

Efficiency and quality in conducting clinical trials in sub-Saharan Africa

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Prof. Dr. Jörg Schibler
Dekan

Dedicated to my parents who have always supported me

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List of abbreviations

AVAREF	African Vaccine Regulatory Forum
CTTI	Clinical Trial Transformation Initiative
DRA	Drug Regulatory Authority
EC	Ethics Committee
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IC	Informed consent
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
QA	Quality Assurance
RLC	Resource-limited Country
SSA	sub-Saharan Africa
Swiss TPH	Swiss Tropical and Public Health Institute
WHO	World Health Organisation

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Summary

Background

The conduct of clinical trials is significantly regulated and requires substantial infrastructure and human resource investments and efforts. Clinical research centers in sub-Saharan Africa face particular constraints by the increasing trial related workload and administration, paired with capacity limitations. At the same time, trials are critically important for improving public health in these settings. We investigated the challenges in clinical trial conduct to optimize the efficiency of processes in sub-Saharan Africa while maintaining quality. Our working hypothesis was that the Good Clinical Practice guideline, is not adapted to these particular situations, and that its possibly overly strict interpretation was the main challenge.

Methods

We used an exploratory mixed methods design: First, we performed key informant interviews asking questions about quality, guidelines, challenges, and inefficiencies in clinical trials. We interviewed 60 clinical trial staff of different professional levels in two clinical research centers in Kenya, Ghana, Burkina Faso, and Senegal. The study covered English- and French-speaking, and Eastern and Western parts of sub-Saharan Africa. Content analysis was performed to identify themes across settings and positions, respectively. Emerging themes from data interrogation were tested in further interview analysis. We used MAXQDA software for the analysis. Second, we developed an online survey investigating trial protocol suitability based on the main interview themes. We distributed the survey by email to trial staff based in sub-Saharan Africa. We used the statistical software STATA for the analysis of categorical variables and to perform explorative factor analysis.

Results

We found various internal factors associated with constraining trial efficiency in sub-Saharan Africa. Internal factors are limited to those that exclusively relate to clinical trial teams and sponsors. These factors may be influenced independently of external conditions and may significantly increase trial efficiency if addressed by the respective teams. Identified internal factors were summarized in the two broad themes “planning” and “site organisation”. “Planning” factors related to budget feasibility, clear project ideas, realistic deadlines, understanding of trial processes, adaptation to the local context, and involvement of site staff in planning. “Site organisation” factors covered staff turnover, employment conditions, career paths, workload, delegation and management.

Protocol suitability surfaced as another prominent internal topic in interviews with trial staff. By following the topic up in an online survey we found that the main constraints of protocol suitability were a lack of clarity, implementability, and adaptation to trial participants as well as to available workforce and infrastructure. In both, qualitative and quantitative investigations local site staff involvement in protocol development was identified as the most helpful measure to increase protocol suitability.

Unexpectedly, the administrative burden resulting from the guidelines was not perceived as a difficulty; rather, researchers were grateful for having guidance by a globally accepted standard. Only in regards to informed consent did some clinical trial staff (one-third) perceive the guideline as insufficiently applicable.

Conclusions

Our data suggest that adequate and coherent planning, clear task allocation and strengthening of management capacity may help to overcome the identified internal factors and allow clinical trials to proceed more efficiently. In addition a careful assessment of the setting with a particular focus on available workforce and infrastructure as well as the needs and availability of trial participants was perceived to be beneficial.

Trial protocol suitability is rarely addressed; however, we found this to be fundamental as it has a direct impact on the execution and outcomes of the work. Our results indicate that preliminary

discussions and reviewing of the protocol with trial staff are most helpful in increasing protocol suitability. We concur with the interviewees and consider the involvement of operationally experienced staff to be most useful.

To mitigate informed consent challenges we suggest making use of the flexibility that the GCP guideline offers as well as identifying and tackling challenges prospectively. We deem that clarifying guidance for informed consent issues in resource-limited settings would be helpful for trial staff.

