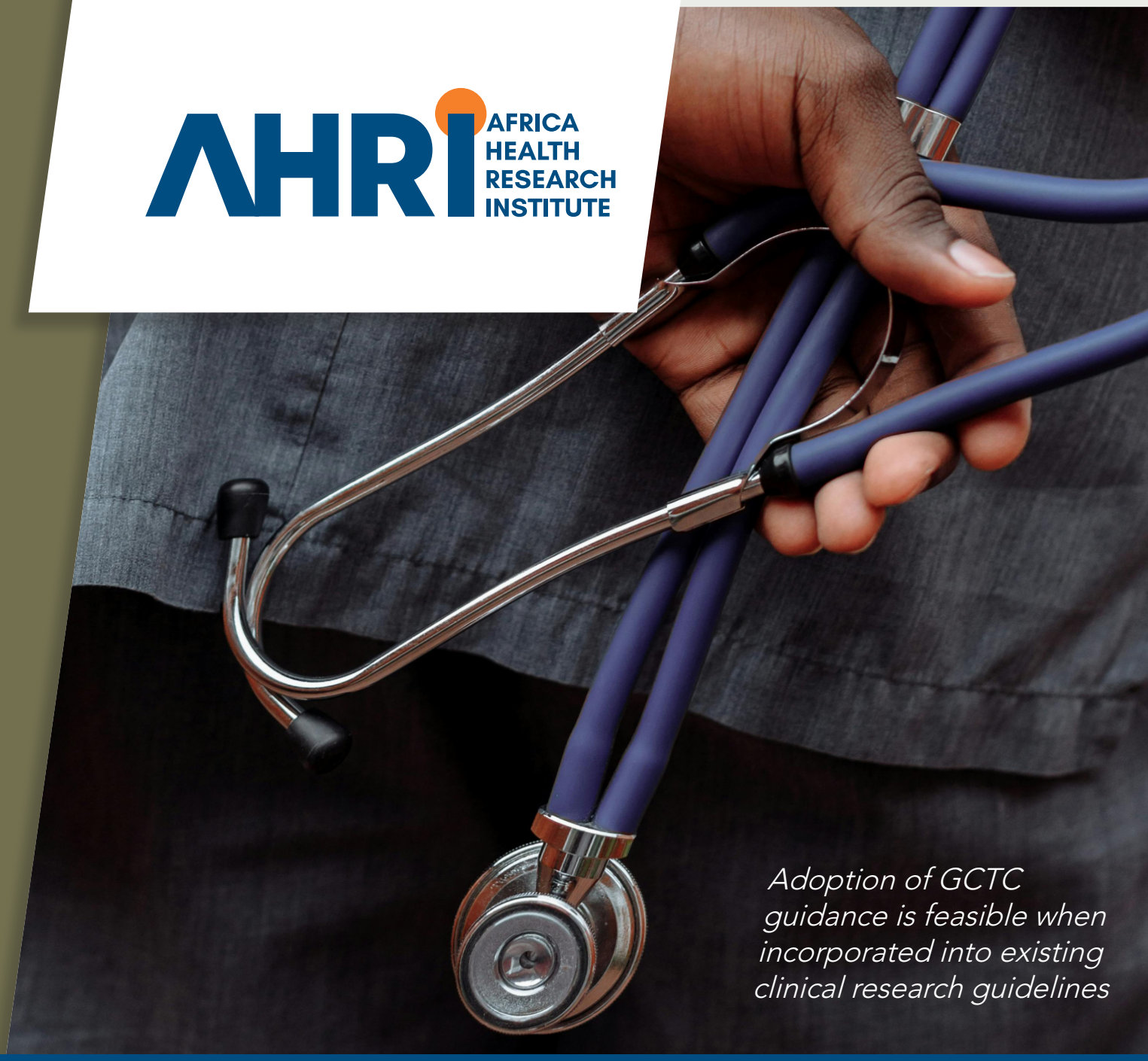
AHRI
AFRICA
HEALTH
RESEARCH
INSTITUTE



Adoption of GCTC guidance is feasible when incorporated into existing clinical research guidelines

Knowledge, Practices and Perceptions of Good Clinical Trials Collaborative (GCTC) Guidance in the Conduct of Clinical Trials in South Africa

2025

ABOUT THE REPORT

The regulation and guidance in the conduct of clinical trials has evolved over the years to become more standardised globally, with an increased emphasis on respect for persons, beneficence, and justice. The International Harmonisation (ICH-GCP) is an example of an effort to harmonise different regulations into a single global standard for conducting clinical trials. However, there continues to be limited guidance on some aspects of conducting clinical trials, such as decentralised trials, data ownership and sharing, transparency in sharing results, and culturally appropriate communication. A group of diverse experts has described the key underpinnings of a good clinical trial in the Good Clinical Trials Collaborative (GCTC) Guidance, addressing some of the identified gaps. This study aimed to assess the knowledge and practices of GCTC Guidance among key stakeholders involved in the implementation of clinical trials in South Africa. Therefore, this report outlines their opinions on the GCTC Guidance and its principles, as well as how they can be incorporated into the conduct of clinical trials in South Africa.

This report highlights challenges and potential areas for improvement in the conduct of clinical trials, based on participants' knowledge of national guidelines and their experiences in clinical trial research. Specific attention is given to issues such as participant randomisation, exclusion of relevant populations without scientific justification, context-sensitive community engagement, and protocol designs.

The report aims to support ethics committees, sponsors, regulators, policymakers, and clinical trial implementers in improving the design, oversight, and implementation of clinical trials. The report also provides recommendations on incorporating the GCTC Guidance in the 2020 South African GCP guidelines and training for clinical trial implementers. This report contributes to ongoing efforts to advance equity in the clinical trials ecosystem and capacity strengthening for local researchers in low and middle-income countries.

STUDY TEAM & COLLABORATORS

Africa Health Research Institute Study Team

Prof. Limakatso Lebina
Director for Clinical Trials Unit (CTU)
Africa Health Research Institute (AHRI)
KwaZulu-Natal – South Africa

Dr Anne Derache
CTU Manager
Africa Health Research Institute
KwaZulu-Natal – South Africa

Nompumelelo Ngobese
CTU Project Manager
Africa Health Research Institute
KwaZulu-Natal – South Africa

Andani Ratshinanga
Project Coordinator
Africa Health Research Institute
KwaZulu-Natal – South Africa

Dr Allanise Cloete
Head of Social Science
Africa Health Research Institute
KwaZulu-Natal – South Africa

Khethokuhle Nkosi
Research Coordinator
Africa Health Research Institute
KwaZulu-Natal – South Africa

Londiwe Shandu
Research Coordinator
Africa Health Research Institute
KwaZulu-Natal – South Africa

The Good Clinical Trials Collaborative

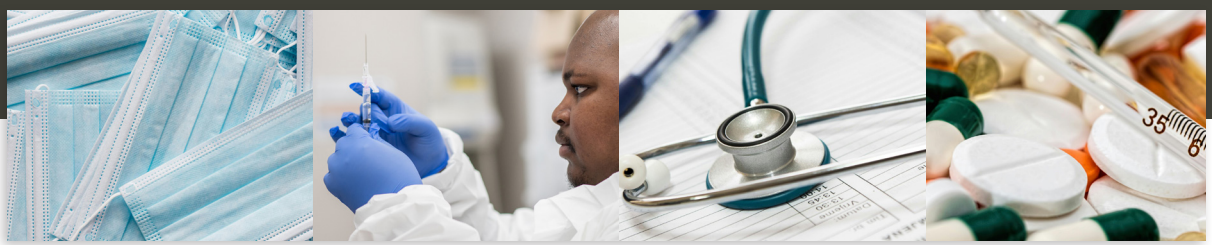
Sir Martin Landray
Senior Lead
The Good Clinical Trials Collaborative

Nick Medhurst
Team Lead
The Good Clinical Trials Collaborative

Rachel Hallett
Capacity Strengthening Manager
The Good Clinical Trials Collaborative
United Kingdom

Katie Thorne
Project Manager
The Good Clinical Trials Collaborative
United Kingdom

Farida Ben-Younis
Senior Research Officer
The Good Clinical Trials Collaborative
United Kingdom



AHRI AFRICA HEALTH RESEARCH INSTITUTE

LIST OF ABBREVIATIONS

BREC	Biomedical Research Ethics Committee
AVAREF	The African Vaccine Regulatory Forum
CRF	Case Report Form
CRO	Contract Research Organisation
DoH	Department of Health
EDCTP	The European and Developing Countries Clinical Trials Partnership
EU	European Union
G7	The Group of Seven
GCP	Good Clinical Practice
GCTC	Good Clinical Trials Collaborative
GloPID-R	The Global Research Collaboration for Infectious Disease Preparedness
HIV	Human Immunodeficiency
ICF	Informed Consent Form
ICH	International Council of Harmonisation
ICTRP	International Clinical Trials Registry Platform
LMIC	Low- and Middle-Income Country
NHREC	National Health Research Ethics Council
RCT	Randomised Controlled Trial
RECs	Research Ethics Committees
SA GCP	South African Good Clinical Practice
SDGs	Sustainable Development Goals
SAHPHRA	The South African Health Products Regulatory Authority
SANCTR	South African National Clinical Trials Register
TB	Tuberculosis
US	United States
WHA	World Health Assembly
WHO	World Health Organization

GLOSSARY OF TERMS

Good Clinical Trials Collaborative (GCTC): Established in 2020, the collaborative is a not-for-profit organisation focused on promoting new guidance to enable better randomised controlled trials (RCTs) globally. It is led by Professor Sir Martin Landray, co-architect of the COVID-19 RECOVERY trial, and supported by the Wellcome Trus and the Bill & Melinda Gates Foundation

GCTC Guidance: Developed in May 2022 by GCTC, the Guidance aims to strengthen the capability of individuals, institutions, and systems to produce reliable evidence through RCTs that enable informed changes in healthcare practice.

Good Trials Prism: A strategic collaboration between the GCTC and four major clinical trials networks, namely the ADVANcing Clinical Evidence in Infectious Diseases (ADVANCE-ID), Africa Health Research Institute (AHRI), The Oxford University Clinical Research Unit (OUCRU), and The Global Health Network.

REDCap (Research Electronic Data Capture): It is a secure, password-protected web-based application for building and managing online surveys and databases. It also allows the capturing of information and exportation into statistical programmes for analysis.

Workshops: Interactive sessions with implementers of clinical trials in South Africa to promote and raise awareness of the GCTC Guidance. The workshops also served as a platform for implementers of clinical trials to give their opinions on the feasibility, acceptability, and adoption of the Guidance in the South African context through discussions and workshop surveys. The workshops also served as a platform to encourage the implementation of the Guidance in South Africa.

Surveys: Questionnaires designed to assess key stakeholders' current GCTC Guidance knowledge and current RCT practices before the workshops. Following the workshops, surveys were used to collect stakeholders' opinions on the feasibility, acceptability, and potential adoption of the Guidance in the South African context. Follow-up surveys were completed three to six months after the workshop.

Key stakeholders: The relevant key stakeholders for this study included international and local pharmaceutical companies, university-affiliated institutes, international and local clinical research organisations, funders, sponsors, independent research units, and regulators.

Key stakeholder interview: An in-depth interview using a structured questionnaire with funders, implementers and regulators involved in clinical trials to gather information on their experiences, regulatory framework, laboratory and pharmacy infrastructure, monitoring of clinical trials, and community perceptions. The interviews also included their opinions/ input on the feasibility, acceptability, and required changes to facilitate the adoption of the GCTC Guidance in the South African context.

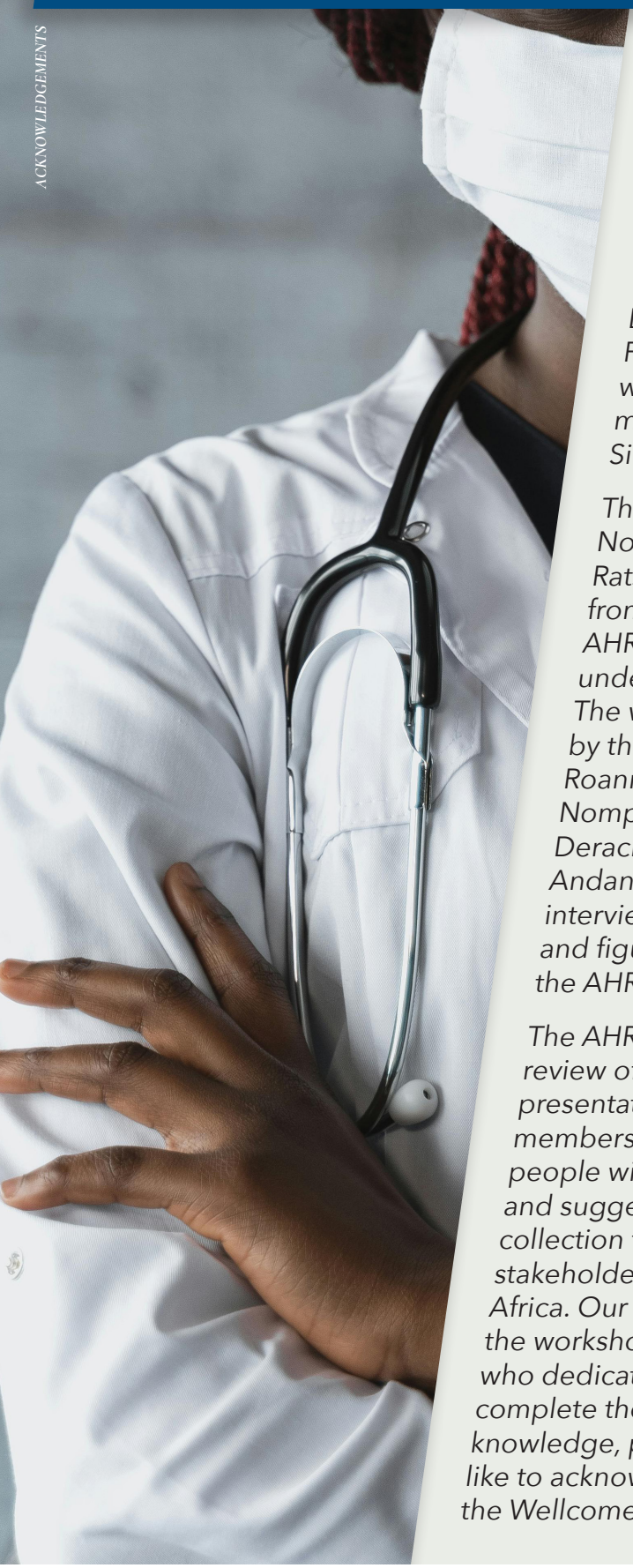
Randomised Controlled Trials (RCT): A study in which people are allocated at random (by chance alone) to receive one of several clinical interventions. One of these interventions is the standard of comparison or control.

SA NDoH 2024: The South African Department of Health's 2024 Guidelines for conducting clinical trials. Also referred to as South African Ethics in Health Research guidelines: Principles, Processes and Structures – 2024.

SA GCP 2020: South African Good Clinical Practice guidelines: Clinical Trial Guidelines to promote good practice in the conduct of clinical trials in South Africa.

Participant: A person who voluntarily took part in our study after signing an informed consent and provided information on their knowledge and experiences.

ACKNOWLEDGEMENTS



This report on the knowledge, practices, and perceptions of Good Clinical Trials Collaborative (GCTC) Guidance in the conduct of clinical trials in South Africa was prepared by researchers from Africa Health Research Institute (AHRI) and The PRISM Team under Protas: Limakatso Lebina, Anne Derache, Nompumelelo Ngobese, Andani Ratshinanga, Allanise Cloete, Khethokuhle Nkosi, Londiwe Shandu, Njabulo Dayi, Nick Medhurst, Rachel Hallett, Katie Thorne, Farida Ben-Younis, and Sir Martin Laundry. The report was reviewed and approved by the PRISM project management team, represented by Nick Medhurst, Simona Lam, and Sir Martin Laundry.

The data collection tool was developed by Nompumelelo Ngobese, Anne Derache, Andani Ratshinanga, and Limakatso Lebina, with contributions from the PRISM team and other researchers within AHRI. Database development and management were undertaken by Njabulo Dayi and Andani Ratshinanga. The workshops' training materials were developed by the AHRI study team and edited and formatted by Roanne Peters and Hannah Keal. Andani Ratshinanga, Nompumelelo Ngobese, Limakatso Lebina, and Anne Derache conducted the GCTC awareness workshops. Andani Ratshinanga conducted the key informant interviews. The data analysis, preparations of tables and figures, and writing of the report were done by the AHRI Study Team.

The AHRI Study Team is grateful for the support and review of the training materials (leaflet, PowerPoint presentation slides) by the PRISM and the GCTC team members. The AHRI Study Team appreciates the many people with whom they interacted for comments and suggestions in finalising the protocol and data collection tools, as well as for referring them to key stakeholders in the conduct of clinical trials in South Africa. Our heartfelt thanks go to the participants in the workshops and the key informants' interviews, who dedicated their time to attend the workshops, complete the surveys, and share their valuable knowledge, practices, and perceptions. We would like to acknowledge funding of this project from the Wellcome Trust under the PRISM project.

AHRI AFRICA HEALTH RESEARCH INSTITUTE

CONTENT

About the report 1
List of abbreviations 4
Glossary of terms 5
Acknowledgements 7
List of figures and tables 11
Figures 11
Tables 11
Executive summary 12
Background 12
Methods 13
Main findings 13
Limitations 13
Recommendations 13

1. INTRODUCTION 14
1. Clinical research guidance landscape 14
1.1 ICH-GCP 15
1.1.2 South African clinical research guidelines 16
1.2 Overview of clinical research in South Africa 16
1.2.1 Regulatory authorities and registries 16
1.2.2 Review of registered trials in South Africa 17
1.3 Economic contribution of clinical trials 19
1.4 Challenges in guidance 19

2. METHODOLOGY 20
2.1 Study design 20
2.2 Study aim 20
2.3 Study objectives 20
2.4 Study procedures 20
2.4.1 Stakeholder mapping 20
2.4.2 Key informant stakeholder interviews 22

2.4.3 Survey completion on REDCap 22
2.5 Data management and analysis 22
2.5.1 Quantitative data analysis 22
2.5.2 Qualitative data analysis 22
2.6 Ethical considerations 22

CONTENT

3. STUDY RESULTS 24
3.1 Sample characteristics 24
3.1.1 Participants' demographics 24
3.2. Perceptions of the clinical trial ecosystem in South Africa 29
3.2.1 Challenges observed in the conduct of clinical trials 33
3.2.2 Challenges with randomisation in clinical trials 33
3.2.3 Groups often not included in trials without a good scientific justification 34
3.2.4 Improvements needed in the conduct of clinical trials regarding the inclusion of diverse populations 34
3.2.5 How can monitoring and auditing of trials improve the quality of the conduct of clinical trials? 35
3.2.6 How to facilitate and encourage adherence to the allocated study arm 35
3.2.7 Common errors in designing CRFs that result in large volumes of data that are not relevant to the research question 37
3.3 Knowledge, perception and relevance of the GCTC Guidance 37
3.3.1 Overview of knowledge of the GCTC Guidance 37
3.3.2 Application of GCTC in organisations 39
3.4 Acceptability and applicability of the GCTC Guidance 39
3.4.1 Relevance of GCTC to roles in clinical trials 40
3.4.2 Need for GCTC training 40
3.5. Aspect of GCTC that requires training 41
3.6. Challenges that can be resolved by implementing the GCTC Guidance 41
3.7 Barriers to implementing the GCTC Guidance in organisations 42
3.8 Roadmap for incorporating the GCTC Guidance 44
3.8.1. Feasibility and adoption of incorporating the GCTC Guidance in the conduct of clinical trials 45
3.8.2 GCTC principles incorporated into the organisation 47
3.9 Possible impact of adopting the GCTC Guidance on RCT practices 47
3.9.1 Alignment of GCTC in organisation roles 48
3.9.2 Challenges resolved by implementing the GCTC Guidance in organisations 49
3.10 Implementation, promotion, and awareness strategies 50
3.10.1 Social media campaign 50

3.10.2 Educational workshops, seminars, symposiums, and training sessions 51
3.10.3 Partnerships with academic institutions 51
3.10.4 Online platforms 51
3.10.5 Engagement with regulatory bodies 51
3.11. Stakeholders to implement GCTC 52

4. DISCUSSION 54
4.1 Limitations 57
4.2 Recommendations 57
4.3 Conclusion 58

REFERENCES 59

LIST OF FIGURES & TABLES

FIGURES

Figure 1: Key timelines in international guidance for conducting clinical research 14
Figure 2: Procedures for workshops and surveys 21
Figure 3: Procedures for key informant interviews 22
Figure 4: Disease groups participants have worked on 26
Figure 5: Participants' current roles and number of years working in those roles 27
Figure 6: Reasons clinical trials failed to be informative 28
Figure 7: Likelihood of recommending the GCTC Guidance to their organisation 41
Figure 8: Roadmap for integrating the GCTC Guidance into organisations 45
Figure 9: Feasibility and adoption of the incorporation of the GCTC Guidance in the conduct of clinical trials 45
Figure 10: Implementation, promotion, and awareness strategies for the GCTC Guidance 50

TABLES

Table 1: Disease categories being researched in South Africa 18
Table 2: Workshops conducted and number of delegates per workshop 22
Table 3: Characteristics of participants that completed surveys and interviews 24
Table 4: Summary of the key challenges observed in the conduct of clinical trials in South Africa 29

EXECUTIVE SUMMARY

BACKGROUND

Randomised controlled trials (RCTs) play a central role in generating the evidence needed to inform the development and implementation of health interventions. Unfortunately, useful evidence from good RCTs is often lacking. This can be because RCTs were never conducted, or those that were conducted failed to produce scientifically robust and clinically relevant results, or the findings were never published. This can fail to identify and utilise effective interventions or can continue using ineffective or hazardous interventions. Such problems waste resources, cause unnecessary harm or suffering, and reduce trust in those who develop or use health interventions. It must be made easier to conduct good RCTs to inform the development of better interventions and the delivery of future care. There is a clear need for guidance to promote the unique benefits of RCTs across all contexts, which focuses on the unique strengths of randomisation while setting out the underpinning principles necessary to generate reliable results safely and ethically, regardless of context.

