / A good RCT uses a proportionate approach to safety assessment and reporting: Principle 7 and its key messages effectively cover the following points in detail; the importance of a proportionate approach to safety assessment and reporting, how to manage the safety of individuals in the RCT by considering risks and population pre-existing epidemiology, how to evaluate safety-signals from within the RCT that are important from a public-health perspective, the importance of providing new safety information to the Data Monitoring Committee that can evaluate and respond to external safety signals through a proper assessment of the broader context, and finally the importance of circulating contextualised safety updates to relevant parties (in this project referred to as RCT stakeholders). This principle is very aligned to lessons learned from RCTs conducted during the COVID-19 pandemic. The only suggestion is for the guidance to highlight the importance of good quality public engagement, education and participant communication in these urgent and anxious situations. This engagement should be not only on safety-signals, but also around vaccine risks and benefits to support a complete understanding of the situation and prevent misconceptions.

Clinical Trial Stakeholders

1. RCT Approvals, Oversight, Regulators

- Ministries of Health
- Drug approval bodies
- National Ethics Committees
- Approved Ethics Committees

2. RCT Initiators

- Research Networks & Consortiums
- Investigators
- Sponsors- Industry, Academic, Public-Private Partnerships

3. RCT Reviewers

- Advocacy Groups (health and human rights & civil society voice)
- Auditors: Funders,CROs, Drug Approval Authorities, ECs
- Social Scientists / Community Scientists

4. Trial Conduct

- Community Liaison Officers
- PAGs/PPAGs
- Trial Staff
- Participants
- RCT Managers
- Community Advisory Boards
- Clinical Research Units and Centres

5. RCT Quality/ Recruitment Partners

- Research Networks
- Contract Research Organisations

6. Community Stakeholders

- Local Governments
- CBOs and NGOs
- Community Gatekeepers
- Community Members
- Community Representatives

7. RCT Beneficiaries

- Advocacy Groups
- Healthcare Providers
- Policy Makers
- Publics

Key Learnings Theme 1:

Conducting an RCT in the Global South

Trial protocols are rule-books for RCT teams, auditors, quality monitors and ethics reviewers. Consultations with Global South RCT experts were framed to understand what challenges occur at the protocol development phase and during protocol implementation, and how these challenges can impact trial conduct and participant experience. Experts also reflected on possible ways to mitigate these challenges; discussing what can be done to address them, what is already being done to address them, and which challenges are yet to be addressed. The discussions moved far beyond the production and implementation of the protocol, into deliberation around funding and implementation contexts and how these factors impact the room to adapt and tailor RCT protocols for maximum effectiveness in their contexts.

Randomised Clinical Trials are expensive to conduct and require skilled and experienced principal investigators to shoulder the ownership and responsibility of conducting a good quality RCT. Experts reflected that organisations with the funds for research and those that distribute funds, determine what research is prioritised and conducted. Funding for investigator-initiated RCTs is limited and clinical trial sites in LMICs often recieve protocols that are designed externally and implemented in the country. Therefore, protocol developers and funders need to think critically about doing research in community settings with extremely limited access to healthcare or weak health systems.

RCT success is highly dependent on the setting and the context. Protocols that are "handed-down" to sites as a part of multi-country or multi-site RCTs can, through community engagement, be tailored and changed to suit participant schedules and cultural contexts. However, there are some aspects that cannot be changed at this point, especially around the nature and design of the study. Therefore, priorities for PIs and trial managers are a) the need to strike a balance in the protocol such that it allows for flexibility and responsiveness to on-ground/during trial scenarios and b) the need to ensure that the protocol is satisfactorily tailored to the needs of RCT communities and participants.

"We disrupt community life when a clinical trial is set up. A new economy, people and new distractions. Communities that accept clinical trials are doing good for us as a whole, and deserve recognition."

Sierra Leone

1.

Experts noted that when protocols are handed down to researchers or sites by RCT sponsors in a pre-final stage, meaningful community engagement practice and site-specific adaptations are likely to be affected.

Examples from Consultations

RCTs represent economic and commercial opportunity. A trial team in a country with a more mature RCT landscape and economic empowerment is therefore better placed to advocate for meaningful adaptation and tailoring of protocols to site-specific needs.

At times handed-down protocols do not allow enough time for meaningful community engagement to take place. In such cases, elements of the protocol that could be aligned more with community input like the inclusion/exclusion criteria, benefits of the RCT, and trial related procedures can be overlooked.

"Researchers have to run backwards to engage the community, it becomes more about convincing them." Nigeria

"Patient care is easy to change. Nature of study is very difficult to change and sponsor requirements are difficult to change." South Africa

---

Sponsors in these cases might only go to Community Advisory Boards for very specific tasks, rendering their capabilities tokenistic and for the purpose of a "rubber stamp"

"CABs can function in a very conventional way. You ask people to become members and they comment (usually on the wording of the informed consent document)- which doesn't mean anything." Thailand

---

PIs in LMICs need to be "empowered" to advocate for site-specific needs with sponsors; which suggest that more effort needs to be made to increase meaningful two-way dialogue between these two stakeholders.

CASE STUDY ON PROTOCOL ADAPTATIONS

HPTN 083 PrEP Study: A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir. The study compared the efficacy of CAB LA to daily oral TDF/FTC for HIV PrEP. It enrolled 4,570 cisgender men who have sex with men (MSM) and transgender women (TGW) who have sex with men. The study was conducted at 43 sites (in Argentina, Brazil, Peru, United States, South Africa, Thailand and Vietnam)[4]

The protocol was developed overseas before the research site was involved. When the site took it on, the research team reached out to MSM and transgender communities for their feedback. From this, they learned that the exclusion criteria of transgender women who have had buttock implants would mean recruitment would be difficult. Implants are very common in Asia amongst transgender women. While feedback might not change the core protocol, engaging the community alerted the team on the need to provide different muscle groups for injection (for example thigh). It also alerted the team to the community's main concern outside the study— the interaction of PrEP with feminizing hormone use. This study illustrates the need for responsive and adaptive participatory protocol development processes that takes into consideration the entire study site landscape as well as context.

4. https://www.hptn.org/research/studies/hptn083

2.

Global South systems for RCT approvals, oversight, conduct and risk management may vary significantly from their Global North counterparts. This can cause back and forth between the two representatives coming from differing experience. Reaching a middle ground can be challenging. In such cases it is essential for trial protocols to have room to align with local context needs and preferences, and for trial teams to listen to and trust local expertise.

Examples from Consultations

The system to obtain approvals for storage of trial products or data might differ. For example - in Sierra Leone the Pharmacy Board of Sierra Leone is responsible for approvals of where medicines are stored, and in Europe a national licensure is required. This causes audit-related challenges.

In India, it was noted that certain health data for participants that is mandated by the protocol may not be available due to unavailability of records and health data.

Ultimately the research is situated within imperfect health systems. Standards of care, client-provider relationships, access to insurance can significantly differ. So, despite protocols and referral pathways being 'approved' or sanctioned in terms of research standards, they may still cause harm. For example; a referral for women experiencing violence in Thailand could be detrimental if the system is insensitive, but it would be considered to meet RCT protocols and ethics.

It is important for RCT protocol writers to identify, assess and mitigate such situations by aligning strongly to the needs of RCT participants and communities. For example; RCTs can be designed with an eye on general health needs in the community; offering alternative medications/vaccines for the control group, regular access to healthcare services, and improvements to existing healthcare infrastructure.

3.

Depending on the approach of the funder or trial network, these multi-country trial initiators have the resources required to increase room for context, population and setting-specific adaptability in protocols and flexibility in trial implementation.

Examples from Consultations

The extent to which the drivers (i.e sponsors/RCT initiators) of the protocol understand the value of cultural context of the trial community determines their attitude to protocol designed and implementation.

"Sponsors and other trial team members should go through some form of cultural and local adaptation and orientation apart from GCP training"
Sierra Leone

Sponsors that were flexible with protocol amendments during the COVID-19 pandemic listened to community suggestions on trial schedules and settings (Thailand)

Sponsors can support local teams in designing their own high-quality protocols. Some of the ways they do so is by; being open to unforeseen delays, understanding the need for lengthy writing processes for complex protocols, supporting local research teams with additional expertise. (India)

Generally, protocols do not come with specific recommendations on how to implement based on the kind of participant group. Trial conduct, product/intervention and procedures might not be sufficiently tailored to participant needs and preferences. In one case however, the protocol for a large-network supported HIV vaccine trial in Brazil made recommendations to train nurses on how to approach trans and gender fluid participants with their social names and not their legal names.

"Whenever possible, involve the researcher in the routine of the participants and adapt protocols according to the volunteer's needs." Brazil

CASE STUDY ON PROTOCOL ADAPTATIONS

MICROBICIDE TRIALS NETWORK 017, RECTAL MICROBICIDE TRIAL: A Phase II trial designed to evaluate the rectal safety, drug absorption and acceptability of a reduced glycerin formulation of tenofovir gel, as well as oral Truvada, at sites in Peru, South Africa, Thailand and the U.S., including Puerto Rico.