To allow for such measures, allocating enough time for trial preparation and enabling of the uptake of feedback and information on context at an early stage are a requisite. We found that such prospective planning would increase implementability, efficiency and quality in the long run.

Due to a general lack of research on trial practices and our small sample size more research is needed in order to validate and strengthen some of these findings. Trial staff members proved to be a valuable source of information to investigate trial practices. We consider the incorporation of sponsors' perceptions and interests on top of investigations of the study site as important for future research.

1. Introduction

1.1. Importance of clinical trials

Clinical trials generate the highest level of evidence for medicinal policy making and are thus integral to the advancement of medical progress. The International Conference on Harmonization's Good Clinical Practice guideline defines a clinical trial as "any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy" (1).

Clinical trials have led to the general use of proven effective treatments, which has prevented millions of people of premature deaths and suffering from illnesses. According to Yusuf *et al.* clinical trials and their subsequent discoveries would likely rank among the most important milestones in the history of medicine (2). Based on clinical trial data drug regulatory authorities (DRAs) decide on marketing approval of new medicines. In addition, clinical trials are crucial to inform and improve on standard therapies and disease management. The Declaration of Helsinki says "even the best-proven treatment must be evaluated continually for safety, effectiveness, efficiency, superiority, inferiority and quality through research" (3).

Of particular importance are clinical trials on poverty-related diseases as these diseases have previously been under-represented in clinical research (4). At the global level, the three main poverty-related diseases are HIV/AIDS, malaria, and tuberculosis (5). In 2010, the global deaths from HIV/AIDS have risen to 1.5 million, malaria mortality increased to 1.17 million and tuberculosis killed 1.2 million people that same year (6). Poverty-related diseases disproportionately affect the poorest population in the world and are mainly concentrated in rural areas of sub-Saharan Africa (SSA), Asia, and Latin America (6). Hence, there is a need for clinical trials to develop new medicines against poverty-related diseases.

1.2. The Good Clinical Practice guideline

Guidelines are essential to assure ethical and scientific quality standards in clinical trials involving humans. The necessity of guidelines for research with humans was recognized for the first time after World War II. During the war, doctors performed experiments on prisoners which led to the creation of the Nuremberg Code in 1946. The most important ethical principles of clinical trials, which are stipulated in today's regulatory documents, were already contained in the ten principles of the Nuremberg Code (7). In 1964, the Declaration of Helsinki was developed by the World Medical Association (3). The declaration is based on the Nuremberg Code and has continuously been updated (8). Another set of guidelines was produced in 1982 by the World Health Organisation (WHO) and the Council for International Organisation of Medical Science (CIOMS) named "International Guidelines for Biomedical Research Involving Human Subjects" (9). The aim of these documents was to help resource-limited countries (RLCs) in applying the principles of the Declaration of Helsinki and the Nuremberg Code (8).

There was a need for data generated in clinical trials to be mutually acceptable to DRAs which led to the intention of having globally harmonised guidelines. This idea was taken up by the International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). ICH's initiative was driven by Europe, USA, and Japan half of the actors were from the pharmaceutical industry and the other half were DRAs from listed countries (8). A number of ICH guidelines were subsequently created, amongst which the in 1996 developed ICH E6 Good Clinical Practice (GCP) guideline is the most important one. ICH-GCP is "an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve participation of human subjects", and has the purpose of protecting participants' rights, safety, and wellbeing as well

as the data integrity of a clinical investigation (1). GCP was heavily influenced by the ethical principles of the Declaration of Helsinki (10). In the meantime, ICH has developed many guidelines which are divided in the following four categories: safety, efficacy, quality and multidisciplinary. Compared to the ICH-GCP E6 guideline other recent ICH-efficacy guidelines deal with much smaller technical subjects. Today, ICH-GCP E6 guideline is the unified international ethical and scientific quality standard for clinical trials in humans in most regions and especially for research aimed at registering a new medicine at the European Medicines Agency (EMA) in the EU or the Food and Drug Administration (FDA) in the USA. GCP has widely been adopted and incorporated into laws on clinical research. For example, the European Union Clinical Trials Directive relating to GCP was implemented by all EU member states in 2004 and has legal status.