A range of guidelines for clinical research exists, but most fail to guide the underpinning principles of RCTs necessary to generate reliable results safely and ethically, regardless of context. Many guidelines have also focused narrowly on the standards required of trials (including non-randomised studies) intended for submission to regulatory authorities to support a new drug licence. There is an unmet need for guidance to promote the unique benefits of RCTs across all contexts and settings.

The Good Clinical Trials Collaborative (GCTC) Guidance for good randomized clinical trials was established to develop and promote the adoption of new guidance aimed at addressing these issues. The GCTC Guidance is the first ever guidance to be universally relevant to all RCTs of any health intervention, purpose, and setting. It is intended to support all parties involved in the journey of an RCT.

Study aims: The overall aim of this study is to assess the knowledge and practices of GCTC guidance among key stakeholders involved in clinical trial implementation in South Africa.

Study objectives:

- Assess knowledge of GCTC guidance among major clinical trials stakeholders in South Africa
- Assess the perceptions and acceptability of GCTC to South African clinical trials implementers
- Collate data on the required changes to the GCTC Guidance that would facilitate adoption into the South African context
- Develop a roadmap for incorporating GCTC guidance into the South African conduct of RCTs

METHODS

A convergent parallel mixed-methods designwas employed, integrating quantitative and qualitative data collected and analysed concurrently with equal weighting. Data was collected through participatory workshops, surveys by workshop attendees and key informant interviews with implementors of clinical trials in South Africa. Triangulation enabled identification of convergence, divergence, and relationships between datasets, enhancing the robustness of the findings.

MAIN FINDINGS

The main findings of this study on knowledge,practices and perceptions of GCTC guidance in South Africa are that prior knowledge of the Guidance was limited among clinical trial implementers in South Africa. Participants suggested that some of the principles of the GCTC Guidance align with existing clinical trial guidelines currently in use. Furthermore, it was reported that the GCTC Guidance has the potential to address the numerous challenges faced by clinical trial implementers in conducting clinical trials.

Regarding the adoption of the Guidance within the South African clinical trial ecosystem, participants reported that the adoption of the Guidance is feasible if it is incorporated into other existing guidelines for clinical research. However, several potential barriers were identified, including resistance to change, inadequate infrastructure and resources, and a lack of training on the Guidance. The Department of Health (DoH) and SAHPRA were recognised as key stakeholders for the successful adoption, implementation, and monitoring of the Guidance in the conduct of clinical trials in South Africa.

LIMITATIONS

This study was subject to several limitations. This study assessed participants' knowledge of the GCTC Guidance. It did not employ a validated questionnaire, which may affect the robustness of the findings. Financial constraints limited our ability to conduct workshops in all nine provinces in South Africa. Lastly, the potential for interviewer bias exists, as the interviewer's background and knowledge of the Guidance may influence participants' responses.

RECOMMENDATIONS

Based on the opinions of the key informants and workshop participants, it is feasible to adopt the GCTC guidance principles into practice in the conduct of clinical trials in South Africa. However, incorporation should not increase the number of guidelines or training requirements for clinical trials. The WHO Guidance for Best Practices for Clinical Trials has incorporated the principles of the GCTC Guidance. Therefore, our recommendation for the adoption of the GCTC Guidance and implementation of the Guidance in South Africa will be to increase the awareness of the WHO Guidance for Best Practices for Clinical Trials. This can be achieved by amending the 2020 South African GCP Guidelines to include the principles of the WHO Guidance for Best Practices for Clinical Trials. The updates will then be included in the trainings that implementers of clinical trials receive every three years.

1. INTRODUCTION

Globally, at the midpoint of the Sustainable Development Goals (SDGs), none of the targets are on track or have been achieved, although some health indicators are showing movement in the right direction.[1] The COVID-19 pandemic also reversed over a decade of gains in life expectancy at birth, reducing it to 2012 levels of 71,4 years.[1] The world continues to grapple with a high burden of communicable and non-communicable diseases and inequitable access to health services. There is therefore an urgent need to find innovative approaches to reduce ill health and improve life expectancy. Advances in healthcare knowledge through randomised clinical trials require contributions from human participants, researchers, and sponsors. The achievement of these scientific goals should not be at the expense of the rights of participants and researchers.[2] Clinical trial design and conduct should adhere to the highest standards of safety and ethics.

The World Health Organization (WHO) defines a clinical trial as "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes".[1] Randomisation is the process of assigning a participant in a clinical trial to the intervention or comparison groups.[3] RCTs play a central role in generating the evidence needed to inform the development and implementation of health interventions.[4] To establish whether a health intervention has a reliable effect, it is necessary to ensure that any biases or random errors inherent in the study design are both small compared to the expected treatment effect.[5]

Unfortunately, useful evidence from good RCTs is often lacking.[6] This can be because RCTs were never conducted, or those that were conducted failed to produce scientifically robust and clinically relevant results. This may be due to an inappropriate trial population, lack of robust intervention allocation, inadequate size, irrelevant measures of outcome, or a design that is inappropriate for the context. In some cases, even when such trials are conducted, their findings were never published.[7] This can fail to identify and utilise effective interventions or can continue using ineffective or hazardous interventions. Such problems waste resources, cause unnecessary harm or suffering, and reduce trust in those who develop or use health interventions. Greater facilitation of high-quality RCTs is essential to guide the development of more effective interventions and to enhance future care delivery.

Clinical trials require special considerations to explicitly describe the additional robust ethical standards to address the complex designs and invasive interventions and procedures that might pose more than minimal risk.[8] Therefore, there is a clear need for guidance to promote the unique benefits of RCTs across all contexts, which focuses on the unique strengths of randomisation while setting out the underpinning principles necessary to generate reliable results safely and ethically, regardless of context.[9]

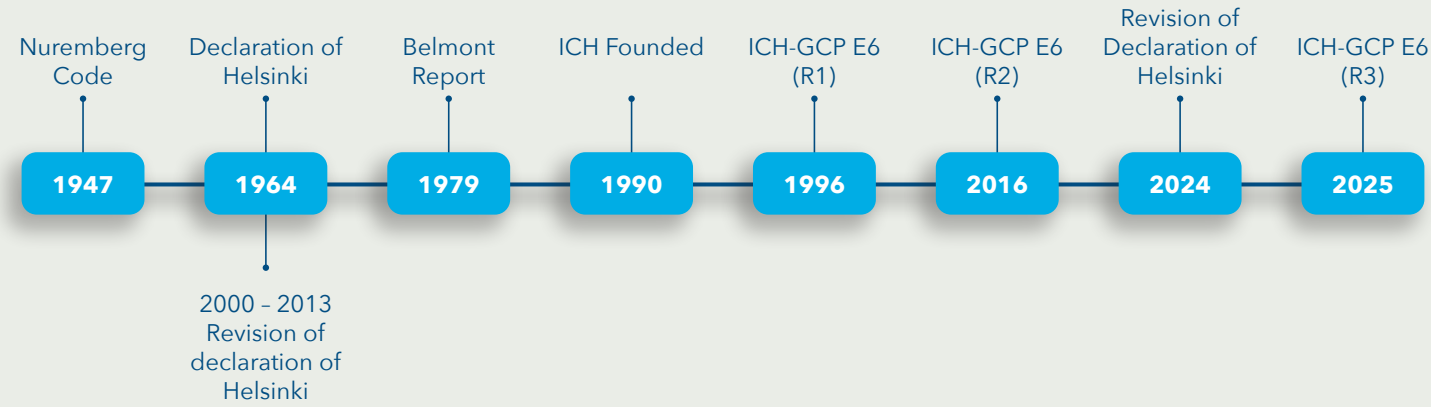


Figure 1: Key timelines in international guidance for conducting clinical research

1.1 CLINICAL RESEARCH GUIDANCE LANDSCAPE

The clinical research guidance landscape consists of a network of international and local frameworks that govern the conduct of clinical trial research.[9] These frameworks ensure that clinical research is conducted ethically and responsibly, protecting research participants. The two acclaimed international guidelines are the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use–Good Clinical Practice (ICH-GCP) and Good Clinical Practice (GCP).

GCP is an international, ethical, scientific, and quality standard for the conduct of clinical research involving human participants. Some of the principles of GCP include the protection of the rights, safety and well-being of research participants; ensuring that the conduct of clinical research is consistent with the Declaration of Helsinki; and providing reliable results. [10, 11] The history of GCP stems from the historical conduct of unethical human research studies.[7] These led to the development of regulations that govern the design and implementation of research that involves human participants.[10] The first of these was the Nuremberg Code in 1947, influenced by unethical medical experiments conducted by Nazi doctors during World War II.[11, 12] The Nuremberg Code was the first document to outline ethical principles for research involving human participants. The Nuremberg Code (1947) was followed by the Declaration of Helsinki, developed in 1964 by the World Medical Association (WMA).[10, 13] This Declaration of Helsinki is a statement of ethical principles for medical research involving humans, including research on identifiable human material and data. The Declaration of Helsinki introduced the principles of informed consent and risk-based decision-making.[10, 13] The Declaration of Helsinki has gone through multiple revisions, with the latest revision being approved on 19 October 2024.[10, 13] The US Public Health Service (USPHS) Untreated Syphilis Study at Tuskegee, wherein African American men were intentionally infected

with syphilis and not offered treatment without their consent between 1932 and 1972, led to the Belmont Report in 1979.[14-16] The Belmont Report was developed to emphasise further the need for the protection of human participants involved in research.[10, 14]

1.1.1 ICH-GCP

Over the years, different countries developed their own drug development guidelines, laws, and regulations, which led to the need for harmonisation of these guidelines. In April 1990, industry associations and regulatory agencies from Europe, Japan, and the US met in Brussels, leading to the establishment of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).[17] The Guideline "E6", which was approved on 17 July 1996 and implemented from 17 January 1997, became the most important guideline covering clinical studies, commonly known as the ICH-GCP Guideline. The objective of the ICH-GCP Guideline was to establish a joint standard for the ICH region, ensuring mutual acceptance of clinical data by regulatory authorities.[10, 17] The core principle of the ICH GCP Guideline is also the protection of the rights, safety, and well-being of participants, as well as the collection of high-quality data in the conduct of clinical research. On 6 January 2025, the International Council for Harmonisation (ICH) endorsed the latest revision of the ICH Guideline (ICH E6(R3) (2025)).[18] This revision introduces an new structure that includes eleven core principles, placing greater emphasis on quality by design, proportionate risk-based approaches, clear accountability of sponsors and investigators, and the generation of reliable, trustworthy trial results.[18] However, the GCTC consider that R3 remains vulnerable to over-interpretation and rigid implementation.[7]

1.1.2 South African clinical research guidelines

South Africa currently has two research guidance documents for clinical research and GCP, namely the South African GCP Clinical Trial Guidelines (referred to as SA GCP 2020)[2, 19] and the Department of Health Ethics in Health Research Guidelines, Third Edition 2024 (referred to as the NDoH Guideline 2024).[19] The SA GCP 2020 aligns with the International Council for Harmonisation (ICH) Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 (R2) 2016 (ICH GCP 2016) and the NDoH 2015 guidelines.[2, 18] SA GCP 2020 provides researchers and all stakeholders interested in research with clearly defined GCP standards for locally conducted studies that take into account the local contexts and realities to ensure that clinical research that involve South African participants are designed and conducted according to local requirements as well as with good scientific and ethical standards within the recognised framework for GCP.[2] The NDoH Guideline 2024 aim to establish a minimum national benchmark of norms and standards for conducting responsible and ethical research involving human subjects in South Africa.[19] The primary purpose of these guidelines is to provide individuals interested in clinical research with guidance on conducting clinical research ethically and responsibly, thereby protecting research participants.[2, 19]

1.2 OVERVIEW OF CLINICAL RESEARCH IN SOUTH AFRICA

The South African clinical trial ecosystem is well established and diverse, comprising independent research institutes in both the public and private sectors. This has led to South Africa becoming one of the leading locations for conducting clinical trials in Africa, because of its well-established research infrastructure, a variety of medical experts, a genetically diverse population, mixed access to healthcare, and a high burden of communicable and non-communicable diseases. The major players in the implementation of clinical trials in South Africa include pharmaceutical companies, South African universities, contract research organisations (CROs), South African sponsors, independent research units, and regulatory organisations.

According to CenterWatch, an online platform that provides clinical trial listings, clinical trial news and research resources[20] most of the organisations involved in clinical trial implementation are based in large metropolitan areas. Hence, the provinces with the most clinical research sites are Gauteng (Johannesburg and Pretoria), Western Cape (Cape Town) and KwaZulu-Natal (Durban). Secondly, most of the trials focus on therapeutic areas like oncology, infectious diseases (e.g. HIV/AIDS and TB) and cardiovascular-related conditions. Urban areas are the most preferred, as they provide easy access to diverse populations, infrastructure (such as laboratories and transport routes), specialised services (like equipment calibration), and skilled personnel.[21] Although rural areas also bear a high burden of disease, more advocacy is needed to increase access to clinical trials in these communities.[21, 22]

1.2.1 Regulatory authorities and registries

Similar to other countries, South Africa has numerous regulatory authorities that have to approve clinical trials or any clinical research before they are implemented.[2] According to the SA GCP[2] and NDoH 2024[19] the major regulatory bodies or authorities include:

The National Health Research Ethics Council (NHREC) is a statutory body established under the National Health Act. It provides direction on ethical issues related to health and develops guidelines for the conduct of research involving humans and animals. The NHREC is mandated to register and audit Research Ethics Committees (RECs).[2, 23]

The South African Health Products Regulatory Authority (SAHPRA) is a statutory body established to provide for the monitoring, evaluation, regulation, investigation, inspection, registration, and control of health products, scheduled substances, clinical trials, and related matters in the public interest. SAHPRA's mission is to promote access to health products and protect human and animal health in South Africa through science-based regulatory decisions by providing guidelines to conduct clinical trials and standards and regulations for the conduct of clinical research. SAHPRA ensures compliance with the internal standards, including the GCP.[2, 24]

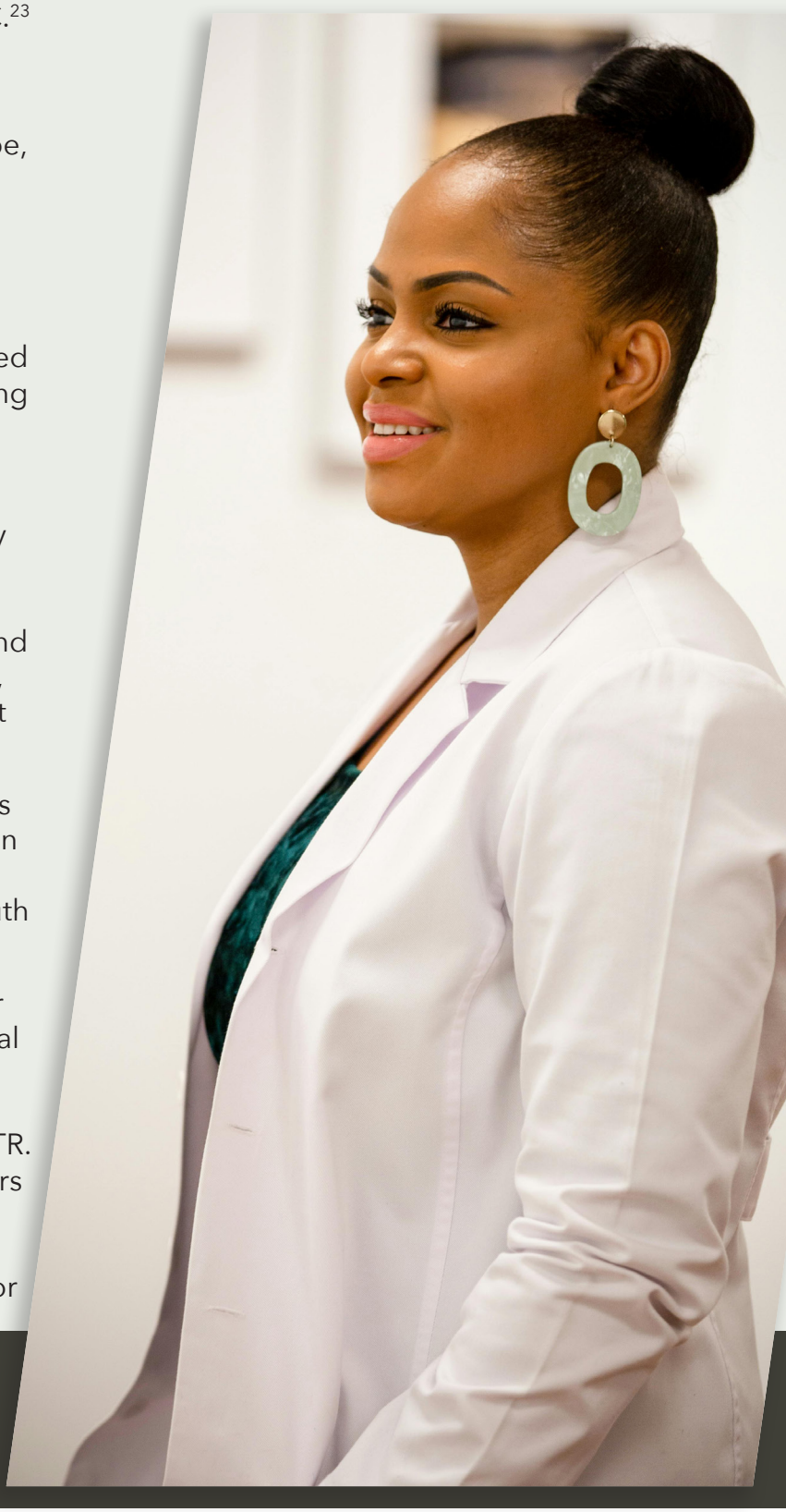
Research Ethics Committees (RECs) (University-affiliated committees and private ethics committees): The primary responsibility of RECs in South Africa is to ensure that all proposals for conducting health research involving human participants undergo rigorous, independent ethics review. This responsibility is exercised to protect research participants and ensure that their

rights, safety, and well-being are respected and protected.[2, 19] RECs may approve the research protocol, require amendments to the research protocol, or reject the research proposal on ethical and/or scientific grounds.[2, 19] All institutions where research is conducted are required to establish an ethics committee or have access to an independent ethics committee that is registered with the NHREC.[23]

National Health Research Committee (NHRC) is a national statutory body responsible for determining the nature, scope, and coordination of health research carried out by public health authorities. Its mandate is to ensure that priority health problems and needs receive appropriate attention and resources and to advise the Minister of Health on the implementation of an integrated national health research strategy. In identifying priorities, the NHRC takes into account the burden of disease, the cost-effectiveness of interventions to address the burden of disease, the resource implications (especially at the lowest levels of health care delivery), and the health needs of vulnerable persons, including women, older persons, children, and persons with disabilities. Where appropriate, the health needs of whole communities must also be considered.[2]

Together, these regulatory bodies/authorities regulate clinical trials to ensure the protection of participants and maintain the scientific integrity of all clinical trials conducted in South Africa.[2, 19]

South African National Clinical Trials Register (SANCTR) is a publicly available online clinical trial registry created by the Department of Health (https://sanctr.samrc.ac.za/). All South African-based trials are registered on SANCTR. This enables collaboration among researchers by sharing research information, informs the public about clinical trials in South Africa, helps individuals find suitable clinical trials for potential participation, reduces the duplication of research efforts, and promotes the optimal use of limited resources. Once the REC and SAHPRA approvals are entered on the register, each trial is assigned a unique DoH study number. Trials cannot begin without this DoH number.[2, 19]



1.2.2 Review of registered trials in South Africa

As of February 2025, 4 607 clinical trials are registered on the SANCTR.[25] Of these, 93% are categorised as RCTs, while 5% are non-randomised clinical trials. Non-randomised trials and observational studies each account for 1% of the registered trials. Additionally, 79% of the trials are related to drug treatments, whereas vaccine and medical device trials each comprise 1% of the total registered studies. Regarding trial phases, 40% are Phase III trials, while Phase I and Phase II trials are 18% of the registered studies.