The trial was cited as a best practice in protocol development, due to the significant community input from all trial sites that went into the trial protocol, before it was "baked in". Some significant changes that were made from these community consultations included; amendments to the inclusion criteria and the language used in the protocol. Trans women were included within the inclusion criteria, and the language used in the protocol was tailored to suit fluid interpretations of gender amongst the population.

4.

The lack or deficit of resources, like appropriate research and medical infrastructure is likely to cause sponsors to turn down valuable research sites. It was also noted that RCTs are initiated in Global South countries that already have the capacity for research rather than in those where research infrastructure has not yet been developed.

Examples from Consultations

"All RCTs related to COVID are Global North agenda, 1 out of 10 trials are being done in the Global South for development of the assets and treatment. Most trials were initiated and stayed within the Global North , the rest are being done in countries which have the capacity (like South Africa). It's an irony that protocols mention that they will build capacity in the participating country, but it is being done in a country with capacities" Nigeria

Pharmaceutical trials have a "preset" system. Feasibility checks by pharmaceutical companies are very detailed and lengthy. At times these sponsors do not procure equipment for the RCT and might as a result, exclude clinical trial sites on account of infrastructure. (South Africa)

The sponsor might be in favour of choosing a site like a hospital in case medical equipment isn't available at the community based site. (South Africa)

"The sponsor has the upper hand. The sponsor can take away the study from the community. The participants have a right. The community doesn't have bargaining power." South Africa

5.

Good protocols from the "west" have introduced a standard for local research. These standards can potentially help researchers to develop protocols that focus on those local research needs that foreign funders do not prioritise.

Examples from Consultations

"Thailand has come a long way and applies these good protocol standards to local work. There was a time where Thailand had never seen a protocol that was 300 pages and had such sophisticated structure. These international trials set the standard but also raised the research standards in Thailand for RCTs." Thailand

6.

Regulatory bodies and regulatory ethics committees were cited as being bureaucratic and slow with approvals and in some cases lacking adequate competence, capacities and/or resources to review RCT protocol. Stakeholders like researchers, advocates, and research ethicists facilitate RCT efficiency and practice in the following ways:

Examples from Consultations

Health advocates as well as researchers are interested in increasing locally-driven and initiated research as this has positive outcomes for communities in terms of access to treatments and interventions. Advocacy groups are known to lobby governments, address causes of delay in regulatory systems and obtain funding for research, while also acting as a watchdog of ethical research. (Thailand) (Kenya)

"We need to include regulators early on in the discussions. We only go to them when we want them to approve. Including them, consulting them and letting them also know about speculated timelines can help bring them on board." Kenya

---

Even when research protocols are highly localised and have significant buy-in well before the approval process, protocols with innovative elements may be roadblocked by an immature approval ecosystem. Researchers find ways to gather considerable resources (time or financing) needed to overcome this. Researchers largely invested in relationships, capacity building (supporting government or regulatory body upskilling) or financial resources to navigate the landscape. (Thailand)

Academic institutions, research networks, and advocates play a hand in training and capacity building of regulatory ethics committees and influential community gatekeepers like CABs. (CABs at clinical research sites in South Africa can turn down an RCT protocol if they feel the need to do so) (South Africa, Thailand, Kenya)

Researchers reported the technique of designing ideal and comprehensive protocols to account for changes proactively and ensure that ethics approvals cover a broader scope of implementation related possibilities. (Brazil)

CASE STUDY ON PROTOCOL ADAPTATIONS

To evaluate the efficacy of teacher-delivered transdiagnostic mental healthcare for children inl primary schools of India, this study is designed as a stepped-wedge cluster randomised controlled trials (SW-CRCT), with an embedded qualitative evaluation. Implementation process and context will also be examined. It will be conducted in lowcost private primary schools in rural and tea plantations of Darjeeling Himalayas of India.[5]

As there aren't existing guidelines for RCTs with novel approaches and in the public health space, this trial team spent a year conducting formative research on the context. The protocol writing team also involved anthropologists who introduced the lens of context and how that might impact the analysis of the results. The context of these rural school-sites according to their location (proximity to urban/periurban spaces, remoteness, near forest lands or tea plantations) and sociocultural-political context provided a new lens through which to analyse the trial results. The protocol was developed therefore through preprotocol qualitative research, the inclusive and multidisciplinary approach was beneficial for the study design and analysis plans.

5.For more information: https://ichgcp.net/clinical-trials-registry/NCT04723277

7.

Overly bureaucratic and restrictive governmental approval bodies can also hamper research practice and site selection. As a result, RCT protocols might be designed to circumvent constraints, impacting fair site selection.

Examples from Consultations

Protocols are not only written from the perspective of the RCT, but also to overcome regulatory and governmental hurdles that might slow down recruitment and increase costs. In Thailand, protocols can be designed to circumvent the need for permission from the Ministry of Public Health (MOPH), leading to the exclusion of hospital sites which require MOPH approval.

Successful examples of site-selection can be found through individual connections and 'champions' on the ground or through support via large-scale multi-country trials which have the backing, clout or resources to get things done.

Academic institutions and large teaching hospitals are frequently chosen RCT sites due to their access to medical resources and links to large pools of potential participants and communities. However, a community based site in South Africa reported decreased access to hospital / medical clinics as sites of recruitment for RCTs due to the time-consuming and complex process of obtaining approvals from the district and province level governmental bodies.

CASE STUDY ON PROTOCOL ADAPTATIONS

The RCT of Parenting for Lifelong Health for Young Children in Thailand is a randomised, controlled, observer-blinded, single-site trial with two parallel groups and a primary endpoint goal of reductions in child physical and emotional abuse at one month and three-months post-intervention. Randomisation will be performed at the individual level with a 1:1 allocation ratio.[6]

Maltreatment of children is a complex and sensitive topic. While procedures for identification of child protection and adult welfare concerns were part of the protocol from the very beginning appropriate localised alignment with Thai Legislation and Human Rights Guidelines is recommend for all studies that involve the gathering of sensitive information on children, this included localised reporting guidelines for serious cases of abuse and alignment of reporting of intimate partner violence through links to the health system in Thailand.

6. https://pubmed.ncbi.nlm.nih.gov/34051772/

8.

RCTs in public health emergencies are impacted by rushed timelines and are filled with "unknowns" that cause anxiety to RCT participants, affected groups and the public. Upholding research integrity and trust in science is crucial to curb myths and misinformation. This should be supported with public engagement, participant communication and ethical RCT practice.

Examples from Consultations

Experts frequently cited COVID-19 as an example where the lack of public engagement was linked to rampant myths and misinformation. This shows the non-negotiability of public engagement around vaccines, science, and required behaviour change.

Experts recommended that in epidemic situations, protocol development should be broken up into sections that are handed over to be approved by Ethics Committees as and when they are finalised to save time (Brazil).

The Sisonke COVID-19 vaccine trial in South Africa, was temporarily paused in April 2021 to review new data.[7] Based on this experience, an expert suggested that a good practice during epidemic situations would be for PIs and trial sites to have the "ability" to pause RCTs to review new safety data, revise inclusion and exclusion criteria to ensure participant safety and well being, without this pause impacting on logistical issues and intensified fear among study participants.

Effective communication and the informed consent process is necessary to educate participants on risks, benefits and what to expect, to ensure that people are motivated to participate with a clear understanding and not based on fear. (South Africa)

It becomes imperative to provide vaccines/promised benefits to all participants of the emergency trial upon unblinding (Brazil)

7. Sisonke Phase 3b Study press release: https://www.samrc.ac.za/media-release/sisonke-phase-3-b-study-temporarily-paused-until-us-fda-reviews-6-cases-rare-clotting

9.

The skill, experience and intent of principal investigators can facilitate the conduct of RCTs that have meaningful community outcomes and community engagement. Conversely, the lack of investigator-initiated research, and overburdened professional work schedules can hamper the above.