Despite of ICH-GCP's achievement of harmonizing clinical trial practices, there is consistent criticism about the development of the guideline such as the critique that not enough countries have been involved in its development and that it was conceived by informal consensus (11). Yusuf states that GCP was developed without much direct involvement of those who actually conduct trials (12). Lang *et al.* say that the guideline was elaborated with focus on the needs of industry and drug registration with minimal representation from academia and non-commercial organisations (13). Hanna *et al.* say that the GCP guideline development process in 1996 was neither inclusive nor evidence based (14). Besides the direct influence and the veto power of the pharmaceutical industry, it is being criticized that the countries involved in the GCP development only represented one-tenth of the world's population. However, all DRAs require that clinical trials comply with a national or international GCP code to be assured that the right and wellbeing of the patient is respected and data integrity provided. These facts raised criticism that RLCs have to work along GCP without having had a say during its development (15).

Several initiatives have tried to tackle the lack of adequate clinical trial standards in RLCs. The WHO created the WHO-GCP for trials on pharmaceutical products to provide a global ethical standard, as well as to complement existing regulations, especially for countries that do not have own regulations (13). However, the only difference to ICH-GCP is that principles 5 and 6 of the WHO-GCP were joined to principle 6 in the ICH-GCP. The African Vaccine Regulatory Forum (AVAREF) published a draft AVAREF-GCP guideline specifically for vaccine trials in SSA. The AVAREF-GCP differs from ICH-GCP by including a chapter called "Provisions and prerequisites for a clinical trial" that stresses the importance of risk-benefit considerations as well as ethical principles and references the Declaration of Helsinki and CIOMS. Additionally, in SSA more and more countries develop national GCP guidelines e.g. South Africa, Ethiopia, and Ghana (16-18).

Another criticism found in literature is that ICH-GCP is out-dated. However, the guideline is currently being amended for the first time since its introduction in 1996. A draft of the amended GCP guideline was available for consultation. The 300 comments that have been sent to the ICH are currently being processed and implementation of the amended ICH-GCP is expected for November 2016 (19). The draft addendum mainly focuses on the application of new technology as well as risk-based quality management and monitoring (20).

1.3. The interpretation of the GCP-guideline as a hindrance of efficiency in clinical trials

In industrialized countries, ICH-GCP itself is rarely criticized. Instead, criticism is directed towards GCP's interpretation. The ICH-GCP states in nine instances that GCP should be interpreted and applied in an appropriate manner compared to the risk of the research (1), but there is increasing evidence in literature that the sponsor's interpretation of GCP has been above what is actually required (21-23). In the final business plan of the addendum to ICH-GCP it is criticised that GCP has been misinterpreted and implemented in a way that impedes innovation (24). For example by focusing

on less important aspects of trials (e.g. the completeness and accuracy of every piece of data) at the expense of critical aspects (e.g. carefully managing risks affecting the integrity of key outcome data). One possible explanation for the present rigid interpretation of GCP is the pressure by ethics committees (ECs) and DRAs who have a very meticulous approach to assessing systems and procedures. Shortcomings may only be detected with significant delays but may have major consequences on work already concluded and therefore operational risks are avoided by all means. Another critique is that ICH-GCP was a “one size fits all”-approach lacking the assessment of the individual risk of different development phases, substances, and trials (12).