Twenty-seven disease categories are being researched, as outlined in ***Table 1***, and the majority fall under the categories of infections and infestations. Of the 4 607 clinical trials registered in South Africa, 39% were recorded as not yet recruiting, 28% as completed, and 17% as actively recruiting. An additional 6% were active but not recruiting, 5% had been stopped early or terminated, and 3% were reported to be near recruitment completion with follow-up ongoing. Furthermore, 1% of the trials have been suspended, while less than 1% (18/4 607) have been withdrawn. Of the 4 607 registered clinical trials, only 1 222 have known result reporting statuses, with 276 trials having results available and 946 trials lacking reported results.

Table 1: Disease categories being researched in South Africa

DISEASE CATEGORY	NUMBER	PERCENTAGE
Infections and infestations	2 059	45%
Other	573	12%
Cancer	375	8%
Respiratory	385	8%
Haematological disorders	259	6%
Nutritional, metabolic, endocrine	232	5%
Mental and behavioural disorders	182	4%
Digestive system	141	3%
Musculoskeletal diseases	124	3%
Nervous system diseases	123	3%
Skin and connective tissue diseases	97	2%
Cardiology	43	1%
Eye diseases	37	1%
Paediatrics	40	1%
Circulatory system	24	1%
Kidney diseases	23	0%
Urological and genital diseases	20	0%
Pregnancy and childbirth	20	0%
Ear, nose and throat	19	0%
Obstetrics and gynaecology	19	0%
Injury, occupational diseases, poisoning	17	0%
Surgery	13	0%
Anaesthesia	10	0%
Genetic diseases	8	0%
Orthopaedics	6	0%
Neonatal diseases	2	0%
Oral health	2	0%

The Commercial sector/industry dominates funding for clinical trials in SA, accounting for 73% (3 069/4 186) of clinical trials registered in South Africa. Other notable contributors include funding agencies (20%), charities/societies/foundations 1% (58/4 186), government bodies 1% (51), hospitals 0% (2), other funders 1% (41), other collaborative groups 1% (21), self-funded 1% (50), and universities 1% (41).

1.3 ECONOMIC CONTRIBUTION OF CLINICAL TRIALS

According to the Clinical Trials Market Size, Share & Trends Analysis Report, the global clinical trials market generated a revenue of USD 80 738,5 million in 2023 and is expected to reach USD 123 539,7 million by 2030.[26] The South African clinical trials market was reported to have generated a revenue of USD 323,9 million and is expected to reach a projected revenue of USD 495,5 million by 2030.[26] Clinical trials play a significant role not only in generating evidence needed for the development and implementation of health interventions but also in providing substantial economic benefits and societal value. Clinical trials and their accompanying research and healthcare can directly benefit the patients in that trial, particularly those who would have otherwise had little to no access to adequate healthcare.[27] Patients also have the opportunity to gain early access to new treatments.[28] Clinical trials attract investment, which creates jobs; they also help build research and healthcare capacity, and improve local infrastructure, leading to increased economic growth.[27]

1.4 CHALLENGES IN GUIDANCE

Outline the GAP in guidance

A range of guidelines for clinical trials exists, but most fail to guide the underpinning principles of RCTs necessary to generate reliable results safely and ethically, regardless of context. In addition, some researchers are concerned that existing regulations are out of date and have become a barrier to conducting well-designed clinical trials, often making them harder and more expensive to run. Bowman et al. (2022) argue that although the intention of the ICH-GCP guideline was to protect participants and ensure the reliability of results, its over-interpretation and rigid implementation have become unnecessarily obstructive, preventing good trials from being conducted affordably. This highlights the limitations of existing guidance and the need for clearer, principle-based approaches that enable trials to be both rigorous and feasible.[29]

Why GCTC was developed

Many guidelines have also focused narrowly on the standards required of trials (including non-randomised studies) intended for submission to regulatory authorities to support a new drug licence. There is an unmet need for guidance to promote the unique benefits of RCTs across all contexts and settings. The GCTC was established to develop and promote the adoption of new guidance to address this issue. The GCTC brought together a diverse, multidisciplinary group of more than 100 expert individuals and organisations to identify and describe the key underpinnings of a good clinical trial. Now published on the Collaborative's website and its principles incorporated in the WHO Best Practice for Clinical Trials Guideline, the GCTC Guidance is the first ever guidance to be universally relevant to all RCTs of any health intervention, purpose and setting, and is intended to support all parties involved in the journey of an RCT. The GCTC guidance is structured around five key principles: RCTs should be informative and relevant, respectful of participants, collaborative and transparent with methods and results openly reported, designed to be appropriate for their context, and efficiently and well managed. To support the adoption of these principles, the Collaborative has also developed an online learning tool and an evaluation tool, designed for anyone working in clinical research who wants to enhance their understanding of good clinical trial practices, regardless of their level of expertise.[7]

2. METHODOLOGY

2.1 STUDY DESIGN

This study employed a convergent parallel mixed-methods research design. Mixed-method research integrates quantitative and qualitative data within a single study.[30] It emphasises the collection, analysis, and integration of both types of data to offer a deeper understanding of research problems than either approach can provide alone.[31] As a single data source may prove inadequate, a second method is essential to augment the primary method, and initial findings necessitate further elucidation.[30] The convergent parallel design in mixed methods facilitates a comprehensive analysis of the research issue by triangulating quantitative and qualitative data.[32] In this design, we gathered both data types concurrently, prioritised the methods equally, ensured independent data analysis, combined the results during the overall interpretation, and aimed to identify convergence, divergence, contradictions, or relationships between the two data sources.[33] Thus, in our project, qualitative and quantitative methodologies were implemented simultaneously to examine areas of convergence or divergence between the qualitative and quantitative findings.

2.2 STUDY AIM

The overall aim of this study is to assess the knowledge and practice of GCTC guidance among key stakeholders involved in the implementation of clinical trials in South Africa.

2.3 STUDY OBJECTIVES

Assess knowledge of GCTC guidance among major clinical trials stakeholders in South Africa. Assess the perceptions and acceptability of GCTC to South African clinical trials implementers. Collate data on the required changes to the GCTC Guidance that would facilitate adoption into the South African context. Develop a roadmap for incorporating GCTC guidance into the conduct of RCTs in South Africa.

2.4 STUDY PROCEDURES

2.4.1 Stakeholder mapping

All clinical trials conducted in South Africa, along with their locations, are registered on two online public databases: sanctr.samrc.ac.za and Clinicaltrials.gov. These registers, as well as Google search and snowballing, were used to identify the major role players in clinical trials in South Africa. The implementers of clinical trials were categorised into the following categories: pharmaceutical companies, universities, CROs, South African sponsors, independent research units, and regulatory organisations. A total of 552 key implementers of clinical trials were identified.

2.4.1.1 Procedures for the workshops and surveys

Key stakeholders of clinical trials at different levels and roles were invited to participate in the workshops.

Interested participants were sent an electronic informed consent form (ICF) to complete the day before the workshop via REDCap, a secure, web-based software platform designed to support data capture for research studies.[34] Once the ICF was completed, the participants received a REDCap-based pre-workshop survey via email to assess their knowledge of GCTC guidance and their current RCT practices.

The workshop was a full-day, interactive session facilitated by research team, during which the GCTC Guidance and its five principles were presented. The delegates were encouraged to provide their opinions or input on the feasibility and acceptability of each principle in the South African context.

The workshops were conducted in various provinces in South Africa (Gauteng, Western Cape, and KwaZulu-Natal), and an online workshop was conducted.

Figure 2: Procedures for workshops and surveys

After the workshops, delegates were sent two surveys:

- The first post-workshop survey, sent immediately after the workshop, aimed to capture further key stakeholders' opinions or input on the feasibility, acceptability, and required changes to facilitate the adoption of the GCTC Guidance in the South African context.
- The second post-workshop survey, sent three to six months after the workshop, aimed to assess how the workshop had affected the key stakeholders' RCT practice.

A total of eight in-person workshops and one online workshop were conducted, with 115 participants attending these sessions. A total of 116 ICFs were completed, while participants completed 111 pre-workshop surveys, 102 first-post-workshop surveys, and 29 second-post-workshop surveys. However, some participants did not respond to all questions within the surveys. The numbers reported within this report reflect the actual number of participants who responded to each individual question and may therefore differ between questions.

The following table summarises the location of the delegates/participants who participated in the workshop and survey section of the study.

2.4.2 Key informant stakeholder interviews

Figure 3: Procedures for key informant interviews

Of the 552 identified implementers of clinical trials, 105 were invited to participate in in-depth interviews. The ICF was shared with potential participants before their scheduled interviews via Research Electronic Data Capture (REDCap). The interviews were conducted either in person or via Microsoft Teams and were recorded. A semi-structured interview guide, along with a brief demographic questionnaire, was used to collect information from key informants on the implementation of clinical trials in South Africa, including their experiences, perceptions and knowledge of GCTC, regulatory framework, laboratory and pharmacy infrastructure, monitoring of clinical trials, and community perceptions. A total of 22 in-depth interviews were conducted *(See **Figure 3**)*.

2.4.3 Survey completion on REDCap

Workshop survey data were collected and managed using REDCap electronic data capture tools hosted at the Africa Health Research Institute (AHRI).

Table 2: Workshops conducted and number of delegates per workshop

PROVINCES	NUMBER OF WORKSHOPS	NUMBER OF DELEGATES
Gauteng	2	36
KwaZulu-Natal	5	54
Western Cape	1	18
Online	1	7
Total		**115**

2.5 DATA MANAGEMENT AND ANALYSIS

The project was a mixed-method study employing both quantitative and qualitative methods. One hundred and fifteen implementers of clinical trials participated in the study, while 22 of these implementers also participated in the qualitative interview section of the study.

2.5.1 Quantitative data analysis

Data for the quantitative aspect of the surveys was analysed using descriptive statistics including counts, percentages, proportions, median and interquartile range.[35, 36]

2.5.2 Qualitative data analysis

Qualitative interviews were audio-recorded and transcribed by the research team. All interviews were in English; therefore, translation of interviews was not required. Thematic analysis was used by reading through the transcripts, and codes were generated.

Thematic analysis was used to analyse the long survey questions. Two team members independently reviewed the responses given by the participants, identifying patterns and themes that emerged from the participants' responses. Through an iterative process, the two team members then compared and refined the codes to develop themes. This process ensured that the emerging opinions and main viewpoints of the participants were captured.

Both analyses used NVivo, a computer software program that allows researchers to manage, analyse, and visualise qualitative data and documents systematically and individually, as a tool to assist in generating the themes and codes.[35, 36]

2.6 ETHICAL CONSIDERATIONS

Ethics approval for the study was obtained from the Biomedical Research Ethics Committee (BREC) at the University of KwaZulu-Natal on 18 February 2024 (Clearance number: BREC/00006308/2023). To uphold the principle of informed consent, participants were provided with a detailed information sheet outlining the study's purpose, procedures, risks, and benefits. Written informed consent was obtained before participation. Anonymity and confidentiality were ensured by assigning participants a unique participant ID, using pseudonyms, and removing identifying information from surveys, transcripts, and reports. All information, including surveys, transcripts, personal data, and research data, was securely stored in a password-protected online database accessible only to the research team. In terms of privacy, interviews were conducted in settings that were convenient and comfortable for participants, with care taken to avoid intrusion into personal spaces. This approach ensured that participants felt safe, respected, and in control of their boundaries throughout the research process for this study. Participants were informed of their right to withdraw from the study at any time and that participation was entirely voluntary.

3. STUDY RESULTS

3.1 SAMPLE CHARACTERISTICS

3.1.1 Participants' demographics

A total of 111 delegates completed the pre-workshop survey, and 22 key informant interviews were conducted. Of the 133 participants, 99% were residing in South Africa. The majority of participants (82%) were based in urban areas, while 16% were based in rural areas. Additionally, 2% of the participants reported they were based in peri-urban and semi-urban areas. Participants had experience working in various countries, including several in Africa, such as Nigeria, Kenya, and Uganda, as well as in European countries, like the United Kingdom, Romania, and Germany. They also worked in Southeast Asian countries, including Thailand and the Philippines, as well as in Australia and the USA. Their characteristics are summarised in ***Table 3*** below.

Table 3: Characteristics of participants that completed surveys and interviews

Indicator	Results n(%)
Gender (n= 133)	
Female	93 (70%)
Male	39 (29%)
Prefer not to say	1 (1%)
Age (n=133)	
18-24 years	1 (1%)
25-34 years	32 (24%)
35-44 years	45 (34%)
45-54 years	33 (25%)
>55 years	19 (14%)
Prefer not to say	3 (2%)
Do you have experience in the start-up phase of clinical trials? (n=131)	
Yes	96 (73%)
No	35 (27%)
How many years have you been working on clinical trials? (n=131)	
0-4 years	48 (37%)
5-9 years	24 (18%)
10-14 years	18 (14%)
15-19 years	16 (12%)
>20 years	22 (17%)
Don't know/prefer not to say	3 (2%)

How many clinical trials have you worked on? (n=131)	
0-4 clinical trials	40 (31%)
5-9 clinical trials	19 (15%)
10-14 clinical trials	12 (9%)
15-19 clinical trials	9 (7%)
Don't know/prefer not to say	11 (8%)
What phase of trials have you worked on?*	
Phase I	66 (50%)
Phase II	80 (60%)
Phase III	99 (74%)
Phase IV	43 (32%)
Other	17 (13%)
Don't know/prefer not to say	13 (10%)
Educational disciplines*	
Public health	42 (23%)
Social science	20 (11%)
Medical science	57 (32%)
Environmental health	2 (1%)
Science	21 (12%)
Management	15 (8%)
Other education levels	16 (9%)
Don't know/Prefer not to say	5 (3%)

**Multiple responses were allowed per participant*

Participants had experience working in clinical trials focusing on various disease groups (See *Figure 4*).