Examples from Consultations

Researchers with an intent to influence positive outcomes for vulnerable groups can spend many years in "pre-project" mode conducting qualitative research to understand needs in-depth. This knowledge impacts the decisions taken during protocol development, and the approaches built into to the trial conduct to ensure the success of the RCT and intervention/treatment uptake. (Thailand, India)

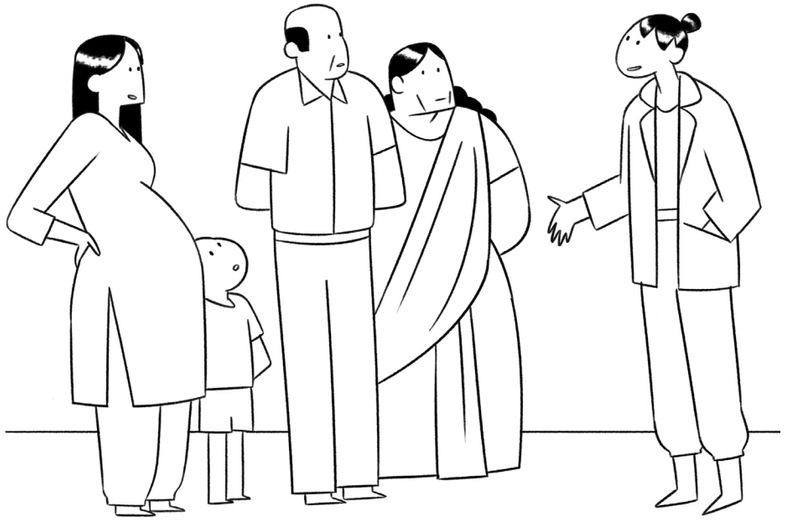
Researchers may also spend many years in building ownership and empowerment in communities in order to recruit and/or involve them in trial design and conduct. Community engagement is highly tailored to the RCT context and community. In some cases, researchers may also change the research design to suit the needs of the stakeholders without compromising the study rigor. (India)

"Research stands on the tripod of sponsor, investigator and community. Once you remove any leg of the tripod, the tripod (research) falls off. CE is a must." Nigeria

---

Researchers may be overburdened with expectations from their routine work or teaching hours which limits their time to conduct RCTs. (Thailand)

"In some cities, you have centres that are highly qualified for research. In other regions, especially in the north/northeast of the country, there are no such qualified research centres" Brazil



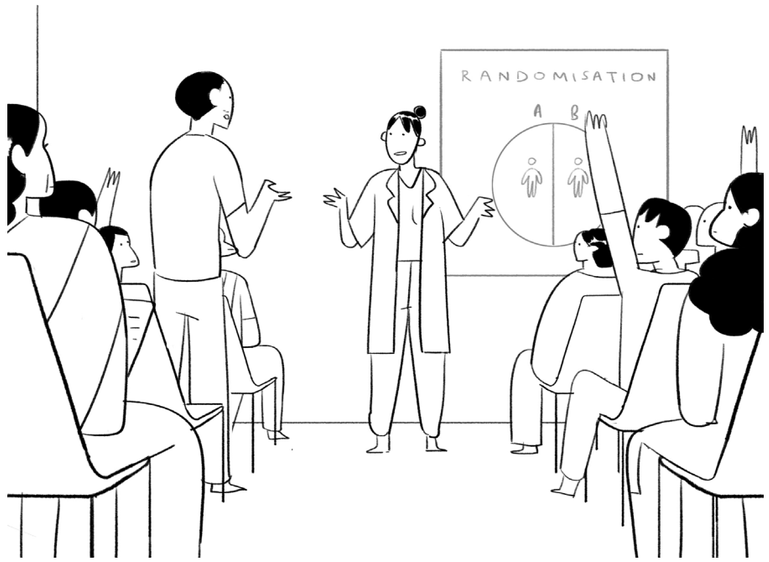
Key learnings Theme 2:

The Importance of Community Engagement in RCTs

Community engagement activities can be implemented for instrumental purposes (purposes that are good for RCT results and facilitate recruitment, adherence, retention) as well as intrinsic purposes (broader purposes that are valuable for the community and the conduct of research as a whole). Therefore, this kind of engagement presents significant opportunities to enhance the scientific integrity and ethical integrity of a clinical trial. Additionaly, a significant relevance of community engagement is to prepare individuals and communities for RCTs in contexts where the exposure to RCTs is low. It is a tool to build and sustain both; trust in RCTs and the value of RCTs. Community acceptance of the RCT, RCT success, participant adherence behaviours is extremely dependent on community and individual preparedness for research.

In this report, community engagement is a catch-all term for all kinds of activities and mechanisms for participant-level engagement and community-level engagement as both are complementary and inseparable in the contexts of enquiry. Participants and their families, community members interacting with the RCT, community leaders like village chiefs, community influencers like media, local doctors, teachers, all come under the gambit of beneficiaries of RCT-related community engagement. The term “public engagement” was used in the context of the engagement of wider publics, beyond the immediate RCT community, by scientists, politicians, media, community leaders especially around new and experimental medical products and interventions.

The following section details community engagement practice, mapped out from discussions that aimed to understand: the current utilisation of community engagement, unintended and intended outcomes of community engagement activities, and new roles for community engagement across project geographies. The inclusion of community engagement in RCTs was in some cases unplanned, and in others were elaborately planned and formalised activities that directly influenced design, implementation and knowledge dissemination along the pre-trial to post-trial continuum.



Community engagement actors

The visual highlights key "community engagement actors" who are responsible for facilitating meaningful and effective community engagement with RCT participants and communities. There are other stakeholders as well, like media personnel, local politicians, doctors, health workers who can become key actors depending on the RCT and the context.

Community Advisory Boards (CABs)
These bodies have become a formalised mechanism for approval of community-based RCTs in countries like Kenya, Thailand and South Africa. CABs are made up of people who are representative of different community stakeholder groups that are gatekeepers and influencers of opinion.

NGOs, Advocacy Groups or Community-Based Organisations (CBOs)
These bodies are interested in influencing and working on positive community health and life-quality improving outcomes. They are connected to "affected" groups, vulnerable and marginalised populations. They can be spaces of support and safety, and also are mobilised when community/individual rights are infringed by RCT design and conduct.

Trial Staff
Doctors, nurses, counsellors and drivers are frequent touchpoints between participants and RCT procedures. They are responsible for informed consent, "adherence counselling", and follow ups. At research sites where protocols are received, they may also be responsible for feasibility checks on site capacity, equipment, and staff qualifications.

Community

RCT Managers
In multi-country studies, multi-site studies, and RCTs with vulnerable groups, the Principal Investigators or trial managers become advocates for local needs. It is essential for them to be "empowered" enough to be able to represent community and local realities to sponsors.

Community Liaison Officers (CLOs)
They belong to the community and are a part of the RCT team. They play multiple roles throughout the trial journey. They build community confidence in the RCT, are responsible for communicating any feedback from participants and participant advocates, and manage rumours and at times community anxieties and "riots".

Community Representatives
These stakeholders can advocate for community needs and engage communities in RCTs. They have a "lived experience" of trial participation, or disease or belong to a close-knit community. Advisory Groups of these community engagement actors can be set up during the trial and across similar RCT areas to share experiences and improve RCT conduct.

1.

Participants or community members consulted were not engaged in the early stages of RCT design; like protocol development or feedback on research design. In RCTs where CABs and community engagement teams are formalised (South Africa, Thailand, Sierra Leone) participants recalled engagements with these community engagement actors at the time of recruitment or during the trial.

Examples from Consultations

An example of the community's trust in the CAB is that participants are willing to share the experiences with CAB members freely and they feel comfortable sharing any concerns. In addition, CAB members are their neighbours, people they go to church with, people they have grown up with so a deep bond of trust exists. (South Africa)

CASE STUDY ON COMMUNITY ENGAGEMENT

This randomised controlled trial (factorial RCT) aimed to test the preliminary efficacy of an individual level counselling intervention to reduce sexual risk and a community level intervention to promote acceptance of men who have sex with men (MSM) living with HIV. The study was conducted among MSM in an urban and a rural setting in Tamil Nadu. The study incorporated a meaningful community engagement process throughout as follows.[8]

The study was designed in consultation with the Community-Based Organisations (CBOs) who implemented the study. Community Advisory Board (CAB) members were chosen carefully to represent urban and rural sub-groups, different socioeconomic classes and sexual identities. Both CAB members and representatives of partner CBOs were actively involved in designing the study tools and educational materials, and in organising events/workshops to promote acceptance of MSM living with HIV. Peer recruiters, peer interviewers, and peer counsellors recruited from the partner CBOs were trained and involved in recruitment, data collection and counselling intervention, respectively. Information about the study were shared with government stakeholders. Community role models, who were open about their HIV status participated in the community events and workshops to reduce stigma faced by MSM living with HIV. During the study, participants were asked for feedback on the intervention through exit interviews (brief surveys) and at the end of the intervention, some of the study participants were interviewed in-depth to understand the mechanisms by which the intervention helped them or not. After the trial, partner CBOs were engaged on how best to share results with government stakeholders. Community workshops were held to share preliminary findings with the community before report publication. Peer researchers presented findings at stakeholder meetings, which enhanced community ownership. The peer-reviewed publication was shared with government stakeholders at the state and national levels.

8. Chakrapani, V., Subramanian, T., Vijin, P. P., Nelson, R., Shunmugam, M., & Kershaw, T. (2020). Reducing sexual risk and promoting acceptance of men who have sex with men living with HIV in India: Outcomes and process evaluation of a pilot randomised multi-level intervention. Glob Public Health, 15(3), 438-451. doi: 10.1080/17441692.2019.1675081

2.

In order for community engagement to be meaningful for the community and RCT, the process needs to be more than a tokenistic gesture. When referring to the CAB mechanisms, trial teams and participants noted that there was a risk of this actor being perceived as tokenistic or in "cahoots" with the trial team.