There is also an on-going debate on the appropriate interpretation of ICH-GCP for RLCs, which is missing, and some researchers fear the enforcement of the industry standards in RLCs as they are becoming the globally accepted practice (4, 13, 25-28). However, most authors think that ICH-GCP is the right guideline for clinical trials in RLCs and that full adherence to ICH-GCP (14) or at least to its core elements (28, 29) is appropriate and should be preserved. Some authors claim that ICH-GCP’s administrative requirements distract attention from the participant and are not feasible for clinical trial teams in RLCs (26, 29). Along with the ethical challenges, the guidelines need appropriate interpretation in these settings (4, 26). A reason for not applying ICH-GCP in an adapted manner in RLCs could be that sometimes the mostly northern sponsors (30) demand that trials in RLCs meet all conceivable expectations of their northern DRAs in terms of guidance interpretations. Authors criticizing the current trial practices in RLCs underline that an appropriate, adapted application of the guidelines does not equate to substandard conduct of trials compared to wealthier countries (4, 13, 28). These authors argue that a risk-adapted approach is urgently needed and possible without compromising quality (26, 29). This debate is not supported by any systematic research but has been introduced largely by northern expatriates working in RLCs.

The following initiatives and research projects have tried to tackle the lack of adequate interpretation of the GCP-guideline in RLCs; A common platform for clinical researchers in RLCs is the ‘global health trials’ community, which hosts discussions about GCP application (31). Round table discussions concluded that ICH-GCP guidelines are ‘non-negotiable’ and equally applicable in the north and the south. They recommend to coherently establish ethical reviews in the sponsor’s country and locally, plus Data and Safety Monitoring Boards. Ethical challenges such as informed consent (IC) and standards of care were also discussed (32, 33), whereas the development of general recommendations on this sensitive topic was regarded as being difficult (32).

Nevertheless, guidance on risk- and context-adapted application of ICH-GCP in RLCs is still missing, prompting CT teams and sponsors to devise their own approaches. The excessive focus on procedural rather than substantive aspects of the GCP guideline in clinical trials might be a main hindrance of efficiency in clinical trials. We considered the appropriate interpretation of the guidelines as a major unexplored and underused area for increasing efficiency in clinical trials operations.

In the forthcoming text GCP always refers to ICH-GCP.

1.4. Importance of efficiency and quality in clinical trials

The conduct of clinical trials in humans is highly complex and bears many challenges; people are submitted to potential risks of health, trials are complex undertakings, and big amounts of data are collected; hence a good organization and very precise working manner are prerequisites. Facing this huge undertaking of conducting a clinical trial it is important that efficiency is not neglected. Increased efficiency in clinical trials would not only reduce costs but also lead to more productive work settings with manageable workloads and requiring less time to perform a trial. This is consistent with the main justification of the currently developed addendum of ICH-GCP, which is “the encouragement of implementation of more efficient approaches to clinical trial design, conduct, oversight, recording and reporting” (20).

The efficiency of trial operations have become even more important in the light of the fact that costs for the conduct of clinical trials have steadily increased. Besides the potentially inefficient application of GCP in trials, there are many reasons for the increased costs and include increasing protocol complexity, the sophistication of medical technology, but also a sharp increase in the ethical requirements. Also the number of data collected in clinical trials is increasing Thomason *et al.* states that there is too much information being generated to process efficiently (34) while O'Leary *et al.* is concerned about the data that is being collected for regulatory purposes only and not for publication or scientific use (30). Besides the GCP-guideline there is a growing number of other guidelines and regulations leading to growing administrative workload. For example, there were 15'163 pages of regulations on FDA Center for Drug Evaluation and Research (July 07 2016).

This trend stands in sharp contrast to the efforts to make health systems productive and to the restricted funding available for clinical research. Moreover, the added value of described additional efforts in terms of increasing the quality of clinical trials remains unknown (35).