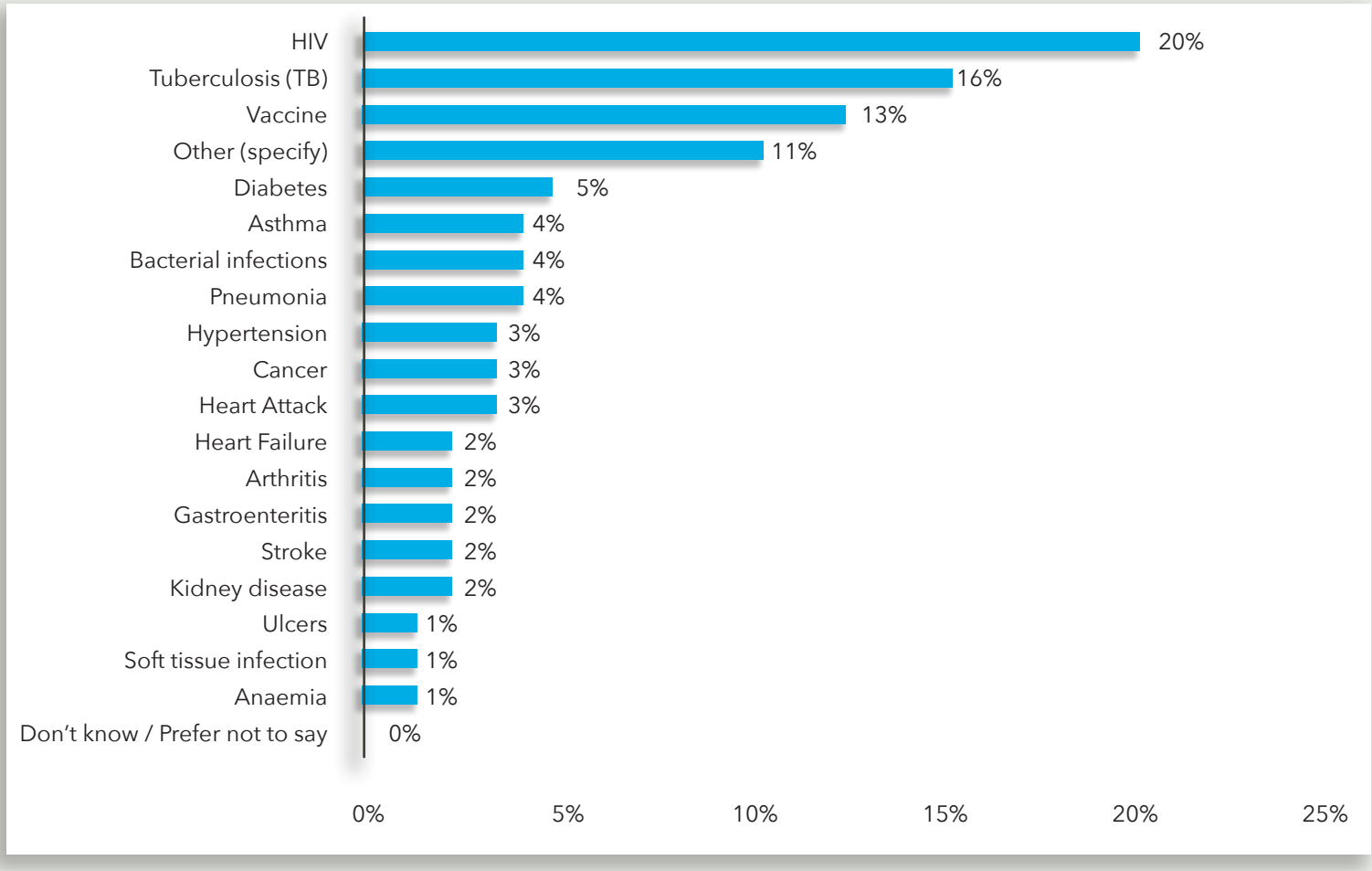


Figure 4: Disease groups participants have worked on

Current roles and experience in clinical trials

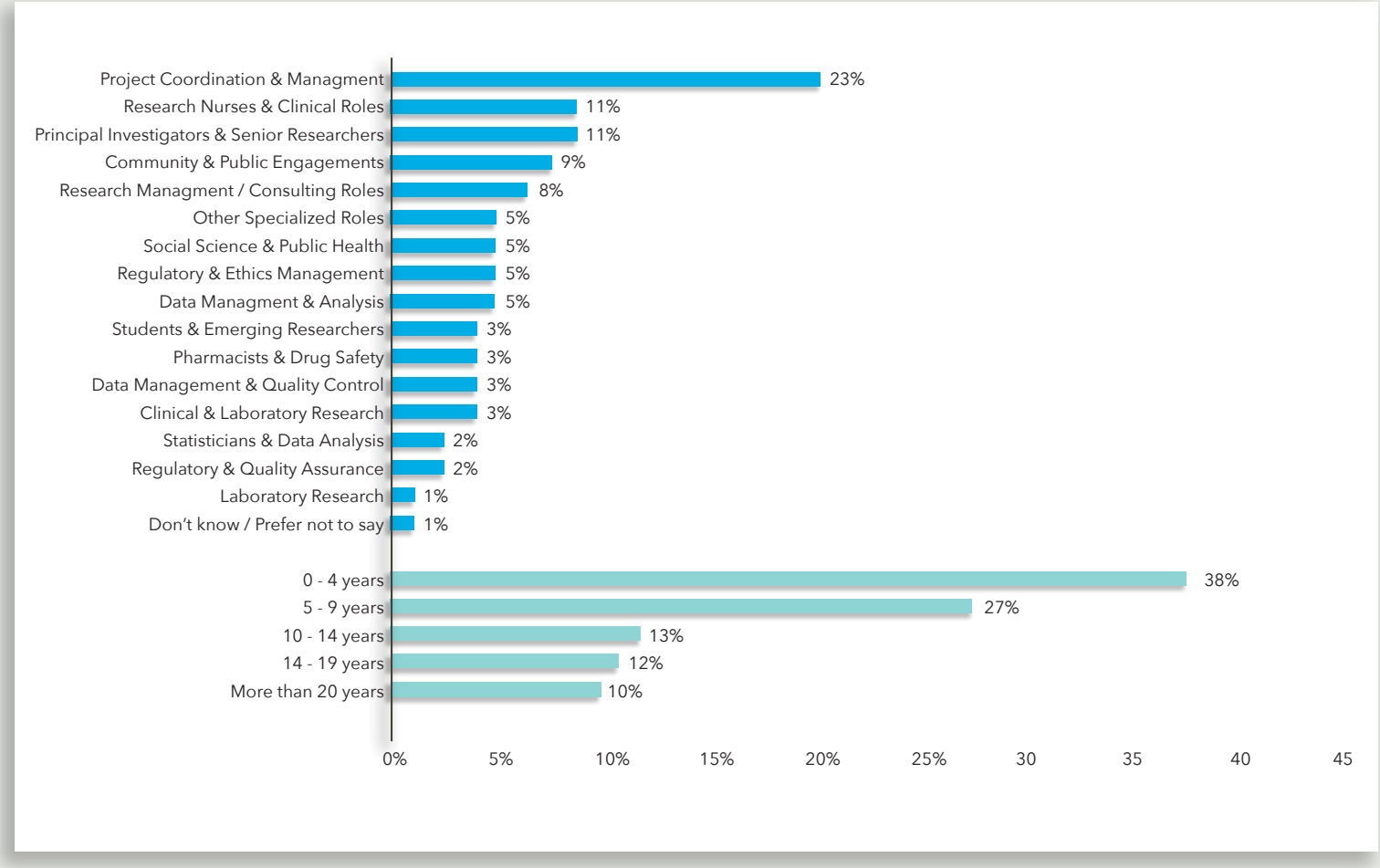


Figure 5: Participants' current roles and number of years working in those roles

Roles played in the implementation of clinical trials

Participants mentioned a wide range of responsibilities within clinical trials, spanning from the early stages of protocol development to community engagement and site operations. Their involvement includes writing grant proposals and protocols, designing study tools such as case report forms (CRFs) and SOPs, setting up clinical trial sites, training study teams, engaging with the community, recruiting participants, and contributing to publications.

"I've worked on the protocol development stage, and more recently, I've become involved in community engagement activities, sharing ideas with the community through the Community Advisory Board at [organisation name]. I've also contributed to early trial phases, including staff recruitment, writing SOPs, and participating in site initiation and pre-site initiation visits ..."

(Research nurse and clinical role: Duration in current role: 5 to 9 years)

Have you ever been involved in clinical trials that failed to be informative?

Only 19% (21/109) of the workshop participants reported having been involved in clinical trials that failed to be informative. Recruitment targets not met (21%), futility (15%), stringent eligibility criteria (12%), and other reasons (12%), such as severe adverse events and an ineffective investigational product, were raised as reasons the clinical trials failed to be informative (See ***Figure 6***).

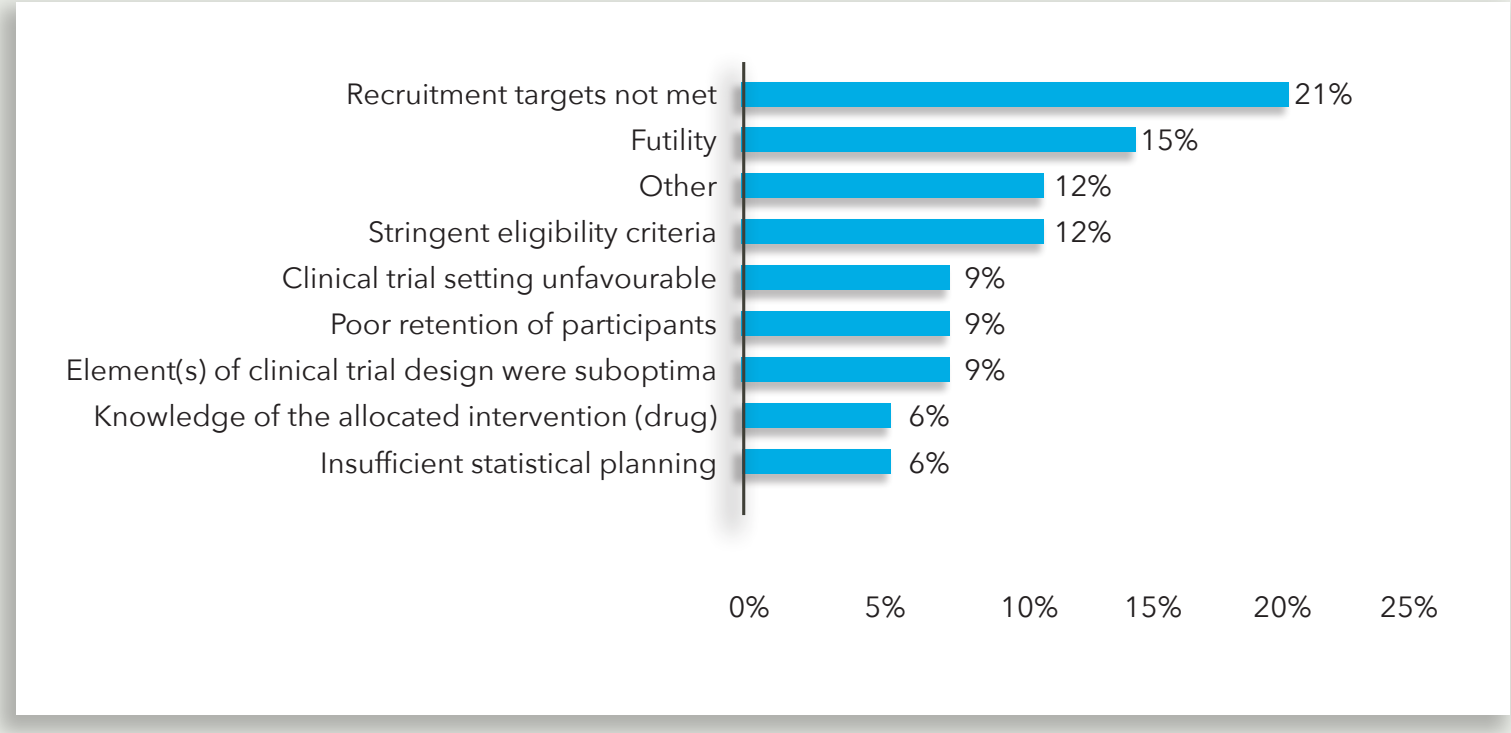


Figure 6: Reasons clinical trials failed to be informative

Some of the key informants indicated that a negative clinical trial outcome does not imply uninformative results.

> ***"Um, no, they've always been informative. I've had clinical trials which had a negative outcome, but the negative outcome's also been informative, so no."***
>
> (Other specialised roles and global health: Duration in current role: 4 years and 20+ years in Global Health)

3.2. PERCEPTIONS OF THE CLINICAL TRIAL ECOSYSTEM IN SOUTH AFRICA

3.2.1 Challenges observed in the conduct of clinical trials

In South Africa, numerous clinical trials have been carried out successfully, and several are still ongoing. Clinical trials improve health management and provide new, innovative treatments that are accessible. In the pre-workshop survey, we evaluated the participants' perspectives on the clinical trial ecosystem, focusing on the design, operational, and implementation feasibility challenges associated with clinical trials.

Eighteen per cent (13/111) of the participants indicated that no challenges were observed in the clinical trial designs, operations and feasibility. Those who had reported experience working in clinical trials reported significant challenges related to the design, operation, and feasibility of clinical trials.

These challenges included issues related to a lack of administration, unclear timelines, inadequate sites, participant recruitment and retention, data collection tools, clinical trial design, and the exclusion of certain groups from clinical trials (See ***Table 4***). Additionally, concerns were raised about the clarity of the information provided to participants, which may have affected their understanding and willingness to fully engage in the trial. Addressing these challenges is crucial to ensuring the integrity and success of clinical research.

Table 4: Summary of the key challenges observed in the conduct of clinical trials in South Africa

Design phase	Preparatory phase	Implementation phase
• Ill-defined study objectives and outcomes • Data collection tools not aligned with protocol or efficient clinic flow • Design not contextualised in community or their health needs • Few people trained on protocol writing/study design • No input from key stakeholders, including sites, in study design • Exclusion of some geographical regions and population groups • High cost, limited funding • Exclusion of geographical areas and populations	**Regulatory challenges** • Delays in regulatory approvals • Complicated and lengthy Import and export permits approvals **Minimal investment in site and personnel** • Lack of appropriate infrastructure • Network connectivity • Unreliable electricity supply • No specific clinical trial training for healthcare workers • Inadequate planning and administration • Recruitment of appropriate skilled personnel • Community engagement	**Inefficient recruitment and retention** • Low levels of literacy on clinical trials • Stigma to participate in clinical trials • Relocation • Family consensus • Availability of legal guidance • Stringent eligibility criteria • Lengthy complicated informed consent forms • Insufficient information and time allocation given to participants for informed consent process. **Other challenges** • Delayed payments • High staff turnover • Few healthcare facilities or referrals • Poor completion of CRFs • Communication between stakeholders

OBSERVED CHALLENGES IN THE DESIGN PHASE

Ambiguously specified objectives and outcomes: If the objectives and outcomes of a clinical trial in the protocol are ambiguously specified, it makes it challenging to collect essential information.

Data collection tools: The design of CRFs is essential for ensuring the accuracy, efficiency, and relevance of data collection in clinical trials. However, when CRFs are designed in isolation without any input from key stakeholders, misalignment with study protocols can lead to inefficiencies and unnecessary data collection.

Design not contextualized in the community or their health needs: Some clinical trial designs are not relevant to the community that they aim to serve.

Few people are trained in protocol writing/ study design. Some of the challenges surrounding clinical trial design are linked to the use of inexperienced individuals with limited study design experience in writing clinical trial protocols, where outcomes are not clearly defined, and inadequate data are captured.

No input was received from key stakeholders, including study sites, in the study design. Clinical trials are complex and require careful design. However, it was reported that some key stakeholders were not involved in the design of these trials.

High cost, limited funding: The financial challenges observed and reported by participants, included high costs for conducting clinical trials, limited funding available, and delayed payments after invoicing.

Exclusion of geographical areas and populations: A challenge arises from the concentration of clinical trials in specific areas, which often benefits only a few individuals. Additionally, it has been reported that many areas are overly researched, making the communities vulnerable to exploitation in studies.

CHALLENGES OBSERVED IN THE PREPARATORY PHASE

REGULATORY CHALLENGES

Delays in regulatory approvals: One of the challenges in clinical trials is the delay in regulatory approvals. For a clinical trial to be executed, multiple boards must approve the study, including SAHPRA, ethics committees, and the DoH at different levels. These approvals typically require time and can delay the study.

Complicated and lengthy Import and export permits approvals: A third (32%; 36/111) of participants experienced delays in regulatory approvals, including import and export permits.

MINIMAL INVESTMENT IN SITE AND PERSONNEL

No specific clinical trial training was provided for healthcare workers: The training provided to clinical trial staff was found to be inadequate or not tailored to trials. There is significant staff turnover in the clinical trial setting. There is a challenge in finding skilled staff for clinical trials, particularly in areas such as oncology.

Lack of appropriate infrastructure: The participants mentioned that implementing

clinical trials in rural settings is challenging because of the lack of availability of healthcare facilities for referrals. Laboratories for processing samples are often also located far from research sites in a rural setting. Furthermore, the clinical trial sites face geographical challenges and lack resources such as reliable network connections and backup power sources (generator/solar) to address electricity supply interruptions.

No specific clinical trial training was provided for healthcare workers: Study participants reported that the training provided to clinical trial staff was found to be inadequate and not tailored to the specific clinical trial procedures and requirements.

Inadequate planning and administration: Feedback from participants indicated that rushed clinical trials often lack proper administration and have unclear timelines for start-up. The lack of suitable sites for conducting clinical trials was also reported.

Recruitment of skilled personnel: A significant challenge is finding qualified staff for clinical trials, particularly in areas such as oncology.

Community engagement was identified as a crucial factor in the successful implementation of clinical trials: Participants indicated that a clinical trial that does not address a pressing local issue is unlikely to succeed. Therefore, community engagement is not optional but essential in clinical trials.

CHALLENGES OBSERVED IN THE IMPLEMENTATION PHASE

INEFFICIENT RECRUITMENT AND RETENTION

Low literacy levels in clinical trials: Stakeholders note that communication challenges arise during trials, with language often serving as a barrier between researchers and participants. Frequently, communication between study principal investigators and participants relies on intermediary staff such as nurses or research assistants. Language not only acts as a communication barrier but also contributes to the exclusion of certain groups, such as migrants, from participating in trials.

Stigma to participate in clinical trials: Some challenges observed included stigma and a lack of awareness of clinical trials. Therefore, recruitment becomes a challenge when people are unaware of clinical trials.

Relocation: Retention is often a challenge in long-term clinical trials, where participants relocate and become difficult to reach due to network and power issues, making it difficult for sites to contact them. Untraceable participants also contribute to the challenges of lost-to-follow-up in a clinical trial.

Family consensus: Recruiting participants can also be difficult when family members disapprove of their involvement in a clinical trial.

Availability of legal guidance: Challenges for clinical trials included the availability of legal guidance for studies involving minors that require consent from parents/guardians.

Stringent eligibility criteria: Clinical trials typically have very stringent eligibility criteria, making it challenging to recruit participants who meet the inclusion criteria for the studies, which can lead to the inability to meet targets.

Lengthy, complicated informed consent forms: There are issues with lengthy and complex ICFs where participants are not given enough information and time when participating.

Insufficient information and time allocation were given to participants for the informed consent process: Communication was also reported to be a problem, as it was not delivered appropriately to the participants. This leads to participants possibly withdrawing their consent to participate in the study at some point because they do not understand, which may affect the study's endpoint

OTHER CHALLENGES

High staff turnover: Participants reported significant staff turnover and a shortage of personnel in clinical trials.

Few healthcare facilities for referrals: When conducting clinical trials, the site needs to work closely with healthcare facilities to help with recruitment. Sometimes, healthcare facilities are not available to assist with participant referrals.

Poor completion of CRFs: The study shared responses around queries and data quality management where poor data collection and completion of CRFs were reported, and this led to a high rate of protocol deviations.

Communication between stakeholders: Communication between sponsors, study stakeholders, and sites was often reported to be inadequate, and sponsors' expectations were found to be unrealistic, particularly in the rural research landscape.

3.2.2 Challenges with randomisation in clinical trials

a) Inadequate randomisation: Eight per cent (8/89) discussed issues with inadequate randomisation. Envelopes being lost was one of the reported challenges when clinical trials used envelope methods. There were issues with maintaining blinding processes and unclear randomisation processes and systems. During randomisation, some key elements were found missing, and randomisation errors were reported. Another challenge mentioned was back-end termination of active randomisation slots in the interactive randomisation system. The participants reported that the randomisation challenges can be improved through proper concealment procedures to ensure true random occurrence.

While challenges were observed with randomisation in clinical trials, another view was that if the study is well designed and the randomisation method is suitable, then there are no challenges with randomisation:

"I wouldn't say there are major challenges with randomisation. If this study is designed properly and the randomisation strategy is appropriate, then there are no major challenges. I think that we need to make sure that randomisation and randomised trials are appropriate and are being done in the right circumstances and for the right reasons, but the process of randomisation these days is usually quite solid."

(Research nurse and other clinical roles: Duration in current role: 5 to 9 years)

b) Stringent exclusion criteria: Recruiting participants who meet the inclusion criteria is a challenge that can result in an inability to meet targets. Solutions to these challenges are reported as an expansion of coverage and access to consider the standard of care.

c) Adherence to allocated trial allocation: Six per cent (5/89) of participants shared that there are challenges with participants' adherence to their study treatment arm. Participants tend to have preferences for a particular treatment arm or might be apprehensive about being assigned to the experimental group. This leads to resistance to adherence or non-adherence to randomisation, which compromises the trial's integrity. Participants want to guess which arm they are randomised to and start making comparisons based on the side effects they experience. Some participants do not adhere to the assigned treatment, which affects the treatment outcome and complicates the interpretation of results. The participants are not followed up to assess if they follow all the instructions and are truthful when giving feedback. In some instances, participants are reluctant to be randomised, as they prefer a specific intervention. Education of participants on adherence is needed to understand the randomisation process and the importance of adhering. Participants who are unwilling to adhere to the allocated intervention arm should not be enrolled in the study. As part of the solutions, sites need to incorporate designs that allow all groups to receive intervention.

"With the participants, I think it's more of continuous engagement and communication, management of side effects, if that is the reason that they would not adhere to the assigned arm. Or if it's an issue of not adhering to the assigned clinical visit schedule, I think more still needs to be done in correcting that. Try to mitigate around the challenges; probably they stay too far, they have relocated and getting to the clinical research site might be difficult, probably, maybe some bloods needs to be, PK bloods, I'm thinking the likes of PK bloods. I think there is a lot that needs to be done. The clinical research site can try to understand what are the reasons that contribute to the participant not adhering to the assigned arm."