Examples from Consultations

CAB structures are very respected and accepted as the community's voice. However, not all CABs are equally efficient/ effective across all contexts. Some operate very efficiently, and others struggle due to limited finances/commitment. CAB members need to be passionate about community issues, especially when there is no monetary incentive for engagement. (South Africa)

"CABs can function in a very conventional way. You ask people to become members and they comment (usually on the wording of the informed consent document)- which doesn't mean anything. In addition you have multi-site, multi-country protocols and changing one thing means a complete review by many review boards. This means often you end up apologizing and saying we tried, but we can't change it. You cannot just have one mechanism, like a rubber stamp that says you already have community engagement like a CAB or platform for your study" PI, Thailand

---

"Community members who are vocal or seen as independent thinkers are usually not invited to be CAB members. Researchers prefer to choose those who are more docile... CAB members are appointed based on familiarity, thereby usually agreeing with the researchers..." Participant, Thailand

---

Building CAB capacity to represent community needs and critically look at research protocols is key. (Kenya)

"Researchers are sometimes too scientific in their communication. They can sometimes be too direct. Instead, they should try to use a more counselling tone. Sometimes CAB needs to step in to provide counseling to give participants some mental and psychological support." Participant, Thailand

3.

PIs recognised that community engagement activities which facilitate participation and involvement prior to the trial can shed light on ways to; increase acceptance of the RCT, deal with rumours/dissatisfaction, and define meaningful outcomes for the community. The following are suggestions to enhance this kind of engagement:

Examples from Consultations

Some researchers felt that the funder needs to send 'signals' to researchers and implementers that community engagement is a real priority and that 'out-of-the-box' community participation is appreciated. This goes beyond the checkbox of CAB or requesting good participatory practice guidelines certification.

Engaging members of the community before the trial protocol is set in stone can highlight insights around barriers to RCT delivery, level of access to services, and trial-related engagement standards during the trial and post-trial.

Community engagement is a way to increase research preparedness so that the RCT runs smoothly and all stakeholders are aware of their roles and responsibilities. One expert suggested this should happen one year before the actual trial.

"We started community engagement 1 year in advance of the study. We have been holding meetings to explain what the CT is, and the two different vaccines that will be tested and how they work. COVID 19 has taught us a lot of lessons in early preparation and engagement" South Africa

Early community engagement can also prepare communities to give better input into RCT protocol design.

"We need to prepare communities for their meaningful involvement in trials. There must be a plan to build capacity for the CAB so that they are able to effectively give feedback." Participant, Thailand

---

When RCT and community outcomes significantly align, interim information from RCTs can help advocacy groups represent community needs better to the government.

"There have been some steep learning curves. In the past feedback involved NGOs protesting in front of company offices, and that was how we are told our conduct or design is flawed." Thailand

9. Juliet Iwelunmor ,Oliver Ezechi,Chisom Obiezu-Umeh,Titilola Gbaja-Biamila,Ucheoma Nwaozuru,David Oladele,Adesola Z. Musa,Ifeoma Idigbe,Florida Uzoaru,Collins Airhihenbuwa,Kathryn Muessig,Donaldson F. Conserve,Bill Kapogiannis,Joseph D. Tucker, The 4 youth by youth HIV self-testing crowdsourcing contest: A qualitative evaluationPublished: May 29, 2020 https://doi.org/10.1371/journal.pone.0233698, 4 Youth By Youth Website: https://4yby.org/
10. https://clinicaltrials.gov/ct2/show/NCT04710784

CASE STUDY ON COMMUNITY ENGAGEMENT

The "4 Youth by Youth" Self-Testing crowdsourcing open call held in Nigeria engaged a broad audience of young people to generate ideas and perspectives on how to promote HIV Self Testing (HIVST). This process informed the development of youth-developed implementation strategies to increase uptake of HIVST among adolescents and youth at risk for HIV. The three main themes that emerged from the entries include: 1) Peer-to-peer distribution and leveraging on existing infrastructures 2) Youth-oriented branding of the HIVST kit 3) Mobile platforms and social media technology. [9]

In Nigeria, research with adolescents remained a gap until in 2018 when a guidance document on obtaining adolescent consent was released. The 4 Youth by Youth contest was initiated by the PI of an upcoming HIV self-test trial involving adolescents. In order to consult as well as empower adolescents, who would later help shape the trial protocol and help in trial implementation as "youth ambassadors," the trial team has spent 2 years in pre-trial engagement. This was a "pragmatic decision" made as the trial success is dependent on acceptance and uptake of the trial product in the community. The approach is now being evaluated in an ongoing randomized control experiment (NCT04710784).[10]

4.

Social scientists and qualitative research can complement community engagement (as well as protocol development). In-depth understanding of community behaviour, practices or attitudes can be tailored into a community engagement plan that can be formalised throughout the trial.

Examples from Consultations

Social scientists, who listen and interact with community members, and community engagement teams can work together to create plans to address myths and misinformation. (Sierra Leone)

"Before even the pilot study we did a formative evaluation (qualitative) of the intervention. Which refined the engagement aspects of the intervention and the feasibility study (pilot) with 60 families. This cumulatively informed the design of the RCT."
PI, Thailand

CASE STUDY ON COMMUNITY ENGAGEMENT

The following case study details learnings around community engagement during an RCT on a vaccine in an epidemic situation. The RCT was a new experience for community members who are unused to good quality healthcare and regular access to services.

The trial had a strong component of community engagement.
In the early stages of the trial, the community engagement team worked in close conjunction with social scientists. This proved to be highly effective in addressing mistrust and rumours in the community, as these social scientists were able to identify underlying reasons for rumours through conversations with community members which the community engagement team was then able to address through community meetings.

"Community Liaison Officers," who are individuals belonging to the community ("brothers and sisters") were employed within the trial team. The community engagement team is responsible for community sensitisation about the RCT, addressing myths, misconceptions and community feedback, building community acceptance of the trial and holding community meetings and sessions with community members, trial participants and village chiefs in the district.

The research project has also built up capacity in the local health system by stationing paediatricians in the local hospital and providing emergency care services in the locality. This is a benefit that will be felt after project closure by the entire community and significantly increases community confidence in this project.

5.

Community engagement during the trial can "diagnose" lost to follow ups or sudden drop-outs. Feedback forums and community meetings with RCT participants and gatekeepers can shed light on trial-related issues. These discussions can also identify solutions to improve participant experience or clear up misconceptions.

Examples from Consultations

"During COVID-19 it's easy for people to disregard study visits due to travel restrictions. But if your community engagement is continuous you quickly will diagnose the 'signs' of this potential loss to follow up. You prepare for this, by delivering study products and tele study visits." Thailand

---

Allowing adequate time for questions and aligning to community needs around confidentiality and safety can maximise the effectiveness of discussion forums.

Community engagement facilitators also mentioned the need to value participants' time by providing snacks and travel reimbursements. Participating in RCTs is a demanding endeavor, especially for participants from low-income settings and participants with acute health conditions. Addressing the overall well-being and needs of these participants is key to a good experience and engagement in future RCTs.

Participants suggested "anonymous" feedback boxes and followed by serious consideration of feedback by trial teams

"It came down to human interaction at the clinic and respect, or a phone call that says "how are you doing". This meant we also allocated more time to research nurses phone calls with participants. People want to feel like they are part of the bigger picture and make a difference." Thailand

CASE STUDY ON COMMUNITY ENGAGEMENT

Community engagement forums for the purpose of feedback to improve retention were set up during an RCT on an HIV prevention intervention

Community forums are part of the landscape of HIV research and implementation science across many studies in Thailand. Knowing that participants had to adhere to the trial product for a long time of four-and-a half years, the trial team held a forum to discuss what can be done to improve retention. It was conducted in Thai and English. The forum highlighted that in order to achieve good retention outcomes, participants and community members wanted to feel like they were part of the bigger picture. It came down to human interaction at the clinic and respect, or a phone call that says "how are you doing". This meant that the trial team allocated more time for phone calls by research nurses to participants.

6.

In hospital-based trials or public health emergencies, community engagement might be challenging to execute due to lack of time and high-levels of anxiety. However, it is also in these situations that participants may not be able to distinguish between research and routine care. As misconceptions and rumours are likely, effective engagement of publics around the RCT and its purpose is necessary.

Examples from Consultations

Distinguishing between routine care and a clinical trial might be difficult for a patient in acute conditions like sepsis or during pregnancy. In these cases, consent for RCT participation might take place in the first few hours after giving birth. (Example from Kangaroo Care Trial, India) One way to address this is to provide broad clinical trial awareness/information sharing in the community on clinical trials running at the hospital

Lessons learned from the COVID 19 pandemic have shown that engagement components like building awareness and conversation around RCTs need to start well in advance. There needs to be active and continuous engagement and dialogue between all stakeholders; sponsors, civil society, media, community leaders and scientists to ensure everyone is speaking the "same language" (South Africa)

"CE is the glue that puts everyone together" South Africa

7.

Community engagement actors like community "liaisons" are trusted members of the community and a part of the RCT team. They are a bridge between the RCT, the RCT team, community stakeholders and participants— especially in community-based or research-naive settings.