Quality in clinical trials is described as the degree of protecting the rights, safety, and well-being of trial subjects and of ensuring the quality and integrity of data obtained from clinical testing. High trial quality is crucial given the fact that clinical trials are experiments with humans which have to be fully protected, as well as given the potential impact of trial data collected on changes in health policy or the introduction of newly registered products. To ensure trial quality, scientific and procedural rigor in the conduct of clinical trials is indispensable. Whilst trying to increase efficiency in clinical trials, quality needs to be ensured by all means and should be the criterion by which to measure success in increasing efficiency. This can result in a challenging balancing act considering the fact that amongst good, fast and cheap, only any two can be chosen.

The lack of research on clinical trial procedures and its efficiency has been stated numerously in literature. O'Leary *et al.* state that examining areas to maintain quality but improve efficiency and reduce costs in cancer clinical trials has little research attention (30). Treweek *et al.* complains that some of the resources invested in randomized trials are wasted because of limited evidence upon which to base many aspects of design, conduct, analysis and reporting of clinical trials (36). In a publication about reducing waste in research, the authors state further research is needed to learn how efficiency can be increased (37). Other authors state that it is critical that clinical trialists pursue research in clinical trial methodology defined as research into how to conduct clinical trials more quickly and efficiently (38). Finally Sgheorghide *et al.* states that "there is a peculiar paradox that exists in trial execution – we perform clinical trials to generate evidence to improve patient outcomes; however we conduct clinical trials like anecdotal medicine: we do what we think works; we rely on experience and judgment and limited data to support best practices" (39).

To the best of our knowledge, there are only a few published reflection papers and qualitative studies on trial procedures (40, 41). These publications mainly focus on recruitment strategies. There has been research published on the concept of risk assessment for clinical trials (42). Every trial is different and has its individual risk, therefore literature promotes the performance of detailed risk assessment to identify the likelihood of errors and the extent of their impact, and to aim quality management measures at the detected risks. Risk-based monitoring has been introduced and is important not only to reduce costs but also to apply monitoring to the most crucial study components (43-45). Several research groups are involved in establishing a comprehensive structured procedure leading to risk-adapted quality management (42, 45).

However, in general, there is little scientific evidence that the procedures for clinical trials are carried out in an efficient and cost-effective way (21) while all literature agree with the consensus that there is a need for more research focusing on the practical difficulties in running a trial. Glickman *et al.* state the development of streamlined best practices to reduced unnecessary work for investigators are needed (46) and Sargent *et al.* state simplifying the conduct of trials is the most effective way to control costs in clinical trials (38). More specifically it is stated that there are very many processes

involved in a trial and learning about and improving each of them may have a minimal effect on its own but taken together these improvements could have a much more profound impact (36).

There are some initiatives surrounding the topic of efficient trial procedures. For instance the Alliance for Clinical Research Excellence and Safety (ACRES) is an initiative which brings together an alliance of stakeholders who share the belief that a high-performing global system for clinical research is key. One of ACRES visions is that ineffectiveness and inefficiencies in the clinical research enterprise must be overcome. TransCelerate BioPharma's mission is to collaborate across the global pharmaceutical research and development groups to identify, prioritize, design and facilitate implementation of solutions designed to drive the efficient, effective and high-quality delivery of new medicines. Another initiative is the European Clinical Research Infrastructure Network (ECRIN) who supports the conduct of multinational clinical trials in Europe. Other initiatives are successfully promoting the involvement of patients in clinical research (47, 48). This contributes not only to therapies that are better adapted to the needs of the patients but may also have a positive influence on the recruitment, IC procedure and ethical review of a clinical trial. There are two US-based groups who conduct research on clinical trial procedures. First, there is the Clinical Trials Transformation Initiative (CTTI) which is a partnership between the FDA and the Duke University. Their aim is to identify practices that will increase the quality and efficiency of clinical trials. Second, the Tufts Center for the Study of Drug Development is an independent, academic, non-profit research group. Their mission is to develop strategic information to help drug developers, regulators, and policy makers improve the quality and efficiency of pharmaceutical and biopharmaceutical development, review, and utilization.