(Research nurse and other clinical roles: Duration in current role: 5 to 9 years)

d) Poor selection of endpoints: Poor selection of endpoints in randomisation was reported and it is difficult to ascertain from a randomised clinical trial which subset of participants benefited from the intervention being studied. A qualitative component should be included in the study, and hypotheses, objectives, and endpoint measures must be clear and feasible. An intervention must be provided.

e) Withdrawal from clinical trial: When a participant withdraws consent, it affects the balance achieved through randomisation and potentially results in unequal groups over time and may affect the validity of the trial results.

f) Randomisation bias: Randomisation may lead to unequal distribution of participant characteristics between treatment groups resulting in recruitment bias. It may also lead to bias and excess enrolment of participants with certain characteristics, as ethnicities, genders, or age groups may not be fully represented. Randomisation gets complicated when multiple stratifications are needed. To improve on these challenges, stratified randomisation is recommended, stratifying participants based on relevant characteristics to ensure a balanced distribution of confounding factors across treatment groups.

g) Inappropriate subject selection criteria. Randomised trials can be difficult, as one cannot control the type of population one can have on the controls and intervention group. This can be resolved by improving the selection method or system and criteria.

h) Participants understanding randomisation process: Participants do not fully understand the processes because when new studies are introduced in the community the focus is always on the new drug and not standard of care, and people start asking questions. It has also been reported that other people influencing the participants is a challenge. These challenges can be resolved through good communication. There is a need to explain clinical terminology to the community and to work closely with social scientists to develop simple communication guidance or tools. People-centric counselling and ongoing training are recommended.

3.2.3 Groups often not included in trials without a good scientific justification

The study found that several groups are excluded from randomised clinical trials without proper justification. These groups include pregnant and breastfeeding women, children and infants, teenagers, men, homeless people, minority race groups, adults aged 60 and above, and individuals living with chronic diseases and people with comorbidities, LGBTQ community, people living with disabilities (physical and mental), people with limited literacy, people living in rural areas or have a low socio economic status, PLWH, and prisoners. Understanding the reasons for these exclusions and their implications is crucial for ensuring that clinical research is inclusive, equitable, and capable of generating results applicable to the diverse populations that healthcare aims to serve.

"The obvious one is really children and women of childbearing age often excluded because of the need or the perceived need to protect them, as they are considered vulnerable individuals. So, I think that sometimes then they are, you know, actually is of detriment to these populations and they don't get adequate access to, you know, high-quality treatment."

(Principal investigator and clinical roles: Duration current role: 0 to 4 years)

3.2.4 Improvements needed in the conduct of clinical trials regarding the inclusion of diverse populations

Fifty-five per cent (49/89) of participants expressed their opinion on the changes required in the design of clinical trials so that they will include a broad and diverse population. The inclusion of both rural and urban areas was reported, as certain groups were excluded from the clinical trial. Eighteen per cent (16/89) reported the implementation of recruitment strategies that target the valid population is also recommended. Inclusion criteria should be more inclusive and less restrictive for various populations. Fifteen per cent (13/89) spoke about the importance of working in collaboration and partnership with the community and applicable stakeholders in the design of protocols. This will assist in recruitment, retention, and addressing any barriers to conducting clinical trials. There is a need to design clinical trials that are contextually relevant.

"I think there must always be a very clear justification for excluding certain groups, and as an ethics committee member, I think that ethics committees have to be a little bit stronger in ensuring that the exclusion of key populations is justified scientifically. For example, pregnant women if it's a new drug as a safety concern, then it may well be justified, but it, but it has to be clearly justified and can't just be a standard acceptance that that some of these groups are excluded from all trials."

(REC Member: Duration in current role: 5 to 9 years)

3.2.5 How can monitoring and auditing of trials improve the quality of the conduct of clinical trials?

Participants reported on how the monitoring and auditing of clinical trials can improve the quality of clinical trial conduct in South Africa. They noted that the process of monitoring and auditing can significantly contribute to improving the quality and integrity of the collected data, while also ensuring that clinical trials comply with local regulatory standards and guidelines. Monitoring and auditing of clinical trials was also noted to facilitate the identification of areas where study staff need further training. Furthermore, the process of monitoring and auditing ensures the safety and well-being of participants. Monitoring and auditing of trials were also noted to improve the quality of clinical trial conduct, as they introduce risk-based monitoring, which ensures that the frequency of monitoring and auditing is proportionate to the identified trial risk. Monitoring and auditing of trials was also perceived as an opportunity to build trust between the research site and sponsors, as both stakeholders have similar goals. Finally, participants emphasised that monitoring and auditing of trials can support effective budgeting of clinical trials, ensuring that resources are allocated appropriately.

"Monitors are part of the team ... They collaborate to ensure the trial runs smoothly, building trust between sites and sponsors"

(Research nurse and clinical roles: Duration in current role: 14 to 19 years)

"Monitoring reports help sites allocate resources effectively ... For example, identifying high dropout rates early allows for budget adjustments to improve retention"

(Principal investigator and senior researcher: Duration in current role: 15 to 19 years)

3.2.6 How to facilitate and encourage adherence to the allocated study arm

Most participants in the study shared their ideas on how to facilitate and encourage adherence to the allocated study arm in the clinical trials. Participants also emphasised the importance of establishing trust and providing adherence counselling to the clinical trial participants during the informed consent process, as well as to staff, to ensure clear communication with the participants about the importance of adhering to their assigned study arm. Counselling should include information on the potential impact on the reliability of the study results. Furthermore, participants suggest that adherence counselling should be conducted at every visit.

Participants emphasised that informed consent is a continuous process, not a one-time event. They emphasised the need for clear, thorough communication to ensure participants in clinical trials fully understand the study and have their questions addressed for better adherence to the allocated arm:

"So again, constant communication. In the informed consent process, I think what we need to recognise is that it's a process—it doesn't stop at the moment they sign the consent. Even before they sign, it's important to take the time to go through the consent document, not just summarise it. Go through it word for word. Take the time to ask if they've understood, and if they have questions, answer them."

(Research clinician: Duration in current role: 5 to 9 years)

Proper follow-up strategies, combined with continuous education, were also reported as crucial in facilitating and encouraging adherence to the assigned study arm. According to participants, providing educational materials and sessions about the treatment, its potential benefits, and the importance of adherence can encourage adherence to the allocated arm. This information should also be given to participants at their level of understanding. Clear communication and feedback, including the clarification of expectations, were also linked to proper communication at follow-up visits.

Participants emphasised the importance of community education before trial initiation as a foundational step to ensure adherence.

"Community education ahead of time …I think, for me, it's the first research indication that the community understands the importance of adherence, especially where financial incentives are so important for various communities. You must bridge the gap between receiving the financial incentive and adhering to protocol, including visits and product use. If we can bridge that gap, we are set up to succeed. And that is not only about the protocol in your question; it's an indication of why we need new products. How do you educate them to get that? Yeah. And then, once they understand, if they participate and do not adhere, we won't have new medication. Versus yes, we know there is an incentive, but there's also your commitment to new medication or devices. And identify who the support systems of your participants are … because if there's a difficult trial, again, you can look at the buddy system to support it, or support groups in the community that will encourage them to adhere to visits as well as to product use."

(Research consultant: Duration in current role: >20 years)

Continuous education throughout the study, especially studies with a long period of follow-up visits, was suggested as a strategy to encourage adherence to the allocated study arm. Education sessions, dialogues, and adherence groups were also indicated as tools that might improve adherence to the study arm. Participants received reminders, such as being called the day before their visit, using diaries, favourite TV programmes, and phone alarms were also suggested.

Furthermore, a proper randomisation plan for treatment and proper blinding procedures were highlighted as important strategies to facilitate adherence to the allocated study arm. The site should keep track of which arm is allocated treatment and ensure that sites have blinded and unblinded teams when the placebo looks different from the Investigational product. This is important for both dispensing and administration, and the unblinded team should ensure that they dispense according to the allocated study arm at all times.

Capacitating site staff and having a strong quality control team also helps facilitate adherence to the allocated study treatment arm. Proper training and ensuring that each staff member is aware of the importance of data integrity, particularly when randomising participants to different arms, is also necessary. Further, good communication and retraining of the staff are important to ensure that they understand how treatment is supposed to be allocated to participants. Providing incentives through small milestone gifts to participants also encourages participation and adherence to treatment.

3.2.7 Common errors in designing CRFs that result in large volumes of data that are not relevant to the research question

Many different types of common errors may occur in designing the CRFs, which may result in large amounts of data that are not relevant to the research question. Participants shared that errors may be a result of a) human errors, b) procedural errors, c) environmental errors, and d) instrumental errors.

Most participants reported that the CRF development was incomplete or inaccurate. Insufficient attention to detail during the development of CRFs can result in missing or inaccurately defined data fields. This may lead to the inclusion of irrelevant data or the omission of critical information, affecting the integrity and utility of the collected data. This may also be a result of not linking the CRF to the data analysis plan and designing CRFs without considering the practicality and feasibility of collecting the required data within the constraints of the study setting, resources, and timeline. This may lead to overly ambitious data collection plans that are difficult to implement in practice. Additionally, duplication and ambiguity in the CRF may make it difficult for site staff to complete or use it effectively.

The quote below emphasises how isolation during CRF design, particularly when undertaken without collaboration or adequate protocol comprehension, can lead to unnecessary data collected.

"I think one issue that can arise during the design phase is when someone develops all the CRFs perhaps sitting in their office without consulting other colleagues who are involved in the development or preparation of the trial. If the CRFs are approved without broader input, that can lead to problems later on. It's really important to involve others and to fully understand the protocol, what is being studied and what data is required. That understanding helps ensure the CRFs are designed appropriately and aligned with the clinical trial objectives, rather than collecting unnecessary or irrelevant information."

(Research clinician: Duration in current role: 9 to 5 to 9 years)

Some participants found that errors stem from the protocol writing. Protocols may not be written appropriately, may be inconsistent with the CRF, or are perhaps not studied and understood accordingly, which results in errors made by the study team. Conducting complex and numerous study procedures on participants may lead to errors and missing data, which can affect the validity and relevance of the collected data.

3.3 KNOWLEDGE, PERCEPTION AND RELEVANCE OF THE GCTC GUIDANCE

Assessing study participants' knowledge, perception, and perspectives on the relevance of the GCTC Guidance is crucial to the successful rollout and implementation of the GCTC Guidance. Hundred and nine workshop participants completed questions regarding their knowledge of GCTC guidance, with 15% (16/109) indicating awareness of the GCTC Guidance, while the others stated that they had never heard of the GCTC guidelines.

3.3.1 Overview of knowledge of the GCTC Guidance

Thirty-eight per cent (6/16) indicated that GCTC is a guideline for conducting good randomised clinical trials to develop, assess, and promote better randomised clinical trials globally. Twenty-five per cent (4/16) stated that it is guidance on collaboration in clinical trials, and 6% (1/16) indicated that GCTC is a guideline protecting the rights of participants, 6% (1/16) stated that it is an advanced version of GCP. Sixteen per cent (3/16) of study participants indicated that they did not know or preferred not to say due to a lack of awareness of the GCTC Guidance, while 6% (1/16) did not provide their opinion on the GCTC Guidance.

Qualitative data revealed that, although there was no direct knowledge of the GCTC Guidance, it was found to be related to several established guidelines that govern clinical trials. These include the DoH guidelines, GCP, and the guidelines of SAHPRA. Similar to the survey data, qualitative data demonstrated that a few key informants were aware of the GCTC Guidance, with most not knowing about it:

> ***"I've never heard about it before, so when you sent it to me, it was new for me."***
>
> (Clinical research consultant: Duration in current role: 10 to 14 years)

In the excerpt below, this key informant revealed that the GCTC Guidance attempts to develop a one-size-fits-all guidance in the following manner:

> ***"I've heard that it is trying to address the concerns of many of us, as trialists, who have been concerned about the one-size-fits-all approach of traditional pharmaceutical trials conducted in high-income countries. It' s just being used as a sort of mould that everybody has to follow, but the context can be very different. And trying to fit your trial into the mould, this mould is, is complicated and doesn't necessarily answer the original idea, which is that you want to answer the question by a randomised controlled trial. So, it sort of lost sight of what the original idea of having a randomised controlled trial is and what the GCTC was about to be, you know, what good clinical practice was about. So, I know that this process has been going on and they've been trying to develop guidance that will be more adaptable to different contexts and make trial access more equitable globally, rather than concentrated in, not just in high-income countries, even within high-income countries …"***
>
> (Principal investigator: Duration in current role: <20 years)

Key informants reported that although they were not explicitly aware of the GCTC guidelines, they recognised that many of the practices they follow in their current work aligned with these principles. They demonstrated a strong understanding of GCTC by effectively adhering to fundamental aspects, such as scientific rigour, the protection of participant rights, and a commitment to transparency throughout the trial process. The GCTC is noted for its clarity and comprehensive nature, making it a useful resource for training new staff members and providing necessary refresher training for existing team members.

3.3.2 Application of GCTC in organisations

All the delegates who knew of the GCTC Guidance agreed that the GCTC Guidance is applicable to their organisation/department. Thirty-one per cent (5/16) believe that it improves the conduct of clinical trials. Other participants stated that GCTC encourages and teaches collaboration in research, and it is related to GCP.

"That might be a solution because currently, for GCP, we've also incorporated. Then that Department of Health, Ethics and health research document that's part of SA GGP guidelines now, maybe something like that, that you incorporate it in your GCP guidelines but it's where you focus now specifically now on randomised clinical dog or it could be like a subset of because when we start with the GCP training, we tell them that these clinical research and that clinical trials is a type of clinical research and then we talk about the different types and then maybe as one of those types we can then highlight randomised clinical. So that it's not a separate section, but it's a section within GCP."

(Research consultant: Duration in current role: 10 to 14 years)

"So … it is applicable. I was looking at it and I am like, okay, this is a good clinical practice basically it put in a nice way and if you read or trained on the randomised clinical trials."

(Research clinician: Duration in current role: 5 to10 years)

"It's not so difficult because it is not too different from the GCP guidelines. I think it's just that it reinforces the GCP guidelines."

(Research management and consulting roles: Duration of current role: 5 to 9 years)

Although participants generally acknowledged that guidelines apply to their organisations, there was an emphasis on the need for the Guidance to be according to the local GCP guidelines. An emphasis was placed on ensuring the GCP was following local GCP guidelines.

"Yeah. So, I think the first thing is that everything must be in accordance with the South African GCP. So, I think I mean the first rule Is that the South African GCP takes precedence over everything else, and I mean I can do the one good thing is that the newer the latest GCP has been harmonised with the ICH and so there's a lot of collaborative activity you know with that. So, I think I think again, I think that from my perspective, I think because you know, we do need to make sure that you know, whatever collaborators or groups we join or get involved in, that we remain true to our local guidance. Which is obviously because we are you know we're doing research in South Africa. The Department of Health mandates the South African GCP. So, I think yeah, so from my perspective, I think, yeah, this. Its yeah, so. I don't think it may be different across different countries. And the way you don't has any good internal country guidance you know to both inform the clinical trials or you don't have any good structures for that, that they may be value in having additional you know, collaborative efforts to ensure that these studies happen."

(Principal investigator and senior researcher: Duration in current role: 0 to 4 years)

3.4 ACCEPTABILITY AND APPLICABILITY OF THE GCTC GUIDANCE

Following the workshop, 94% (81/86) of participants reported increased familiarity with the five principles of the GCTC Guidance. Meanwhile, 4% (3/86) indicated a slight or partial improvement in understanding and expressed the need for further study of the Guidance. One participant explicitly reported no improvement in understanding and provided no additional comment.

The participants believe that the Guidance will assist them in making informed decisions, coordinating effectively, promoting good governance, managing risks, monitoring safety, and ensuring high-quality trial management. While some believe the Guidance will assist in the informed consent form process and emphasise the protection of participants' rights, the application of the Guidance is considered easy and feasible.

3.4.1 Relevance of GCTC to roles in clinical trials

Eighty-six per cent (74/86) reported that the GCTC Guidance is relevant to their roles in clinical trials. In contrast, 3% (3/86) reported that the GCTC Guidance does not apply to their role, 8% (6/86) explicitly responded 'no', and 3/86 reported it somewhat.

The participants believed that the GCTC Guidance was relevant to their roles in clinical trials, as these roles encompass a wide range of tasks, including protocol development, data analysis, researcher support, improving the quality and efficiency of clinical research, ensuring participant safety, ensuring regulatory and ethical compliance, community

engagement, and monitoring activities. They also reported that the GCTC Guidance aligns with existing guidelines, such as GCP, as some participants indicated that they already follow some of the GCTC Guidance principles.

3.4.2 Need for GCTC training

There is a need for GCTC training to build skills, knowledge, and understanding of randomised clinical trials. It is recommended to conduct training on the guidelines to address the challenges encountered during the implementation of clinical trials. Familiarity with these guidelines is essential for helping staff effectively navigate the difficulties that may arise during the trial process. This training will equip the team with the necessary knowledge to handle any issues that may occur during the trial.

"Uhm, as I say at the end of the day, and not only my organisation, the challenges that I've indicated we encounter on a daily basis as clinical trials implementers, so it's very important for us to be aware of the Guidance."

(Community and public engagement: Duration in current role: 0 to 4 years)

"So, GCP is important and, um, gives very important ethical principles that are broader across all health-related research, but there are some particularly complicated things about trials, uh, that you will, you know, that is slightly more nuanced, um, and that we've touched on some of those. Uh, if you just had GCP training, you may not be able to really catch that. So, I think, and it may need to be thinking about who in the organisation should get GCTC training, but I think having some GCTC, to really have some particular trial training over and above. I think a good clinical practice, I think would be useful. For people who are involved in trials at least. "

(Other specialised roles and global health: Duration in current role: 4 years and 20+ years in global health)

Some participants expressed a need for more training on GCTC, as they find it shorter than GCP. However, others are either unaware or uncertain about the training they require because they do not fully understand the differences between GCTC and GCP.

Participants, however, reported that they would recommend the GCTC Guidance to their organisation, with 47% indicating that they would highly recommend it (See ***Figure 7***).

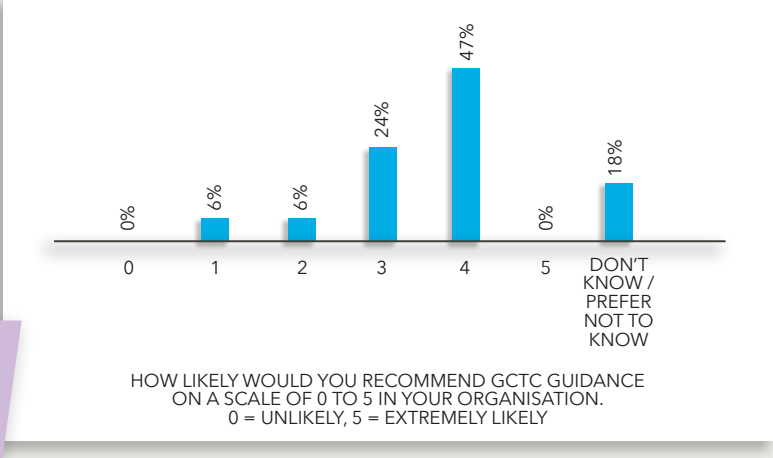


Figure 7: Likelihood of recommending the GCTC Guidance to their organisation

3.5. ASPECT OF GCTC THAT REQUIRES TRAINING

Half of the study participants (40/86) indicated that they do not require any training on any aspect of the GCTC Guidance after the workshop. Fifteen per cent (6/40) of the participants understood the GCTC Guidance very well, while 10% (4/40) of the participants reported not identifying any aspects that required training. However, 8% (7/86) of participants needed training on all aspects of the GCTC Guidance following the workshop. While 31% (27/86) of participants reported requiring training on certain principles of the GCTC Guidance, 33% (9/27) reported needing training on Principle 1, 2 on Principle 2, 5 on Principle 3, 1 on Principle 4, and 8 people on Principle 5.