Examples from Consultations

Community Liaison Officers are a part of the trial community engagement teams. They are meant to advocate for the rights and wellbeing of participants, and relay feedback to trial management, leaders and doctors. (South Africa, Nigeria, Thailand, Sierra Leone)

Their responsibilities include (but are not limited to): sending messages about the RCT into the community; updating and involving CAB members, and engaging with community gatekeepers, like village chiefs in a manner that respects traditional practices and rituals. They are also responsible for the safety of transport of medicines like ART (South Africa) and clarifying any misconceptions or negative feelings about the RCT and its process through dialogue with community stakeholders. They play a role in managing crises in the community in the event that community members perceive the RCT has caused adverse events and valuing community time and feedback by providing reimbursements and relaying messages.

Over and above these, community liaison officers can be involved in protocol design and implementation plans. They can be involved with the formation of the CAB, play a role in the DSMB and communicate with media, political bodies as well as the trial management. (Nigeria)

One expert reflected that it might be even more appropriate to have these actors (essentially community representatives who have been employed by the RCT) trained by independent organisations to prevent a conflict of interest, and ensure that they are truly empowered. (Nigeria)

"There is one community liaison to ensure smooth coordination with the community. The liaison is usually selected among clinical nurses within the research team with no decision power, especially given the asymmetrical power relations between doctors and nurses." Thailand

8.

The experience of community engagement during an RCT can have far more long lasting outcomes for the community such as, increased research capacity and appetite for research. Community representatives could be advocates for future research, champions and intermediaries for post-trial engagement like result-sharing and recognition of those who contributed to research. Below is a summary of meaningful community engagement outcomes throughout the RCT continuum:

Before the trial:

- Affected groups and vulnerable groups can set research priorities
- CABs, CLOs, and ex-participants can inform RCT design and best practice
- Day-to-day aspects of a protocol like site-selection, inclusion/exclusion criteria, clinical trial procedures formats of communication delivery, result dissemination, post-trial access research priorities can be co-designed with relevant stakeholders with affected groups
- Ideas can be crowdsourced from community members to enhance components of the trial related to benefits, access to ancillary care, trial adherence and uptake
- "Target" groups can be empowered to implement recruitment and follow-ups

During the trial:

- RCT awareness and recruitment can be done in collaboration with community members who are part of the trial team like community liaison officers, or ex RCT participants
- Feedback mechanisms can be formalised to facilitate honest feedback and bring negative experiences to the fore through community forums, and informal meetings with participant touchpoints like nurses
- Ex-participants and parents of participants can be empowered to represent and advocate for the needs of participants to the trial team
- Interim results can be shared with relevant parties like advocacy groups
- Crises or anxiety in the community linked to the trial (for example caused by an adverse event, misconception or unblinding) can be managed through one-on-one interactions or community platforms

Post the trial:

- Result-sharing can be done through suitable channels, tailored to participant and community preferences
- Forums for discussion can be set up for healthcare access advocates, CABs, PAGs etc to determine what ideal post-trial access looks like
- Broader public engagement around the trial product can be facilitated in the case that it will be accessible to all
- Feedback can be gathered from community gatekeepers and influencers from the RCT community on what future priorities for RCTs in that setting might be
- The role of participants and communities in RCTs can be acknowledged and recognised in meaningful ways

Key learnings Theme 3:

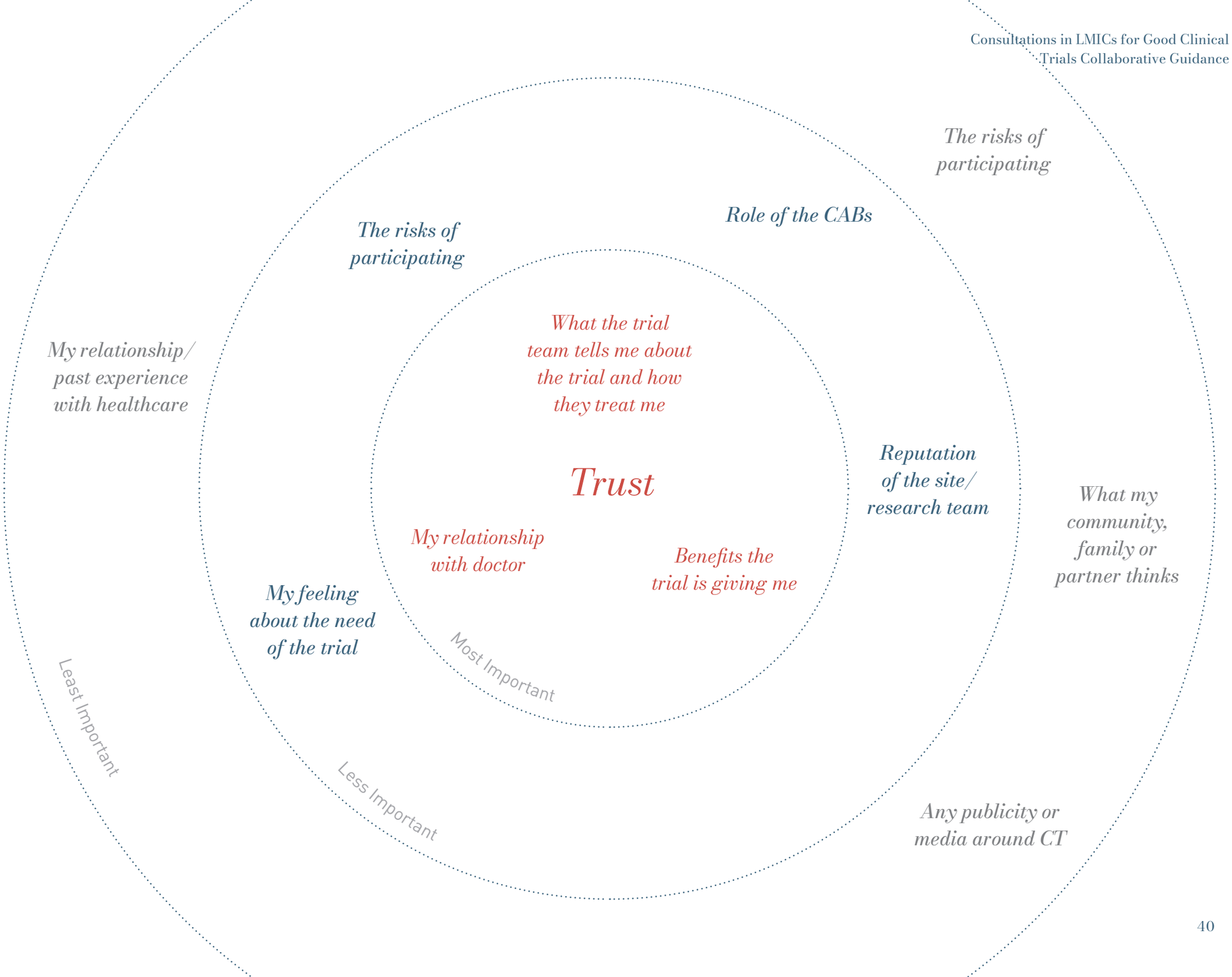
Trial Integrity from a Participant's Point of View

The scientific evidence and results generated by RCTs is just one component that impacts RCT integrity from the perspective of participating communities and individuals. RCT participation is a highly unique experience and at the same time an experience that is nestled in a much broader context of regular "lived" experiences. Therefore, integrity is built by the quality of the trial conduct, good experiences during the trial, trial team behaviour, and last but not least— participants and community benefits from the RCT.

"Clinical trials help the communities, they help with drug manufacturing. They help to create a consultative process. They help us to understand about our different lifestyle and the food we eat and how it affects our health"
Participant, South Africa

Key motivations and reasons to participate

This visual is a summary of the factors that impact people's trust in an RCT.



1.

Trust in a trial is influenced by three key factors – "my relationship with the doctor", "what the trial team tells me about the trial and how they treat me"and "benefits the clinical trial is giving me." It was less influenced by "my past experience with healthcare", "what my family/partner/ community thinks" and "any negative publicity/media around the trial". However, some of these factors become more or less important based on specific situations.

Examples from Consultations

CAB members noted that especially in public health emergencies, media around clinical trials and treatments influence perceptions and trust. They have to engage potential participants in dialogue to manage misinformation. (South Africa) Conversely, media can also bring good news and hope around life-saving RCTs and influence trust positively. (Sierra Leone)

Past experience with healthcare has the potential to leave certain groups of people, especially those who are marginalised and frequently exposed to systemic exclusion (like transgender communities, sex workers, MSM etc) at a trust deficit. Their trust will be determined by the promises / contract determined at the point of decision-making as well as the post-trial fulfilment of these promises. (Thailand)

"We ask is the trial scientifically sound or proven? Trial quality and credibility depends on whether the trial is scientifically verifiable. We will ask if the FDA has approved this drug and is there any research done previously to support the trial?" Participant, Thailand

In settings with lower literacy and limited access to digital media, the stamp of approval or good words given by family members, community leaders, and even doctors can significantly determine trust in an RCT.

"They will forgive any crime as long as the relationship with the doctor is good." Nigeria

2.

At the time of decision-making participants have noted viewing their participation as a contractual agreement between themselves and the trial team. If "promises" made by the trial team are broken during or after the trial, it is viewed as a breach of trust.

Examples from Consultations

"This benefit is a big thing for me. Small things can make you lose trust in the trial. Assuming when I was doing the study now, they promised they would give me 1000 naira and after coming, they did not give me again, I would lose trust and interest in the study and if they call me again, I will not come".
Participant, Nigeria

In certain groups, especially those who are marginalised and have had negative past experiences with research, a trust deficit already exists between potential participants and RCT. Therefore, there are three factors that these potential participants reflect on when making the decision to participate in an RCT; a clear value exchange between the RCT and the participant, the balance between benefits and risks to the participant, and finally relationship-related aspects with doctors, healthcare providers and community stakeholders. Once this is clear, other factors build or erode trust during the trial. (Thailand)

3.

The kind of incentives preferred by RCT participants is highly dependent on the individual and community needs. It was suggested that trial teams need to understand individuals and their motivations to participate in the RCT before it begins.

Examples from Consultations

Participants who come from comfortable economic backgrounds are less likely to be concerned with financial benefits but would like personal trial-related benefits like post trial access to the trial product or intervention. Scientific relevance of the RCT and trust in the scientific institution are also key motivators.

Vulnerable and/or marginalised populations who are exposed to higher risks are motivated by immediate benefits of trial; like access to medication, access to information, good quality healthcare, spaces free of stigma/judgement

In circumstances where participants are faced with the lack of access to basic healthcare, they are motivated by the financial compensations (offered as reimbursements or as a participation fee if legal) as well as access to healthcare like medical assistance; advice from doctors; health check-ups and screenings

"Though without the reimbursement, I would have still gone for the follow-up visit (this visit was every day for 7 days), I would not have been motivated enough like when I was reimbursed. I kept the transport money aside every day so I am able to ensure I have my transport fees for my follow up visit" Participant, Nigeria

4.

In hospital-based trials, the first point of contact and the first point of consenting is usually with the treating doctor. This can have implications on the ability of participants to distinguish the RCT from routine healthcare. Therapeutic misconception, low literacy, and power asymmetries can further blur the voluntariness of consent-giving. It is imperative for the RCT team to provide participants with time for reflection and make efforts to clarify the distinction between RCT participation and routine care.

Examples from Consultations

Participants irrespective of socio-economic status were stocked with the belief that the health care services access was synonymous to clinical trials (Nigeria)

The doctor-patient relationship is a highly valued relationship for participants and can lead to people consenting to participate without a clear understanding of risks.

"Do participants really have agency to make a decision freely? If the nature of the interaction within the trial is relationship based, it can be problematic due to power dynamics or feeling obliged (feeling krang jai)" Participant, Thailand

---

Participants at times could not recall being given a consent form, or time to consult family members which impacted their ability to reflect and understand true voluntariness.

"I was not consented for study participation. I went to the operation theatre and I was only informed after about my enrolment into the study. All went well but if things had gone awry I would have taken it serious" Participant, Nigeria

5.

In other scenarios, the first point of contact can vary; participants recalled learning about an RCT through a Whatsapp group set up by the RCT team, through personal social or professional networks, through NGOs, and via RCT community engagement teams or CAB representatives. In these cases decision-making to participate is not on the spot and can be more thought through; time can be taken to reflect, discuss and weigh pros and cons.

Examples from Consultations

"I got informed about the CT from colleagues and coworkers in the hospital I work in. I then sent a message to the contact number stating my interest in taking part of the trial, answered a simple form with my data and scheduled an appointment for the first screening" Participant, Brazil

6.

Informed consent is a crucial process (like community engagement) that correlates to the success of both scientific and ethical outcomes of RCTs. An inadequate informed consent process can be seen when— it is treated as a checklist activity with ineffective communication, there isn't enough time given to participants to reflect, the RCT team comes across as unfriendly or coercive thereby reducing the opportunity for dialogue. This then leaves room for exploitation; an incomplete understanding of rights; lack of clarity on the costs of randomisation; lost to follow ups, and non-adherence to RCT requirements.

Examples from Consultations

"We were never explained everything. They focused on the good and attractive but not the risky stuff." Participant, South Africa

7.

Following are a set of recommendations for improvements to informed consent from ex and current RCT participants.

Informed consent is a process and regular engagement at every trial-related interaction can increase awareness regarding RCT procedures and creates spaces for dialogue. To decrease boredom/ routineness of these sessions, informed consent seekers can be more personable and playful in their approach.

Having one point of contact from the trial team who is reliable and can clarify doubts as they arise to assure participants is important. This PoC can also remind participants about procedures, risks, and benefits (as mentioned in informed consent form) in longer trials.

True voluntarism can be determined by increasing time for reflection and questions (an expert suggested a minimum of 24 hours). Therapeutic misconception, power asymmetries, fear of losing access to healthcare, the pressure of health crises can lead to unsuccessful informed consent outcomes.

Having mechanisms to check the understanding of participants and provide access to copy of signed consent forms for participants can enhance accountability of both parties (as a contract).

Transparency around the trial can be enhanced through updates and communication tailored to the participant group. Scientific words must be translated to a language known to the participant. Explaining pros and cons of the RCT related to its benefits and risks in a manner that is simple and not cumbersome to the participant is necessary.

"CT instructions and informed consent according to the participant's age group, education level, access to information, and type of recruitment (via TV or radio shows, direct approach, or social media)." Brazil

8.

Bad experiences were heavily dependent on trial team behaviour; shaped when nurses or doctors were rude or judgemental, drivers were rude, or participants were asked repeated questions with no discernible reason. Feedback channels during the trial can bring these issues to the fore.

Examples from Consultations

RCT participation can be challenging mentally on participants as it involves spending time away from normal routines and work, and introduces new concepts and experiences through its design.

"My feeling is very important because there may be many things bothering my mind, and I am about to be used as 'a clinical rat'. So anything that happens, I have to be sure that they do not bring any harm to my body and they should consider how I feel before they use me as a clinical trial participant" Participant, Nigeria

Lack of care or humanness on the part of researchers was immediately picked up on

"Researchers are sometimes too scientific in their communication. They can sometimes be too direct. Instead, they should try to use a more counselling tone. Sometimes CAB needs to step in to provide counseling to give participants some mental and psychological support. For example, a trial participant said "I don't want to take medicine anymore", the researcher responded coldly "If you don't want to, then don't" Participant, Thailand

---

Participants noted that at times when this trust is impacted during the trial, it is very tough to build it back.

"It could be rebuilt if the doctor calls me and apologises." Participant, Nigeria

---

Participants from the MSM community were even more attuned to judgemental / exclusionary behaviour (Nigeria)

"There is this thing that people are complaining about the body shaming characteristic behaviour. The team should be able to listen effectively to my story. You don't have to make me feel bad about myself." Participant, Nigeria

---

Community meetings and participant advisory groups during the trial are extremely effective to address situations if they do arise. CLOs are responsible for listening to the complaints of participants, relaying this to the trial team, and ensuring that the feedback is communicated to improve participant experience.

9.

An incomplete understanding of RCT risks and trial related procedures, as well as rude trial staff at follow-up visits can have negative consequences on participant adherence. Expectation-setting during informed consent and feedback channels during the trial are important to preserve trial integrity.

Examples from Consultations

At times participants noted feeling "trapped" in an RCT if the experience of participation went against their expectations at the time of decision-making

---

They reported feeling "judged" by trial team staff if they weren't adhering to the RCT.

This could have a profound impact on the experience of the trial for participants who have an existing trust deficit and have felt excluded/mistreated by the health system.

"Trust can be rebuilt by explaining in detail all the risks associated with participation. If participants are fully informed, then the risk encountered in the trial will not be strange to the participants. Irrespective of the risk experienced in a trial, some participants may still participate in another trial as long as their initial experiences of risk were not strange to them if they were fully prepared for such." Participant, Nigeria

---

Participants can influence negative behaviours related to adherence in others as well which can compromise trial integrity.

The importance of preventative behaviour can become unclear due to misconceptions about the RCT treatment. Participants reflected upon this unclear understanding when being probed about being non-adherent. This strongly suggests an imperfect informed consent. (South Africa)

CASE STUDY ON A PARTICIPANT EXPERIENCE

The following case study highlights participant and trial team experiences during an HIV prevention RCT in South Africa.

During clinical trial debriefs, the trial team engaged RCT participants to understand reasons behind non-adherence. Some participants admitted that it was not easy to remember to take the pill. Other participants admitted being afraid of side effects. Participants also disclosed that they found a way to test whether a pill was a placebo or the original pill by placing the tablet in a glass of water. This caused them to either stop adhering to the daily intake or stop taking the pills altogether. The participants influenced each other to not take the tablets and present false information to the nurses to stay on in the clinical trial.