3.6. CHALLENGES THAT CAN BE RESOLVED BY IMPLEMENTING THE GCTC GUIDANCE

The implementation of the GCTC Guidance addresses several challenges observed in clinical trial processes, particularly in ensuring a clearer understanding of studies among principal investigators, study staff, and other relevant stakeholders. Participants highlighted that GCP training is mandatory every three years, but there is a concern that it is often completed as a formality rather than a tool for meaningful application in trials. One key challenge addressed by GCTC guidelines is the ability to provide a readily accessible reference document that study teams can consult continuously. Unlike GCP, which broadly applies to all health research, GCTC is specifically designed for clinical trials, particularly randomised clinical trials. This specificity ensures that teams remain aligned with trial requirements beyond periodic GCP certification.

By implementing GCTC guidelines, study teams can maintain a more structured approach to trial execution. Thereby delivering trials that are more ethical, informative, and efficient by enhancing clarity in trial design and conduct, strengthening focus on participant safety and ethical study procedures, improving compliance, and reinforcing best practices that extend beyond regulatory obligations. The availability of a clear, ongoing reference document ensures that research teams not only complete compliance training but also actively engage with best practices throughout the study process.

> ***"I think its studies are just being made more clear reading through your document. I mean … sorry for that. The PRs, investigators, and the study staff read through your document; they can have another … another clearer view about studies than only doing GCP because GCP needs to be done every three years. And sometimes I get the feeling that they just do the GCP to just get it done. So this is a nice document that can be on your table, and you can always refer back to it and check if you are really on track with what you are doing. And you know, GCP is about all health research, but GCTC is about clinical trials, randomised clinical trials. "***
>
> (Data management and quality control: Duration in current role: 5 to 9 years)

Participants shared the challenges they usually experience when conducting clinical trials, particularly the need for frequent protocol amendments due to poor initial study design. They highlighted that many studies undergo ongoing modifications because they were not well structured from the outset. This results in repeated amendments and additional administrative burdens, which could have been avoided with better planning. This is because organisations often serve as both sponsors and implementers of studies, leading to oversight challenges and a lack

of independent quality control. Without a robust framework in place from the outset, study protocols often require continuous adjustments, which can delay progress and potentially compromise the integrity of the research. The implementation of GCTC guidelines helps address these challenges by promoting better protocol development and trial design. By following GCTC, research teams can ensure that studies are well structured from the outset, minimising the need for frequent amendments, reducing administrative workload, and improving overall study efficiency. This structured approach helps maintain consistency and enhances the quality of clinical trials.

"Ok. So … mhh. One of the challenges would be that I need to have frequent protocol amendments because the study was poorly designed in the first place. You know, as we find as we … You know our organisation has other studies that are sponsored. So, they become their own sponsors and the same person implementing the study. I think you find that, you know, there are so many issues with the, you know, the … the … the protocol, the study design that maybe like you know, had you done this properly in the beginning from the beginning would need to be. You know, amendment this member, this, not to file this clarification letter this you know, so yeah definitely. It will help to minimise that. "

(Principal investigator: Duration in current role: 5 to 9 years)

challenges that can be resolved through the implementation of the GCTC Guidance in their organisation. One challenge that can be determined by implementing the GCTC Guidance is the protection of participants in clinical trials. The implementation will ensure the privacy of participants in the GCTC Guidance, and the lack of clear guidance on how to proceed when participants encounter side effects will be addressed. The implementation of the GCTC Guidance will also encourage collaboration and co-creation between researchers and the community from the initial stages of the clinical trial through to its completion. This will enhance the community's acceptance of trial results. The implementation of the GCTC Guidance will also encourage efficient and well-managed clinical trials. As implementation of GCTC Guidance will help resolve clinical trial coordination challenges, it is essential to understand the fundamentals of why we conduct clinical trials and the overall conduct of clinical trials.

3.7 BARRIERS TO IMPLEMENTING THE GCTC GUIDANCE IN ORGANISATIONS

Study participants mentioned several barriers to implementing the GCTC Guidance. One of the barriers mentioned is resistance to change, which hinders the implementation of the GCTC Guidance in conducting clinical trials in South Africa, as well as the adoption of new practices. This is because people are already accustomed to existing methods and are often reluctant to embrace new ideas. There was mention of organisations conducting clinical trials frequently being overwhelmed by their numerous projects (i.e. staff or other resource capacity). Therefore, convincing them to do so would be challenging, especially if theybelieve everything is functioning well under the current guidelines.

There might be resistance from regulatory bodies or institutions if they see the Guidance as burdensome or redundant. Researchers and institutions accustomed to existing clinical trial practices may resist adopting new standards, especially if they view the GCTC Guidance as requiring more work without clear immediate benefits. Some leaders within institutions may be hesitant to promote new practices, such as the GCTC Guidance, if they do not see a clear return on investment or if they prioritise other initiatives. And finally, clinical trials often operate under tight timelines, and researchers may be reluctant to implement new practices, such as the GCTC Guidance, if they believe it will delay trial completion.

One other challenge is resource constraints. For instance, limited financial and human resources can hinder the implementation of new guidelines. Many healthcare facilities may lack the necessary funding, staff, and infrastructure to adopt and maintain the GCTC principles effectively. Research institutions may struggle to secure sufficient financing to incorporate new ethical and scientific standards into trials, especially in resource-constrained settings. Staff limitations might affect the implementation of the GCTC Guidance. Implementing GCTC principles may require additional human resources or specialised skills (e.g. data management, quality control), which might not be readily available, particularly in smaller institutions.

Adopting the GCTC Guidance may necessitate improvements in trial infrastructure, such as implementing better data management systems or implementing more rigorous quality control measures. Many institutions, especially those in rural areas, often struggle with inadequate infrastructure that prevents them from meeting essential educational and operational standards. This lack of sufficient resources can hinder their ability to provide quality services and support to their communities, highlighting a significant disparity in access and capabilities compared to their urban counterparts.

3.8 ROADMAP FOR INCORPORATING THE GCTC GUIDANCE

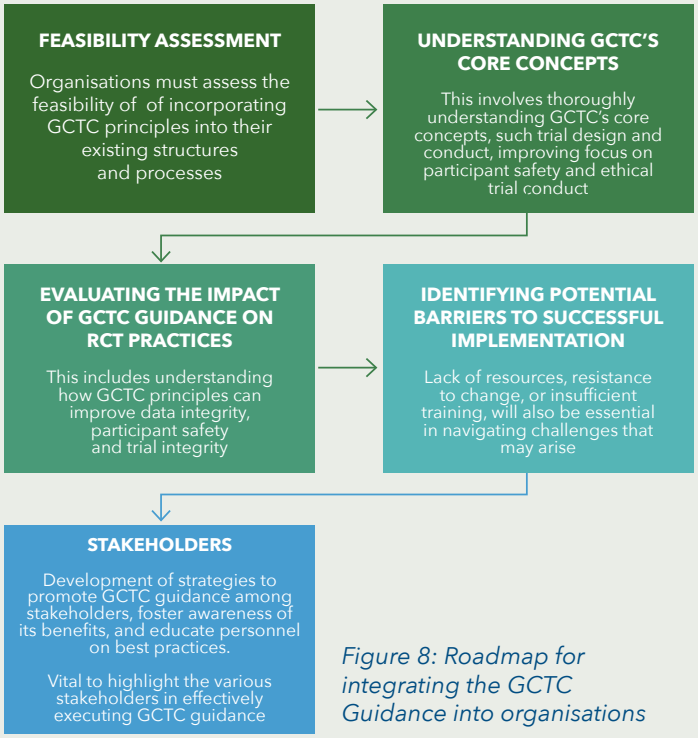


Figure 8: Roadmap for integrating the GCTC Guidance into organisations

Incorporating the GCTC Guidance effectively requires several key elements. First, organisations must assess the feasibility of incorporating GCTC principles into their existing structures and processes. This involves thoroughly understanding GCTC's core concepts, such astrial design and conduct, improving focus on participant safety and ethical trial conduct. Next, evaluating the potential impact of adopting the GCTC Guidance on RCT practices is critical. This includes understanding how GCTC principles can improve data integrity, participant safety, and trial integrity. The newly published GCTC online learning and evaluation tool can support adoption by offering a practical,

interactive course that helps research teams implement GCTC principles effectively.

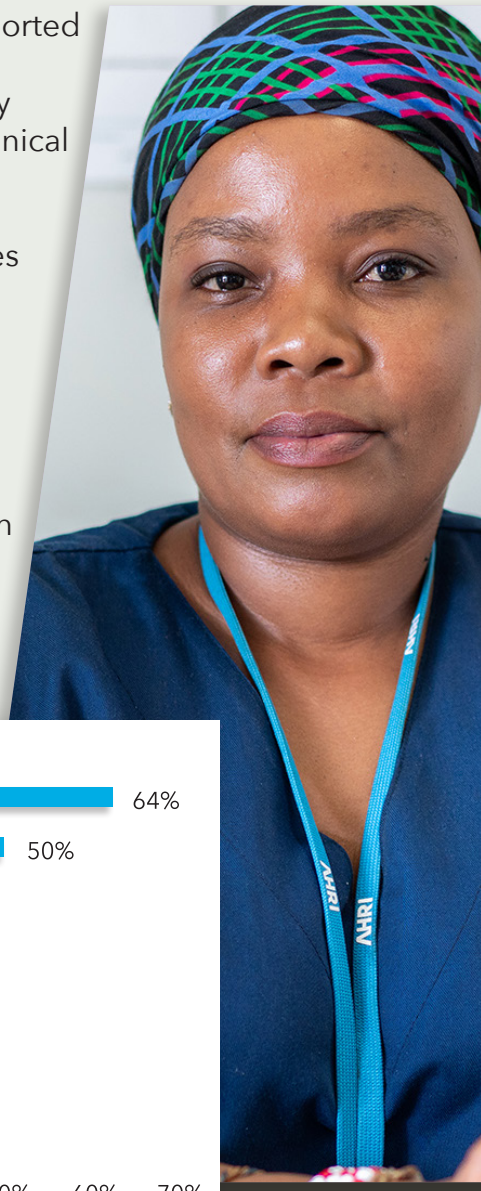
The implementation process should encompass the development of strategies aimed at promoting the GCTC Guidance among stakeholders, fostering awareness of its benefits, and educating personnel on best practices. Identifying potential barriers to successful implementation, such as a lack of resources, resistance to change, or insufficient training, will also be essential in navigating the challenges that may arise. Furthermore, it is crucial to acknowledge the diverse stakeholders involved in effectively implementing the GCTC Guidance.

Organisations can create a comprehensive and clear roadmap for integrating the GCTC Guidance by addressing these aspects in detail.

3.8.1. Feasibility and adoption of incorporating the GCTC Guidance in the conduct of clinical trials

All delegates indicated that they believe that adopting the GCTC Guidance is feasible for conducting RCTs in South Africa. Some of the study participants reported that the adoption of the GCTC Guidance is feasible for the conduct of clinical trials in South Africa because the GCTC Guidance aligns well with existing South African guidelines, such as GCP and ICH-GCP guidelines, particularly in their shared emphasis on scientific rigour, ethical conduct, and participant safety. (See ***Figure 9***).

Importantly, training and ongoing staff support can assist with adopting the GCTC Guidance. Participants noted the GCTC Guidance's emphasis on methodological rigour and ethical standards, aligning with South Africa's clinical research infrastructure and regulatory framework. One participant reported that the foundation of the GCTC Guidance is the ICH-GCP, with the Guidance's principles more aligned to the conduct of RCTs. At the same time, two participants reported that the GCTC Guidance was not different from the GCP guidelines. In contrast, another reported that the Guidance's principles are already being practised in clinical trials in South Africa. Moreover, the GCTC Guidance emphasises the importance of participant engagement and informed consent, which aligns well with the community-oriented approach in South Africa.



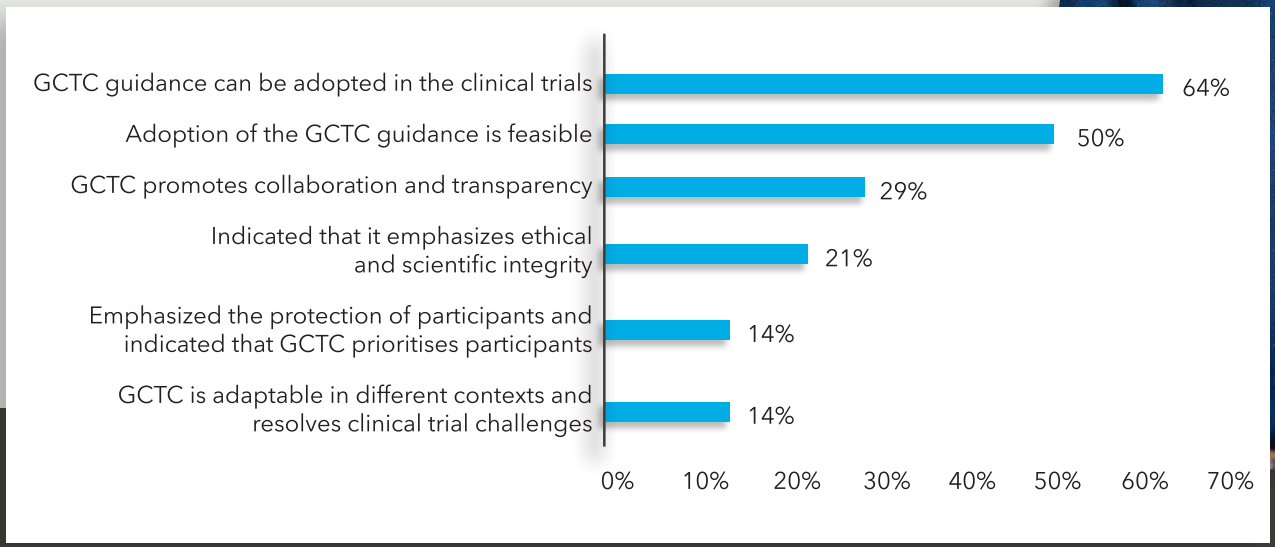


Figure 9: Feasibility and adoption of the incorporation of the GCTC Guidance in the conduct of clinical trials

The GCTC Guidance is perceived as more flexible and easier to understand in its application. However, its effective implementation requires integration with SAHPRA guidelines. The feasibility of conducting clinical trials will be enhanced when investigators recognize that the GCTC is intended to complement, rather than replace, existing SAHPRA guidelines.

Twenty-nine per cent of study participants reported that implementing the GCTC Guidance is feasible for conducting clinical trials, as the Guidance promotes collaboration and transparency in research. Collaboration and transparency foster better relationships between researchers, institutions, and communities. Cooperation and transparency in research are essential in South Africa, as diverse stakeholders are involved in clinical trials. Promoting transparency and ethical practices can help build trust and enhance participant recruitment and retention. Study participants also reported that the adoption of the GCTC Guidance is feasible because the Guidance includes aspects of community engagement, which are essential for the success of clinical trials and the adoption of clinical trial results.

Several participants reported that the GCTC Guidance is contextually feasible, scientifically rigorous, reproducible, and presented in a simplified format, facilitating comprehension and implementation in middle-income countries such as South Africa. This approach promotes the practicality and feasibility of conducting clinical trials within the South African context.

Notably, study participants expressed that the Guidance emphasises ethical considerations and scientific integrity, which are crucial for gaining public trust and ensuring the validity of trial results. Emphasising ethical considerations and scientific integrity can help address ethical challenges and enhance the overall quality of clinical trials. The principles of the GCTC Guidance are crucial in practically upholding the ethical principles of justice, autonomy, beneficence, and non-maleficence.

In addition, it was reported that the Guidance prioritises respecting study participants and protecting their rights and well-being. Respecting participants' rights and well-being improve recruitment and retention rates. Clear communication and adherence to ethical practices can foster trust and encourage participation.

Some participants reported that the GCTC Guidance is applicable within the South African context and can potentially resolve challenges experienced in conducting clinical trials in South Africa. They noted that the Guidance will promote good clinical trials and foster a quality-oriented mindset among implementers. At the same time, adopting the GCTC Guidance is feasible, particularly given South Africa's growing pool of skilled researchers and institutions dedicated to advancing clinical research. The GCTC Guidance can further support this capacity by providing structured frameworks and best practices, enabling researchers to conduct high-quality RCTs. Furthermore, one participant reported that adopting the GCTC Guidance would be feasible if supported by ongoing training and professional development. Such initiatives would assist implementers of clinical trials in integrating the principles into their RCT practices and help address any existing knowledge gaps.

3.8.2 GCTC principles incorporated into the organisation

Following the workshops, some participants mentioned integrating aspects of the GCTC Guidance into their everyday RCT practices

and activities. There were 10/15 participants who reported incorporating elements of the GCTC Guidance by integrating structured randomisation procedures and ensuring protocol adherence, which maintains methodological rigour and enhances the reliability of study outcomes. One participant reported that they ensure strict adherence to the protocol by regularly reviewing the guidelines and ensuring all team members are familiar with them. This involved conducting team meetings to discuss protocol updates and address questions or concerns. The participant also reported prioritising training sessions for team members to enhance their skills in research methodologies and data management practices. This has involved organising workshops and peer training to ensure everyone is equipped to contribute effectively to the study. Two participants reported incorporating the element/principle of working in partnership with people and communities. One participant reported working in collaboration with community members, primarily nursing staff in health facilities, where they conduct their trials. Collaborating with nurses at health facilities has helped build trust and confidence between their organisations and the health facilities, making data collection easier as the staff at the health facilities were now aware of the trial being conducted. The other participants involved the Public Engagement and Community Advisory Board (CAB) in developing the study protocol and the Informed Consent Form. Two participants reported incorporating the elements of GCTC Guidance when developing protocols, to ensure good trial design, which will be practical and produce reliable results. One participant reported incorporating respect for participants in their RCT practices. One participant reported incorporating the elements of the GCTC Guidance by ensuring participants understand the informed consent form and promptly addressing queries to ensure high-quality work.

Some participants did not explicitly incorporate elements of the GCTC Guidance in their RCT practices. One participant reported not incorporating elements of the GCTC Guidance in their RCT practices as they follow the GCP guidelines. However, they acknowledged an overlap between the GCP and GCTC guidelines. They reported that the GCTC Guidance was nothing new but could benefit regulators. One participant acknowledged that, while working in quality assurance, they are expected to incorporate GCP to ensure the success of their studies. While one participant reported they will eventually have to incorporate some elements of the GCTC Guidance as they work in a clinical trials unit.

Participants were asked which of the five key principles of the GCTC Guidance they easily incorporated into their RCT practices. Two participants reported easily incorporating all five principles in their RCT practices. However, most (60% or 9/15) participants reported incorporating Principle 1 (Informative and relevant) and Principle 3 (Collaborative and transparent), respectively. Forty per cent of participants reported incorporating Principle 2 (Respectful of participants) and Principle 5 (Efficient and well managed). Only 20% of participants reported incorporating Principle 4 (Appropriate for their context).

3.9 POSSIBLE IMPACT OF ADOPTING THE GCTC GUIDANCE ON RCT PRACTICES

Survey participants reported on how investing in and adhering to the principles of the GCTC Guidance would strengthen the scientific and ethical quality of RCTs in South Africa. Participants reported that investing in and

adhering to the principles of the GCTC Guidance would improve ethical standards concerning the rights of participants. One participant reported that respect for participants is a core principle of the GCTC Guidance. This includes obtaining informed consent, ensuring participant confidentiality, and minimising risks. Therefore, adhering to these standards can enhance the ethical conduct of trials, protecting participants' rights and well-being, while another participant reported that the Guidance prioritises ethical considerations, including informed consent, participant welfare, and the equitable selection of subjects. Adhering to these ethical principles fosters a culture of respect for participants and their rights, which is essential for building trust in the research process. It also helps to ensure compliance with national and international ethical standards. Implementing the GCTC Guidance, South Africa can enhance the quality and integrity of its clinical trials, contributing to better health outcomes and advancing public health research.