CAB structures were implemented post the trial to assist with community education and awareness. In the case above, if the CT team had communicated to the CAB, they could have engaged the affected participants individually to educate them on the risks of false representation of information and non-adherence.

10.

Trial teams need to make efforts to bring participants closer to the back stage of the RCT. Without this, participants may feel like "guinea pigs", develop misconceptions, or drop out.

Examples from Consultations

"Community members have different levels of knowledge related to trials. That coupled with language barriers can impact their ability to give feedback. It is useful to include researchers who work with the community into the trials." Participant, Thailand

"Researchers need to invest in empowering the community. Community members do not have a good understanding of what the researchers are doing. All of a sudden they are given free medication or a pharmaceutical company just commissions a trial. They usually don't know that these companies have to go through different processes and structures to develop protocols." Participant, Thailand

---

Some participants reported being asked the same questions repeatedly, without knowing the reason for this, which takes a toll on their mental health. (Thailand, Brazil)

Participants seek good quality information from researchers on subjects where they have limited information - especially in diseases with many unknowns like Zika which has many variables for mother and child. (Brazil)

Participants who mentioned these issues seem to have a more lasting negative impression of researchers and may become more discerning about consequent RCTs that they take part in. (Brazil)

11.

RCT participation requires time and attention away from daily lives and work. RCT teams must consider this when planning trial related procedures, trial reimbursements and setting up the trial centre.

Examples from Consulations

From the perspective of mothers or primary breadwinners, the RCT must ensure to provide value for time as this significantly impacts adherence. Bus fare, a day's wage, food and childcare at the research site is significant to improve RCT experience. (Brazil, Sierra Leone)

CAB / CLOs / PI's can facilitate "chilling sessions" for participants to unwind and socialise during the trial. (South Africa)

For community meetings and meetings with community leaders, the RCT team should strive to meet expectations around cultural practices and a fair compensation to value their time and effort. (Sierra Leone)

12.

The impact of randomisation in a clinical trial is felt as an absence or exclusion of benefit for the control group. In RCTs with placebos, and/or with unsuccessful outcomes unblinding can be a time filled with anxiety. Trial protocols, teams and communication plans must take this into account when planning for the RCT and its result-sharing.

Examples from Consultations

Trial team interaction with individual participants is very important to address anxiety-filled moments, especially in community-based settings or where myths and misinformation are rife. (South Africa)

The RCT protocol must address what happens to the control group that receives the placebo or alternate standard of care. For example, in vaccine studies which continue the assessment of booster shots with the treatment group, the control group should also continue getting the same RCT quality of care for as long as the project goes on (Sierra Leone, India)

CASE STUDY ON A PARTICIPANT EXPERIENCE

The following case study highlights participant, CLO and CAB member experiences during a clinical trial for an HIV vaccine regimen in South Africa.

CLO and CAB members followed up a report of a participant death in 2017 as a part of their investigation into participants who were lost to follow up. They discovered that this was a false death claim by the participant who was no longer interested in the trial and didn't want to be followed up. Following this incident the CAB organised community meetings and educated the community on the dangers of fraud and the impact of participant dishonesty on clinical trial outcomes. Education on false reporting was also incorporated in the clinical trial inductions. Fortunately, this was the only incident reported to date.

The unblinding process of this particular trial, due to its unsuccessful outcomes, caused anger, outrage and rumours in the community. The rumours spread quickly prompting community members to organise and conduct a protest to air their grievances. The CLO, who is well known and respected, acted quickly by calming the angry crowd and inviting senior community leaders to address the clinical trial team on behalf of the community. The CLO, senior community leaders and clinical trial team then addressed the grievances and educated the crowd on the clinical trial process, how the vaccine works, risks and benefits, and the reasons why the CT participants could still become HIV positive. The clinical trial team also promised to address all affected participants individually.

13.

Good experiences, like good quality of care, personalised treatment plans, and improved wellbeing can influence participants to take a more active role in supporting trial conduct.

Examples from Consultations

Good experiences include— improvements in personal health, receiving better than routine-care treatment and personal attention from doctors. The pleasant attitude of the doctors and healthcare workers at the clinical site and shorter waiting times for follow ups were appreciated.

Other kinds of benefits to consider include— free medication that might improve health outcomes or prevent disease contraction. For example, ARV could be provided to participants in case of seroconversion or during epidemic-related lockdowns. (South Africa)

"I wouldn't have offered to recruit others into the trial if I didn't have good experiences" Thailand

CASE STUDY ON A PARTICIPANT EXPERIENCE

The C-Free Study, Dreamlopments Foundation is the first community-based model of care in Thailand for diagnosis and treatment of hepatitis C in PWID, using a highly-effective novel treatment combination called sofosbuvir/velpatasvir. The study is based at drop-in centers (DIC) run by partner organizations (Ozone and Raks Thai Foundation). Testing for HCV, but also hepatitis B and HIV are all done at the DIC by trained research nurses. Care and support are provided for all participants who test positive for HBV and HIV. For eligible participants with HCV, physicians give treatment with sofosbuvir/velpatasvir through weekly clinics at the DIC. Participants who are cured are monitored for reinfection and provided support to stay HCV-free.[11]

The participant was waiting for this trial for a long time. It was clear to the participant that the new Hep C drugs offered had fewer side effects, and would also cut down on the bureaucracy of going to a public hospital. The participant wouldn't need to take a whole day off work just to be seen by a doctor.
In the RCT environment, testing was easy, and the doctors monitored closely and customised dosages so that the participant could safely participate in the trial. Doctors even gave their personal numbers to the participant to call at any time with questions.

Impressed with the good experience, the outcome, and the fact that the benefits far outweigh the risks (the Hep B vaccine was free as a part of the trial) the participant offered to recruit others into the trial. When COVID hit, the doctors and nurses weren't able to get to the patients to deliver medication, and this participant became an intermediary between the medical staff and the other participants and relayed feedback and questions to the doctors and nurses.

It is also important to think about the ongoing benefits beyond the trial. Because of the treatment and the trial, the participant had the opportunity to have a better life and contribute more to society. The participant reflected that they might have been able to contribute even more if they had been involved alongside the other community members that were engaged from the very beginning of the trial design.

11. For more information on the study, visit: https://www.c-free.online/model-of-care

14.

Participants' expectations after the clinical trial include meaningful result dissemination, post-trial access to the trial product or intervention, and acknowledgement and recognition for their participation.

Examples from Consultations

Participants were promised results or priority for vaccination in case of approval of the vaccine, however, these promises were broken due to logistical / bureaucratic or other unspecified reasons by the trial team. (Brazil)

15.

Preferences on formats of result-sharing are dependent on the participant characteristics/ demographics and their access to technology. As suggested by ex or current trial participants, post-trial engagement can take place in the following ways:

Phone call or town meeting to share results where internet access might be limited

Comics, booklets, graphs of results to facilitate understanding

End of trial sharing of medical records and follow-up interactions with trial doctors on health "improvements"

Prolonged follow ups after the trial (minimum a year)

Priority for annual vaccinations

Priority to participate in other trials

Messages/ information on how participation contributed, and recognition of participation through public acknowledgement of communities

16.

Participants were not aware they could be involved in trial design but reflected that they would like to be involved in trial design and research prioritisation. They would like to play a role in:

Determining with CABs and researchers what future research priorities should be

---

Determining with researchers or community engagement teams how to increase community preparedness for research

---

Deliberating on the inclusion/exclusion criteria

"It would have been better to involve community members from the very beginning of the trial design but it's also important to think about the ongoing benefits beyond the trial. Because of the treatment I have a better life and can contribute more to society."
Participant, Thailand

"The community should be selective about CT trials. We can't have clinical trials that are always failing."
Participant, South Africa

Conclusion

To further the practice of informative, ethical and efficient RCTs in LMICs:

1.

Sponsors and RCT advocates can support independent investigators and capacity building of researchers to initiate RCTs that have significant scientific value and community outcomes for local contexts. Over the course of the consultations in LMICs this support for independent investigators was noted as an unmet need, and PIs who were able to initiate RCTs emphasised the need to align with community needs and preferences.

2.

Sponsors and RCT advocates can support RCT capacity and infrastructure building in community-based sites. Community-based sites are close to potential participants and have a distinct identity from hospitals. This would enable fair site selection practice, prevent concentration of RCTs in resource-rich settings and decrease trial fatigue for communities close to sites that are frequently selected.

3.

Sponsors and RCT advocates need to think critically about how to balance inequities and improve routine healthcare in RCT settings with weak health systems and where people lack access to good quality healthcare. Investments to improve health outcomes even beyond the RCT can build confidence and preparedness for future RCTs in these settings.

Overarching recommendations from consultations for ethical and scientific RCT practice, key for the growth and improvement of future clinical trials.

4.