3.9.1 Alignment of GCTC in organisation roles

a) Elements of the GCTC Guidance that improve the processes of clinical trials conduct

Forty-six per cent (39/85) reported that no elements of the Guidance might improve the processes they currently follow. One participant reported that their institution or organisation is adhering to ethical guidelines as per country, sponsor, or international guidelines, as they are obligated to comply with GCP guidelines. One other participant reported that the GCTC Guidance assisted with reinforcement and reminded them about the local guidelines. Some participants felt they already followed the principles of the GCTC Guidance as they aligned with the local guidelines, or it confirmed that the processes they have in place aligned with this guidance.

However, 46% (39/85) reported that elements of the GCTC Guidance might improve the processes they currently follow. One participant noted that GCTC guidance can be enhanced by planning before trial implementation to ensure recruitment targets can realistically be met, and more extensive review of informed consent processes and the CRF to ensure the process is as simple and efficient as possible. Another participant reported that the GCTC Guidance can improve collaboration, as it is a process lacking for most researchers. This will help achieve shared goals. The GCTC Guidance can also improve several processes, including dissemination of clinical trial results, accountability and transparency in information provision, protocol review, and statistical planning in trial design. It can strengthen current practices by clarifying processes that often confuse trial staff. The guidance also encourages greater attention to ITT analyses and their implications. Additionally, it supports selecting trials that are more relevant to local context and need. GCTC will help in understanding the processes of randomisation better. One participant reported that current GCP guidelines do not talk much about data collection and treatment, so the guidelines will bridge the gap if well-structured in future. Another noted that the Guidance could help structure how protocols are developed and deciding which protocols to participate in, as it would help evaluate protocols more critically.

b) Elements of the GCTC Guidance that conflict with processes

Seventy-seven per cent (66/86) of the participants reported that no elements of the GCTC Guidance conflict with the processes they currently follow. Others reported

that Principle 2 of the GCTC Guidance (Respectful of participants) aligns with their current GCP guidelines. In fact, according to some, the GCTC Guidance provides a more straightforward way to what they currently follow. For others there are no direct conflicts with the process they currently follow. However, they have challenges they experience as a site, for example as a research site they sometimes accept to conduct trials that are not ideal for their site because they run at a cost (low budget trials) but these trials will benefit their population, as the trials provide access to treatment. Protocols are also developed internationally. Therefore, they do not influence the protocol development, statistical methodology, or other areas mentioned in the Guidance.

It was mentioned that elements of the Guidance conflict with the processes they currently follow. Monitoring processes in their organisation is presently pervasive and time-consuming, which might need to be improved, as observed by some study participants. They report that risk-based monitoring, which is advised by the GCTC Guidance, would be a better approach. One participant reported that some elements of the GCTC Guidance conflict with the processes they currently follow because there are processes (in their organisation) that are just not being done correctly. One participant reported that adhering to strict relevant outcomes is one of the elements of the GCTC Guidance that they are in conflict with.

3.9.2 Challenges resolved by implementing the GCTC Guidance in organisations

Fifteen study participants responded to the question regarding challenges resolved by implementing the GCTC Guidance in their organisations. Five participants indicated that they did not implement the GCTC Guidance in their organisation. However, ten implemented it and presented different challenges they resolved by applying the GCTC Guidance. Five indicated that it improved participant recruitment and retention by respecting participants and maintaining clear communication; they could simplify consent forms and explain clinical trial procedures. They also incorporated feedback from participants, such as understanding participants' reasons for withdrawal from the study, which resulted in the site improving its processes. Two participants indicated that adopting the GCTC Guidance in their organisation helped enhance data quality and integrity by integrating effective quality management practices through stricter data integrity measures like regular monitoring and audits, which ensured data accuracy and integrity. This reduced errors and improved the reliability of the clinical trial results. Four participants shared that challenges resolved by implementing GCTC were around facilitating collaboration and data sharing, which promotes transparency and collaboration and helps overcome barriers to data sharing with stakeholders. Three people reported that implementing the GCTC Guidance helped resolve challenges of maintaining ethical standards. They reported ensuring compliance and general good clinical trial practice by becoming customised to the new GCTC Guidance, integrating SAHPRA guidelines and the GCTC Guidance in their organisation. They respected the rights and well-being of participants by implementing robust consent processes and ensuring participants are fully informed. The other challenges reported as resolved by implementing the GCTC Guidance are designing feasible clinical trials for their contexts, inconsistent protocols, and standardising protocols and rigorous randomisation methods, which enhances research reliability and validity—reduced unnecessary costs in the conduct of clinical

trials in their organisation. Training and development challenges were addressed by introducing regular training sessions for staff members on key aspects of RCT practices, which improved team skills and confidence in their RCT practices.

3.10 IMPLEMENTATION, PROMOTION, AND AWARENESS STRATEGIES

Figure 10: Implementation, promotion, and awareness strategies for the GCTC Guidance

Media, including social media were emphasised as essential channels for promoting the GCTC guidelines. These platforms offer a broad audience reach, ensuring that all stakeholders—including sponsors, researchers, and the public—are well-informed about the guidelines. By leveraging the power of these communication tools, it becomes easier to disseminate important information, engage with various communities, and encourage collaboration among all those involved in the initiative. This approach raises awareness and fosters a shared responsibility towards adhering to the GCTC guidelines.

3.10.1 Social media campaign

The use of social media was also suggested as a strategy to promote and raise awareness of the GCTC Guidance, as well as to facilitate its adoption in conducting clinical trials in South Africa. Using social media platforms like LinkedIn, Twitter (or X), and Facebook, and creating content such as infographics and videos. This also includes the use of radio talks, online briefs, newsletters, and advertisements in public areas, such as flyers or leaflets. Conducting brief surveys on the GCTC Guidance on social media in communities, healthcare facilities, research

"So, in terms of promotion, like I said, I think spaces where clinical trial engagement is occurring need to be promoted with the GCTC Guidance. Academic institutions where the up-and-coming researchers learn about different guidance, I think this also needs to be included in the package of the tools or the lectures provided for the researchers. Research institutes also need to have it as part of the promotion to say now, because everyone knows about GCP. Before you even conduct a trial, you know that you need to be GCP approved, you need a certificate before you even get into the delegation log. So, I think similarly this is something that needs to be embedded as a guidance that has to be adhered by everyone who conducts clinical trials."

(Public health specialist: Duration in current role: 5 to 9 years)

organisations, high schools and tertiary institutes was also suggested. Another suggestion was for implementers of clinical trials who have implemented the GCTC Guidance in their respective organisations to share testimonials on social media. Sharing testimonials can increase awareness of the GCTC Guidance.

3.10.2 Educational workshops, seminars, symposiums, and training sessions

Conducting educational workshops and seminars for implementers involved in clinical trials was one of the strategies suggested to implement the promotion and awareness of the GCTC Guidance and the adoption of the Guidance. In these educational workshops and seminars, the GCTC Guidance and its principles can be introduced through case studies and practicable applications, e.g. informed consent processes, participant recruitment strategies, and data transparency. The workshops could be both in-person and virtual.

3.10.3 Partnerships with academic institutions

Integrating the GCTC Guidance and its principles in the curriculum offered by academic institutions like universities and research institutions can help promote and increase awareness of the GCTC Guidance and adoption of its principles in conducting RCTs in South Africa. Integrating the GCTC Guidance in the curriculum will ensure future researchers and trial professionals are familiar with the GCTC Guidance before entering the workforce. Another strategy would be to encourage research institutions and academic institutions to formally adopt the GCTC principles as part of their internal clinical trial policies and standard operating procedures. This will ensure long-term sustainability and consistent application of the guidelines in their RCTS. Academic institutions could improve awareness of the GCTC Guidance.

3.10.4 Online platforms

Developing online platforms, e.g. the GCTC Guidance website with resources such as webinars, tutorials, educational materials on the GCTC Guidance, guides and training schedules on the Guidance, can help in the promotion and increasing awareness of the GCTC Guidance and adoption of its principles in the conduct of RCTs in South Africa. Online platforms will allow information to be easily accessible to a broader audience, including those in remote areas. Visual materials, such as infographics, videos, and case studies, that showcase the value of adhering to the GCTC principles can also effectively communicate the Guidance to a broader audience. The educational workshops can also be recorded and shared online for future learning. The online platform can also serve as a platform for FAQs. Additionally, the Collaborative has recently published the GCTC online learning and evaluation tool, providing an interactive, self-paced course to support research teams in implementing the guidance effectively. 7

3.10.5 Engagement with regulatory bodies

Working with regulatory bodies, such as SAHPRA and ethics committees, that approve protocols to align guidance principles with national regulations, can ensure the GCTC Guidance is recognised and supported at a regulatory level. This alignment will encourage mandatory adoption by research institutions and trial sponsors. Incorporating the GCTC Guidance into the ethics review process can help promote and increase awareness of the GCTC Guidance and its adoption in

conducting RCTs in South Africa. The GCTC Guidance can be part of the review criteria for all clinical trial protocols. This will ensure that trials adopting the Guidance receive favourable consideration, thereby reinforcing the Guidance's importance.

3.11. STAKEHOLDERS TO IMPLEMENT GCTC

Key informants reported that a multi-sectoral approach is essential for effectively implementing the GCTC Guidance in South Africa; its effective promotion, awareness, and adoption depend on the involvement of various actors across the clinical trial ecosystem.

The support of the National DoH is critical to ensure policy alignment with GCTC principles and facilitate integration into national guidelines, research ethics frameworks, and approval processes for public sector clinical trials. The DoH can enable wider implementation and promote ethical, high-quality research nationwide by embedding GCTC standards into developing national research protocols and coordinating with provincial departments.

As a gatekeeper for trial approval and compliance, SAHPRA's endorsement of the GCTC Guidance is critical to recognising and adopting its principles. Incorporating GCTC principles into the SAHPRA regulatory framework would ensure ethical and scientific rigour across trials and foster accountability within the sector. SAHPRA's role as a regulatory leader positions it to influence both public and industry-led research toward global best practices.

Public research funders and academic institutions are central in advancing clinical research in South Africa. As major contributors to the country's research output, these entities are well positioned to influence adopting ethical and scientifically rigorous practices. By integrating the principles of the GCTC Guidance into funding requirements, protocol development, ethics oversight, and research training, they can set national benchmarks for trial quality and accountability. These institutions and their global partners further enable the alignment of local research with international standards, fostering broader uptake and sustainable implementation of GCTC principles across the sector.

Pharmaceutical companies and CROs are responsible for a significant share of clinical trials conducted in South Africa. Based on the perceptions of the key informants interviewed, their compliance with the GCTC principles would also enhance trial quality and ethical oversight in industry-sponsored studies.

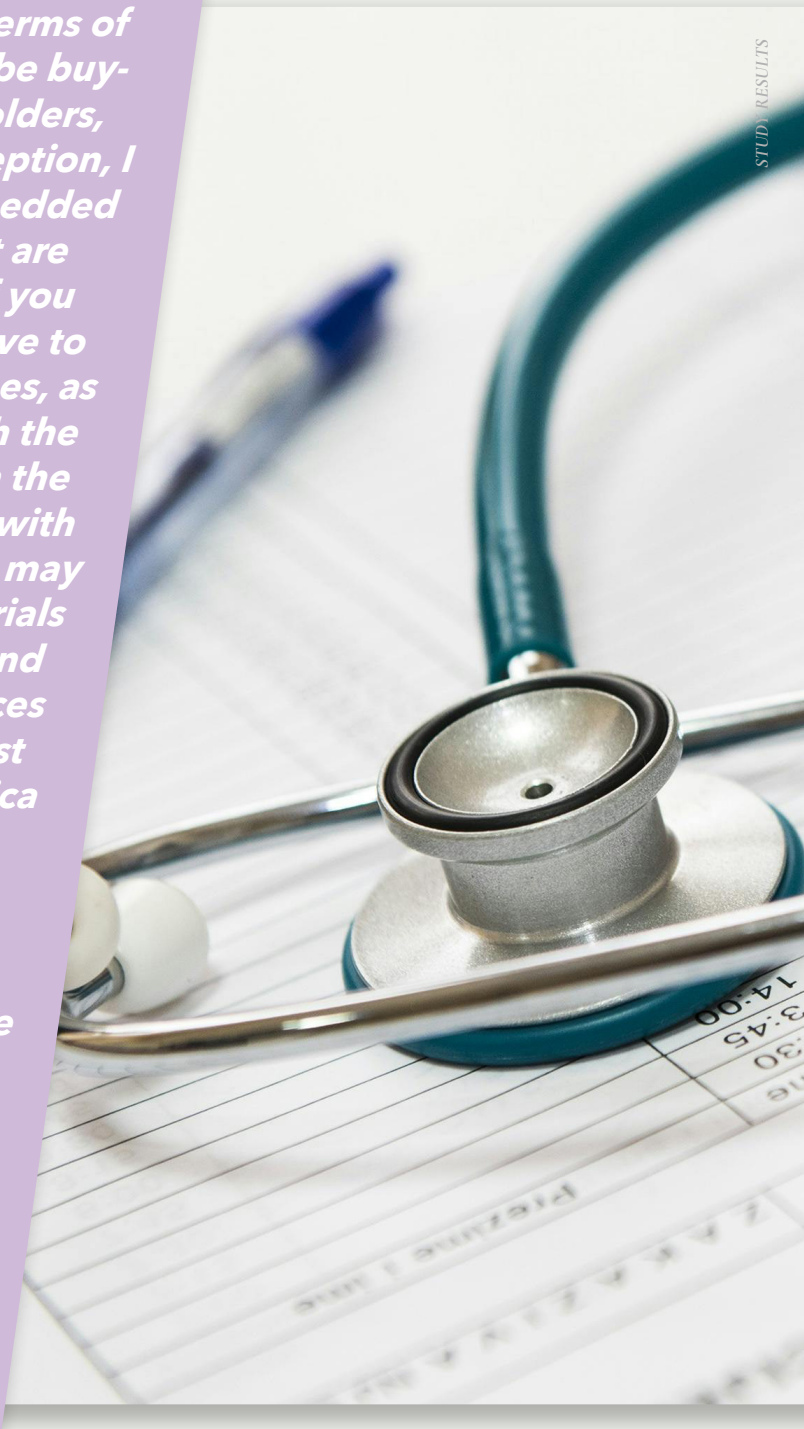
Human Research Ethics Committees (HRECs), the National Health Research Ethics Council (NHREC), and institutional ethics boards are essential safeguards in clinical trial oversight. Integrating GCTC principles into ethics review processes would embed participant protections, community engagement, and scientific integrity at the protocol approval stage, promoting consistent ethical standards across all trials.

Community-based and advocacy organisations are vital in fostering community engagement, advocating for participant rights, and ensuring ethical research conduct. Their understanding of the GCTC principles can help bridge the gap between researchers and communities, enhancing trust, transparency, and accountability—particularly among vulnerable and underrepresented populations in clinical research.

Key informant interviews revealed that most of the GCTC Guidance is already in practice, as revealed in this quotation here:

"Okay, maybe let's start first with the adoption. I think in terms of adoption there needs to be buy-in from different stakeholders, especially at the trial conception, I think this needs to be embedded in the concept notes that are being developed to say if you implement this trial you have to adhere to the GCTC guidelines, as an example. So, it starts with the trial conception so that even the donors have that embedded with the design or the concept that may have regarding the different trials they want to be conducted. And this pertains to the global spaces where it's standardised not just within the context of South Africa because we are going to have a multi-site, multi-country trial, right. And it helps to have that buy-in at that level so that it's a global adoption. That would make it easy in such a that when it is introduced in the country, already it's included within the design but then you also need in counsel you also need NDoH on board because they have got the structure that is responsible for clinical trials, so the buy-in needs to also come from there so that they can be early adopters, so that once they have adopted it, it makes it easy to implement, right."

(Public health specialist: Duration in current role: 5 to 9 years)



4. DISCUSSION

The main findings of this study on knowledge, practices and perceptions of the GCTC Guidance in South Africa are that prior knowledge of the Guidance was limited among the people that completed the surveys or workshops. However, many people indicated that some of the principles in the GCTC Guidance are relevant and well-aligned with other clinical research guidelines such as scientific rigour and the protection of participants' rights. In addition, they also recommended that the GCTC Guidance would be helpful in addressing some of the observed challenges in study designs, recruitment, retention, and communication during the conduct of trials. The participants recommended that the adoption of the GCTC Guidance into practice would be feasible if the Guidance is incorporated into other existing guidelines for clinical research. Some of the anticipated possible challenges for adopting the GCTC Guidance include resistance to change, inadequate infrastructure and resources, and a lack of training on the Guidance. The DoH and SAHPRA have been described as key stakeholders central to the adoption, implementation, and monitoring of guidance in the conduct of clinical trials in South Africa.

Among the participants in the workshop survey and key informant interviews, very few had prior knowledge of the GCTC Guidance. This is not surprising as the Guidance was published in 2022, and the workshops were also intended to increase awareness of the GCTC Guidance. Full implementation of guidelines into practice takes time. There is a significant knowledge gap regarding how guidelines are adopted and adapted for a specific context, as well as the barriers to their full implementation.[37]

Currently, it is recommended that all personnel involved in conducting clinical trials receive GCP training every three years.[38] A qualitative research study among study coordinators found that although formal training on GCP has value, experience is essential to effect practice.39 However, a quasi-experimental one-group, pre-test and post-test design to improve GCP knowledge found that there was a significant improvement in knowledge after GCP training, especially among investigators and study coordinators.[40] Training on guidance also needs standardised and validated tests to assess understanding. Although validated assessment tools exist for GCP,[41] the current GCTC Guidance assessment tool has not been validated. The Collaborative has recently developed the GCTC online learning and evaluation tool to support consistent implementation of the guidance. [7]

Results from this study found that the GCTC Guidance aligns well with current South African guidelines, namely the SA GCP, NDoH 2024, and SAHPRA guidelines. Furthermore, participants reported many of the practices they follow in their current work align with the GCTC principles. This is not surprising as the principles of the GCTC guidelines mirror those of the current South African guidelines which are: beneficence and non-maleficence, justice and respect, and dignity and participants. The results are also consistent with efforts for alignment and harmonisation of clinical trial guidelines by global initiatives such ICH, WHO, The G7, AVAREF, and EMA. Cavaleri and colleagues also highlighted that the absence of a unified global regulatory framework and ethical review framework, including alignment

on trial requirements and timelines, affects the development of sustainable clinical research systems capable of swift responses to health emergencies.[42] While Scheppler and colleagues emphasised that without progress in terms of regulatory convergence and harmonisation the benefits from scientific advancements will not be fully realised.[43] Indeed, in May 2022, at the 75th World Health Assembly (WHA), a resolution was adopted on the Strengthening of Clinical Trials to provide high-quality evidence on health interventions and to improve research quality and coordination.[44] The resolution requested the Director-General to develop WHO guidelines on best practices for clinical research, and on 25 September 2024, the WHO published the WHO Guidance for Best Practice for Clinical Trials. This guideline incorporated the principles of Good Clinical Trials Collaborative guidance.[7, 9]

The study's findings reflected the challenges encountered during the design, preparatory, and implementation stages of clinical trials. The main challenge indicated by the participants in the design stage included protocols and eCRFs that were not well designed. In the preparatory phase, challenges that were observed were around regulatory and minimal investment in site and personnel. Lastly, recruitment and retention challenges were the major challenges found in the implementation stage. Based on the above findings, literature review indicated that there is evidence of challenges with the conduct of clinical trials that can be resolved by implementing the GCTC Guidance. This includes lack of financial or human capacity (skilled personnel) and a research environment that includes infrastructure and operational barriers like administrative activities, recruitment, retention, and the logistics for conducting a clinical trial were reported by Alemayehu, Mitchell, and Nikles (2018)[45] as the challenges that are currently faced by sites conducting clinical trials, which can be resolved by implementing the Guidance. Multiple research ethics committees reviewing the same protocol for the same site, leading to conflicting findings and results in significant delays in the review process, and in certain instances, delays in regulatory approvals,[46] including technology, is essential in a rural setting of sub-Saharan Africa, as it enables participants and study staff to master novel technologies.[47]