Politicians, media, religious leaders and similar stakeholders can play a part in spreading awareness on the dual role of people and RCTs in the development of affordable treatments for important health conditions and the improvement of patient care. When interacting with public opinion/perception influencers in LMICs, RCT advocates and funders should emphasise the need for these influencers to support in sustaining transparent communication and engagement around RCTs. There should be opportunities for these stakeholders to build their capacity based on their responsibility to RCT engagement.

5.

RCT funders and decision-makers should involve and include relevant communities (especially affected groups and marginalised groups) and participants (ex-participants, community engagement team members etc) in the early stages of RCT design.

6.

RCT funders and advocates should emphasise the importance of community engagement, informed consent and result-sharing to those who run RCTs, and support RCT teams to improve the quality of these crucial tools that sustain trust and RCT ethics. The purpose of engagement around recruitment and retention is clear, but engagement pre-trial and post trial can significantly be improved. In the case of informed consent, even though a lot has been institutionalised and discussed, there is still room for improvement.

Overarching recommendations from consultations for ethical and scientific RCT practice, key for the growth and improvement of future clinical trials.

Important factors for the success of an RCT:

RCT participants from Brazil, Thailand, South Africa, Nigeria and Sierra Leone were asked to describe their five non-negotiables for an RCT. These cues for RCT teams have been summarised here. They are essential considerations for RCT design and RCT success.

RCT teams **should employ community members** and those with lived experiences in the recruitment and running of an RCT.

RCT teams **must ensure that community and participant engagement takes place before recruitment**, and that this engagement continues during and after the trial.

RCT teams **should share educational information** through appropriate channels (like trusted institutions, or media channels) about the RCT.

RCT **benefits should be tailored to the needs** of the context and/or community and/or sub-group.

RCT **reimbursement and incentives are paramount**, basic needs like food at trial-related meetings, sanitary equipment should be provided by the RCT.

RCT conduct as a whole should make participants feel safe and secure. Anonymity should be maintained.

RCT **informed consent should have clear communication** of risks, benefits, and what to expect. It must be an ongoing process throughout the trial.

RCT **conduct must respect cultural codes** and strive to minimise power dynamics.

RCT **conduct must maintain good clinical practice**, have ethical clearances, and maintain safety standards.
RCT conduct should have efficient, organised schedules of follow-ups and take care to reduce waiting times as much as possible.

RCT staff who interact frequently with participants, like doctors, nurses, counsellors, drivers, should be **friendly and professionally qualified.** They must uphold the rights of participants and be attentive to participant needs. They should respect and address feedback.

RCT teams should **ensure that outcomes and results are shared** with participants.

Acknowledgements

We would like to acknowledge and thank the following people for their contributions to the project:

Brazil
Michel Naslavsky *University of São Paulo*
Larissa Matos *University of São Paulo*
Roberta de Oliveira Piorelli *Butantan Institute*
Gustavo Coutinho *Rezende Clínicas Hospital of the Faculty of Medicine of University of São Paulo*

India
Dr. Temsunaro Rongsen-Chandola, Dr Nidhi Goyal and Mr Alok Arya from *Centre for Health Research and Development, Society for Applied Studies (CHRD-SAS)*
Dr.Nitya Wadhwa *Clinical Development Services Agency at Translational Health Science And Technology Institute (THSTI)*
Dr. Debjani Roy *Clinical research coordinator, Translational Health Science and Technology Institute, Clinical Development Services Agency at Translational Health Science And Technology Institute (THSTI)*
DLR Prerna - www.darjeelingprerna.org>
Dr Amita Sapru, Dr. Aditi Apte, Dr. Abhijeet Bora, Dr. Shruti Inamdar, Pediatrics Department, *KEM Hospital Research Centre, Pune*
Dr. Kaustubh Joag, Deepa Pandit, Dr Soumitra Pathare, Dr. Laura Shields-Zeeman and Ms Jasmine Kalha *Atmiyata Centre for Mental Health Law and Policy (CMHLP)*
Ms. Himangi Lubree, Mr. Rakesh Patil, Mrs. Meera Tambe, Dr. Arun Gondhali Vadu Rural Health Program, *KEM Hospital Research Centre, Pune, KEMHRC and VRHP leadership*
Dr. Monika Bahl, Dr. Anil Seth *Clinical Development Services Agency at Translational Health Science And Technology Institute THSTI*
Rachna Dhingra *Bhopal Group for Information & Action*
Dr. Venkatesan Chakrapani *C-SHaRP*

Thailand
Dr. Tanyaporn Wansom, *C-Free Study, Dreamlopments Foundation*
Dr. Nittaya Phanuphak *Institute of HIV Research and Innovation (IHRI)*
Dr Amalee McCoy *Oxford University*
Mr Pichet Kamolrungsantisuk
Dr Anchalee Avihingsanon, *HIV Netherlands Australia Thailand Research Collaboration, Bangkok (HIV NAT), Thai Red Cross AIDS Research Centre.*
Dr Eileen Dunne *Silom Community Clinic, US CDC HIV/STD Research Program in Bangkok*

Nigeria
Prof. Morenike Ukpong *Obafemi Awolowo University, Ile-Ife*
Prof. Ayodele Jegede *University of Ibadan*
Professor Oliver Ezechi, *Nigerian Institute of Medical Research Lagos*

Kenya
Rosemary Mburu *WACI Health*

South Africa
Neetha Morar *The HIV Prevention Trials Network*
Joseph Skhosana, Independent

Sierra Leone
Dr. Frank Baiden *LSHTM*
Mr. Deen *Vaccine Trial Community Liaison Officer*
Mr. Jalloh *Vaccine Trial Community Liaison Officer*

Global Experts (Round 1)
Jessica Salzwedel *AVAC*
Luisa Enria *LSHTM*
Mark Marchant *LSHTM*

Red Team (Round 1 - India)
Amrita Sekar, Dr.Neha Chawla,
Prof.Usha Menon *MRC Clinical Trials Unit at UCL, University College London, UK*
Devi Leena Bose *IAVI*
Dr Sunita Sheel *Vidhayak Trust; Health, Ethics and Law Institute of FMES*

We would also like to acknowledge and thank the RCT participants who shared their personal thoughts, journeys and experiences around RCTs.

Annex

Feedback on the Guidance Draft from Global South Experts

The following is a summary of takeaways from feedback calls held with seven Global South experts from India, Brazil, Sierra Leone, Nigeria, South Africa and Thailand in Mid-June 2021. Calls were attended by Quicksand and the GCTC team.

All experts engaged in the feedback have experience managing, conducting and designing vaccine and drug trials in the Global South. They represented a breadth of interests within this which includes; epidemiology and public health, implementation science, research science, social/community science, and ethics.

The introduction to this document is going to be key in holding readers attention, making a case for RCTs and ensuring that potential biases of reader's are addressed beforehand. Experts noticed that the uniqueness of the document was its emphasis on RCTs — so suggested that its value and need must be highlighted upfront. Contextualising with examples/ stats would be helpful.

There is also room to be more descriptive about the intended audience(s) of the document, for example: by clarifying/making a link to why this document might be relevant to particular audience(s)

They felt that monitors, regulators, students/new trial sites will benefit significantly from such a document that lays out the principles of a good RCT. Some suggested that videos/ simple visualisations might grab the attention of potential readers.

They suggested that references (to existing documents in use) must be done to acknowledge what already exists and thought that examples to support the text from trials that were done well/not well would be valuable.

This guidance would be operationalised if — it is presented as one within the basket to research teams (including GCP), it is introduced through teaching, and it acknowledges other references like GPP.

Lastly, by being clear about what this document's limitations are actually empowers ethicists/ community advocates. It is clear that vulnerability and the complex issues (eg: exploitation) related to research participation cannot be done away with through guidance. Articulating this might give researchers the chance to then say that additional work is required to bring in the lens of context specificity that is all the more necessary in the case of vulnerable participants

Experts appreciated the informality, and simplicity of the document. They empathised with the need to keep this particular document short.

There is room for more work on content around "community engagement/involvement". CABs are one possible mechanism for community engagement, but there can be many more. There was a suggestion that community engagement should have an overview on how it can be done and it would be important to encourage people to think outside the box.

Particularly in the section around sub groups (but perhaps can be applicable elsewhere as well) guidance around ensuring that all sites (not just the prominent ones) ensure subgroups are adequately represented. However, this should not take away from the flexibility to do studies on subgroups that have secondary outcomes as that leads to newer areas for research.

The differences in health systems (for eg: different provider-client relationships), between the Global North and South must be acknowledged particularly because RCTs are a pathway to real-world implementation.

Best practices in participant engagement that impact retention and adherence within a trial/study include tailoring ways the participant needs to ensure 1) transparency between the trial and the participant, and 2) focussed trial team interaction throughout the trial with participants.

Guidance should include content around dissemination of trial results to communities that participated in studies/trials, acknowledgement of communities that have supported significant global health advances, and lastly the issue of post trial access (especially in the case of trials that use placebos) is important from the lens of ethics of RCTs.

Quicksand Team: Rachit Shah, Tiara Aurora, Sanmadi KR,
Chitrangna Dewan, Jyoti Narayan, Shelly Sharma