Furthermore, study design is particularly vital for resource-constrained settings with fragile health service infrastructure in need of improvement, which includes stable internet connectivity. The maintenance of digital tools could also be improved by implementing guidance at clinical trial sites.[48] Clinical trials are complex and involve diverse approaches, designs, and objectives that can complicate trial planning, initiation, and conduct. Improved collaboration between sponsors and sites is essential to address these challenges.[49] Experienced individuals in clinical trials should guide sites in study design and investigator site selection to improve randomisation, monitoring, and reporting processes.[50]

The study findings support a positive and favourable response to implementing the GCTC Guidance for clinical trials in South Africa. A substantial proportion of participants expressed confidence in the feasibility of implementing this guidance within their clinical practice. They highlighted that the GCTC Guidance is well aligned with established GCP standards, which is crucial for maintaining high ethical standards in clinical research. This alignment not only facilitates compliance with regulatory requirements but also strengthens the integrity and credibility of clinical trials. Furthermore, several participants pointed out that numerous elements of the GCTC Guidance are operationalised in current

practices, suggesting a readiness for fuller integration into the clinical trial framework. This finding supports the statement by the GCTC (2021) that its principles are derived from and harmonised with GCP standards, thereby making the integration of the GCTC principles into other laws guided by ICH-GCP frameworks easy.[7]

The study also found that GCTC promotes collaboration and transparency. This is consistent with calls to ensure inclusive stakeholder engagement in the clinical trial process.[51] This is crucial in the South African context, where community engagement is important in ethical trial conduct, especially for historically marginalised populations. Participants also emphasised the Guidance's focus on ethical and scientific integrity, reinforcing the value placed on robust trial design and ethical oversight. This aligns with the Declaration of Helsinki and CIOMS guidelines, which underline the importance of scientific validity and ethical conduct in clinical research.[13, 52]

Several participants also noted that many aspects of the GCTC Guidance are already incorporated into current practice. This perception highlights the potential for smooth acceptance and may help reduce the resistance often associated with introducing new frameworks. Nonetheless, concerns regarding capacity building were noted, with participants highlighting the importance of training and continuous staff support to ensure successful implementation. The literature confirms that capacity development is necessary for sustained adoption of clinical trial best practices, particularly in low- and middle-income countries (LMICs).[53, 54]

The implementation of the GCTC Guidance faces substantial barriers, with institutional resistance to change emerging as the most pervasive challenge. Our findings reveal that clinical trial stakeholders in resource-constrained settings exhibit strong reluctance to modify established procedures, a phenomenon particularly evident in environments where overwhelming clinical workloads severely limit capacity for additional training or protocol adjustments. This resistance aligns with broader patterns observed in global health implementation science. Alemayehu et al.[45] demonstrate that such institutional inertia represents a fundamental barrier to adopting updated GCP standards, especially in high-volume clinical environments. The WHO (2022) corroborates this finding, reporting that 62% of LMICs face significant protocol non-adherence due to competing clinical priorities and chronic staff shortages, a statistic that reflects the participants' reported experiences of being overburdened by existing responsibilities.[55]

In addition, the study identified three critical resource constraints hindering GCTC implementation: chronic underfunding limiting training and infrastructure upgrades, severe staffing shortages affecting specialised skill availability, and outdated technological systems incompatible with modern trial standards. These findings align well with the well-documented challenges in global health implementation science, particularly in low-resource research settings. Financial barriers emerged as the most pervasive constraint, with participants reporting insufficient budgets for sustained training and data system upgrades. This aligns precisely with Shumba and Lusambili's (2021)56 analysis of 42 LMIC trial sites, where 89% of failed implementations were attributed to unpredictable funding cycles. Similarly, WHO (2022) identified inadequate line-item budgeting for guideline adoption as the primary predictor of implementation failure across African research institutions.

Promoting and implementing the GCTC Guidance requires coordinated efforts across the clinical trial ecosystem. Through its influence over national research guidelines, the DoH can drive systemic adoption of the Guidance and facilitate consistent application across all levels of the public research landscape. SAHPRA's role is equally pivotal; positioned at the intersection of public and industry-sponsored research, the integration of GCTC principles into its regulatory framework would strengthen sector-wide adherence to ethical and scientific standards. Ethics bodies can also ensure their consistent application across all types of trials, regardless of sponsor or setting and institutionalise key tenets such as community engagement, participant protection, and scientific integrity from the earliest stages of trial planning.

Public funders and academic institutions play a key role in driving change, given their central position in research production, capacity development, and standard setting. By embedding GCTC principles into funding requirements, protocol development, ethics oversight, and research training, they can institutionalise ethical and high-quality trial practices across the public research landscape. In parallel, the pharmaceutical industry and CROs play a critical role in extending these standards to industry-led studies. Their voluntary adoption and operational integration of the GCTC Guidance—through trial design, monitoring, and implementation—can promote scientific rigour and ethical conduct, fostering a culture of responsible research across both public and private sectors. Community-based organisations are vital in promoting public trust in research, particularly among historically marginalised or vulnerable populations. Their promotion of GCTC principles through community engagement and participant education helps bridge the gap between researchers and the communities they serve.

Training these organisations in the content and significance of the GCTC Guidance empowers them to act as champions for ethical conduct, while ensuring that research remains responsive to the needs and rights of participants, reinforcing accountability, transparency, and respect for human dignity throughout the research process. Through policy development, regulatory alignment, capacity-building, and community engagement, the collective action of these stakeholders can foster a research environment in South Africa that upholds the highest standards of ethical and scientific integrity.

4.1 LIMITATIONS

This study was subject to several limitations. First, the response rate for the second post-workshop survey was low. Participants were expected to complete this survey three to six months after their attendance of the GCTC Guidance awareness workshops. Despite multiple reminders being sent, participation remained low. This low response rate restricts the generalisability of the study findings, and as such, the results should be interpreted with caution. Second, the participation rate for the key informant interviews was also low. These interviews were intended to engage stakeholders who were unable to attend the workshops, as well as senior professionals and experienced leaders in the clinical trials implementation. The limited number of participants in this component of the study may compromise the validity and reliability of the qualitative data collected.

Third, key regulatory stakeholders, including representatives from SAHPRA and HRECs, were not well represented in the key informant interviews. The involvement of these individuals would have contributed significantly to a comprehensive assessment

of the GCTC Guidance's perceived impact and recommendations for adoption. Their insights on the GCTC Guidance would also have provided important regulatory and ethical perspectives.

Additionally, although this study assessed participants' knowledge of the GCTC Guidance, it did not utilise a validated questionnaire, which may impact the robustness of the findings.

The original aim of the project was to deliver GCTC awareness workshops in all nine South African provinces, particularly in those with high clinical trial activity. However, due to funding constraints, workshops were only conducted in three provinces: KwaZulu-Natal, Gauteng, and the Western Cape. These provinces were selected as they host the majority of organisations involved in clinical research, allowing the project to leverage existing networks.

Lastly, the potential for interviewer bias exists, as the interviewer also served as the primary instrument for data collection. The personal characteristics of the interviewer, such as professional background and prior knowledge of the Guidance, may have influenced participants' responses. This may have led to bias, including the use of leading questions and/or an overemphasis on topics aligned with the interviewer's perceived interests. While efforts were made to minimise this through training and the use of a semi-structured interview guide, some degree of bias introduced by the interviewer's presence and interaction style remains possible.

4.2 RECOMMENDATIONS

The workshop participants and key informants interviewed for this study identified several challenges in conducting clinical trials. These include low levels of literacy in clinical trials, minimal investment in community engagement and personnel development and poor protocol and data collection tool designs. Recognising the need to address the root cause of these issues in the conduct of clinical trials, the GCTC brought together a diverse group of experts to identify and describe the key underpinnings of a good clinical trial. Based on the opinions of the key informants and workshop participants, adoption of the GCTC Guidance and its principles into practice in the conduct of clinical trials is feasible. However, incorporating the Guidance should not increase the number of guidelines or training requirements for clinical trials. Several barriers to the adoption of the Guidance were identified by participants, including resistance to change, resource constraints, and inadequate infrastructure. However, stakeholders to implement the Guidance in South Africa were also identified, which include the DoH and SAHPRA. As of September 2024, the GCTC Guidance and its principles were incorporated into the WHO Guidance for Best Practices for Clinical Trials. These principles now make up Section 2, titled "Key scientific and ethical considerations for clinical trials", and have been included without any changes. With the assistance of stakeholders identified during the implementation of the GCTC Guidance in the South African context, our recommendation for the adoption and implementation of the GCTC Guidance in South Africa is to increase awareness of the WHO Guidance on Best Practices for Clinical Trials, which has incorporated the GCTC guidance . This can be achieved for example, by amending the 2020 South African GCP guidelines to incorporate the principles outlined in the WHO Guidance for Best Practices for Clinical Trials. As the SA-GCP (2020) recommends that GCP training be refreshed regularly, ideally every three years, these updates will be incorporated into the training that implementers of clinical trials

receive every three years. This would support the practical implementation of the updated Guidance. In addition, WHO will be releasing training on its guidance for best practices in clinical trials to further facilitate adoption and consistent implementation.

4.3 CONCLUSION

In conclusion, despite the lack of prior knowledge and limited awareness of the GCTC Guidance among clinical trial implementers in South Africa, the Guidance was found to help resolve many challenges that these implementers experience in conducting clinical trials in the country. The principles of the GCTC Guidance were also found to be relevant and well-aligned with current South African guidelines in practice. Therefore, the adoption of the GCTC Guidance in the conduct of clinical trials in South Africa is feasible if it is incorporated into other existing guidelines for clinical research.

REFERENCES

1.
(WHO) WHO. Monitoring health for the SDGs, Sustainable Development Goals. Geneva2024.

2.
Department of Health SA. Guidelines for good practice in the conduct of clinical trials with human participants in South Africa. Pretoria, South Africa2020.

3.
Kao LS, Tyson JE, Blakely ML, Lally KP. Clinical research methodology I: introduction to randomized trials. J Am Coll Surg. 2008; 206:361-9.

4.
Kabisch M, Ruckes C, Seibert-Grafe M, Blettner M. Randomized controlled trials: part 17 of a series on evaluation of scientific publications. Deutsches Arzteblatt international. 2011; 108:663-8.

5.
Pannucci CJ, Wilkins EG. Identifying and Avoiding Bias in Research. Plastic and reconstructive surgery. 2010; 126:619-.

6.
Mielke D, Rohde V. Randomized controlled trials-a critical re-appraisal. Neurosurgical review. 2021; 44:2085-9.

7.
Organization TWH. Guidance for best practices for clinical trials. Geneva: World Health Organization2024.

8.
Health Do. South African Good Clinical Practice: Clinical Trial Guidelines In: Health Do, editor. Third edition ed. Pretoria, South Africa2020.

9.
Collaborative GCT. Guidance for Good Randomized Clinical Trials. 2022; Available from: https://www.goodtrials.org/.

10.
Wandile P, Ghooi R. A Role of ICH- GCP in Clinical Trial Conduct. Journal of Clinical Research & Bioethics. 2017; 08.

11.
Vijayananthan A, Nawawi O. The importance of Good Clinical Practice guidelines and its role in clinical trials. Biomedical Imaging and Intervention Journal. 2008; 4:e5-e.

12.
Ghooi RB. The Nuremberg Code–A critique. Perspectives in Clinical Research. 2011; 2:72-.

13.
Association WM. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Participants – WMA – The World Medical Association. World Medical Association; 2024.

14.
Barrow JM, Brannan GD, Khandhar PB. Research Ethics. StatPearls. 2022.

15.
Miracle VA. The belmont report: The triple crown of research ethics. Dimensions of Critical Care Nursing. 2016; 35:223-8.

16.
5/2/2018 Tuskegee Experiment: The Infamous Syphilis Study-History in the Headlines.

17.
ICH E6 Good clinical practice - Scientific guideline | European Medicines Agency (EMA).

18.
CIOM. INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE ICH HARMONISED GUIDELINE GOOD CLINICAL PRACTICE (GCP) E6(R3)2025.

19.
Counci NHRE. South African Ethics in Health Research Guidelines: Principles, Processes and Structures, 3rd ed. Pretoria: NDoH: National Department of Health of the Republic of South Africa; 2024.

20.
South Africa Clinical Research Trials | CenterWatch.

21.
Wemos. CLINICAL TRIALS IN AFRICA THE CASES OF EGYPT, KENYA, ZIMBABWE AND SOUTH AFRICA2017.

22.
Casale M, Lane T, Sello L, Kuo C, Cluver L. Conducting health survey research in a deep rural South African community: challenges and adaptive strategies. Health research policy and systems. 2013; 11.

23.
National Health Research Ethics Council (NHREC) SA. NHREC -Home – National Department of Health.

24.
SAHPRA - South African Health Products Regulatory Authority.

25.
Department of Health RoSA. The South African National Clinical Trials Register (SANCTR). Available from: https://sanctr.samrc.ac.za/Default.aspx.

26.
Research GV. Clinical Trials Market Size & Outlook, 2030. 2023.

27.
Weigmann K. The ethics of global clinical trials: In developing countries, participation in clinical trials is sometimes the only way to access medical treatment. What should be done to avoid exploitation of disadvantaged populations? EMBO Reports. 2015; 16:566-.

28.
Sarah Rickwood FP, Camila Abella Gómez. Attracting Investment in Clinical Development: IQVIA2022.

29.
Bowman L, Weidinger F, Albert MA, Fry ETA, Pinto FJ, Clinical Trial Expert G, Forum ESCP. Randomized Trials Fit for the 21st Century. A Joint Opinion from the European Society of Cardiology, American Heart Association, American College of Cardiology, and the World Heart Federation. Glob Heart. 2022; 17:85.

30.
Bian H. Office for Faculty Excellence. Mixed Methods Research. Office for Faculty Excellence; 2018 [cited 2018 10 June 2018]; Available from: https://www.scribd.com/document/216825927/Mixed-Methods-Research

31.
Gerrish K. Methodological challenges in qualitative research: Kate Gerrish discusses how the researchers who wrote this issue's themed papers tackled their methodological challenges. Nurse researcher. 2011; 19:4-6.

32.
Razali FM, Aziz, N.A.A., Rasli, R.M., Zulkefly, N.F. and Salim, S.A.,. Using convergent parallel design mixed method to assess the usage of multi-touch hand gestures towards fine motor

skills among pre-school children. International Journal of Academic Research in Business and Social Sciences. 2019.; 9:153-66.

33.
Demir SBaP, N. A Convergent Parallel Mixed-Methods Study of Controversial Issues in Social Studies Classes: A Clash of Ideologies. Educational Sciences: Theory and Practice. 2018; 18:119-1949.

34.
Harris PA TR, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support,. J Biomed Inform. 2009; 42:377–81.

35.
Lumivero. NVivo (Version 14). Denver, CO: Lumivero; 2023.

36.
Dhakal K. NVivo. Journal of the Medical Library Association : JMLA. 2022; 110:270-.

37.
Pieper D, Pachanov A, Bahns C, Prill R, Kopkow C, Shehu E, et al. Locally adapted guidelines: a scoping review. Syst Rev. 2025; 14:66.

38.
Shanley TP, Calvin-Naylor NA, Divecha R, Wartak MM, Blackwell K, Davis JM, et al. Enhancing Clinical Research Professionals' Training and Qualifications (ECRPTQ): Recommendations for Good Clinical Practice (GCP) training for investigators and study coordinators. J Clin Transl Sci. 2017; 1:8-15.

39.
Mozersky JT, Antes AL, Baldwin K, Jenkerson M, DuBois JM. How do clinical research coordinators learn Good Clinical Practice? A mixed-methods study of factors that predict uptake of knowledge. Clin Trials. 2020; 17:166-75.

40.
Awatagiri K, Gadgil D, Kannan S, Rane P, Bandekar B, Sawant N, et al. Effect of a planned training session on good clinical practice knowledge in research professionals: A pilot study. Perspect Clin Res. 2019; 10:20-5.

41.
DuBois JM, Mozersky JT, Antes AL, Baldwin K, Jenkerson M. Assessing clinical research coordinator knowledge of good clinical practice: An evaluation of the state of the art and a test validation study. J Clin Transl Sci. 2020; 4:141-5.

42.
Cavaleri M, de Sousa CMA, Hacker A, Higgs ES, Lumpkin MM, Maia CS, et al. A roadmap for fostering timely regulatory and ethics approvals of international clinical trials in support of global health research systems. Lancet Glob Health. 2025; 13:e769-e77.

43.
Scheppler L, De Clercq N, McGoldrick M, Dias J. Regulatory Harmonization and Streamlining of Clinical Trial Applications globally should lead to faster clinical development and earlier access to life-saving vaccines. Vaccine. 2021; 39:790-6.

44.
Organization WH. Strengthening clinical trials1 to provide high-quality evidence on health interventions and to improve research quality and coordination Geneva: World Health Organization2022.

45.
Alemayehu C, Mitchell G, Nikles J. Barriers for conducting clinical trials in developing countries- a systematic review. International Journal for Equity in Health. 2018; 17:37.

46.
Ndebele P, Blanchard-Horan C, Shahkolahi A, Sanne I. Regulatory challenges associated

with conducting multicountry clinical trials in resource-limited settings. J Acquir Immune Defic Syndr. 2014; 65 Suppl 1:S29-31.

47.
Nebie EI, Sawadogo HN, van Eeuwijk P, Signorell A, Reus E, Utzinger J, Burri C. Opportunities and challenges for decentralised clinical trials in sub-Saharan Africa: a qualitative study. BMJ Open. 2023; 13:e075903.

48.
Tiwonge K Mtande CL, Gonasagrie Nair and Stuart Rennie. Stakeholders' experiences of ethical challenges in cluster randomized trials in a limited resource setting: a qualitative analysis. Research Ethics 2024; 20:64-78.

49.
Hoffmann JM, Bauer A, Grossmann R. Academic vs. industry-sponsored trials: A global survey on differences, similarities, and future improvements. J Glob Health. 2024; 14:04204.

50.
Laterre PF, Francois B. Strengths and limitations of industry vs. academic randomized controlled trials. Clin Microbiol Infect. 2015; 21:906-9.

51.
Lang TA, White NJ, Tran HT, Farrar JJ, Day NP, Fitzpatrick R, et al. Clinical research in resource-limited settings: enhancing research capacity and working together to make trials less complicated. PLoS Negl Trop Dis. 2010; 4:e619.

52.
Sciences CfIOoM. International ethical guidelines for health-related research involving humans: Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO). Geneva: Council for International Organizations of Medical Sciences2016.

53.
Bowsher G, Papamichail A, El Achi N, Ekzayez A, Roberts B, Sullivan R, Patel P. A narrative review of health research capacity strengthening in low and middle-income countries: lessons for conflict-affected areas. Global Health. 2019; 15:23.

54.
Franzen SRP, Chandler C, Siribaddana S, Atashili J, Angus B, Lang T. Strategies for developing sustainable health research capacity in low and middle-income countries: a prospective, qualitative study investigating the barriers and enablers to locally led clinical trial conduct in Ethiopia, Cameroon and Sri Lanka. BMJ Open. 2017; 7:e017246.

55.
Organization WH. *Adherence to clinical trial protocols in low- and middle-income countries: A global survey.* Geneva World Health organization2022.

56.
Shumba CS, Lusambili AM. Not enough traction: barriers that aspiring researchers from low-and middle-income countries face in global health research. Journal of Global Health Economics and Policy. 2021; 1:0-.