In addition, some conferences were held with the aim of facilitating operations in clinical trials (21, 49, 50). Some results suggest that it is possible to reduce substantially the cost of clinical trials without compromising the scientific validity of their results (50). But research on the conduct of clinical trials was proposed to be conducted to refine the findings (50).

Although there are some promising ideas and initiatives, the operational aspects of trials, have received far less attention than research in the theoretical area of the regulation and the heavily debated ethical issues. To maintain the momentum in medical progress it is important to find ways to improve the efficiency of operations in clinical trials while maintaining high quality.

1.5. Geographical focus: clinical trials in sub-Saharan Africa

In resource-limited settings the need for optimization of clinical trials operations is even more pertinent. On one hand, this concerns academic research (investigators initiated trials) in all geographic regions, which is often conducted with limited resources, on the other hand, all research on poverty-related diseases is conducted with constraint funding. Since the latter is our core competence the geographical focus of this project is on clinical trials assessing interventions against poverty-related diseases in SSA.

Clinical trials on poverty-related diseases have to be conducted in settings where the illness is present such as endemic areas in SSA, which has also been confirmed by the WHO report 2013 (51). On top of having patients available in disease-endemic areas, indirect benefits of conducting clinical trials in host countries are improved teaching and patient care provided by the host country investigators (52).

1.5.1. Additional challenges of clinical trials in sub-Saharan Africa

Compared to trials in the Northern hemisphere, working conditions are even more complex for clinical trials conducted in SSA.

Structural shortcomings

Clinical researchers in SSA have to cope with poorly developed health-care systems and often a lack of research infrastructure to enable them to perform good quality research (53, 54). Deficits in human resources and experience affect the efficient conduct of clinical research (55). Besides their role as

clinician and investigator, clinical researcher sometimes also have to assume tasks of administrators and caregivers due to a lack of human resources (56). Consequently, the available trained personnel has to manage a very high workload. Especially in rural areas, there are additional capacity constraints such as the lack of essential equipment and infrastructure as well as power cuts and poor internet connections. This may have significant implications on trials for which good communication and a functioning cold chain is essential (54). In addition, environmental catastrophes such as floods occur regularly in some African countries and have to be anticipated for any trial (57).

Ethical challenges

Clinical trials in SSA face a variety of ethical challenges as these trials are conducted in vulnerable participants like children, illiterate, seriously sick, impoverished and displaced (refugee) participants. The study population might have only limited access to education (58). In addition, trial participants are frequently not familiar with the concept of research and may not understand the experimental character of a clinical trial (27, 59). It is thus challenging to assure that trial participants have fully understood the risks and benefits of the trial. For some populations in SSA a clinical trial may present the only access to healthcare, which complicates ensuring voluntary trial participation. In addition, trial participants may base their decision to participate in a trial primarily on the assumption that their medical caregiver takes the best decisions for them. In these regions, it is a challenging balancing act between avoiding undue inducement and compensating trial participants for their efforts and time with monetary reimbursement for traveling to the trial site and food provision at the site.

Challenges with Ethic Committees and Drug Regulatory Authorities

In RLCs, DRAs have only recently been established and lack experience in assessing clinical research (60-62) and the practice in risk-based approaches. Hence, the review time for approving a clinical trial may be lengthy. In addition, local laws may be out-dated and not even consider clinical trials.

Significant training efforts have been made over the past ten years to provide the ECs in SSA with the necessary skills and resources. However, they differentiate considerably in their operations, resources, training needs, and capacities and if the respective committees are not used to review of such projects the waiting time for approval and amendments of the protocol may be significantly increased. The lengthy trial approval process may be exacerbated through the best practice of double ethical review of trials by local ECs in the resource-limited country as well as in the country of the sponsor or funding agency (63).

1.5.2. Clinical trial practices in SSA

The topic of efficient trial execution is of particular importance in SSA as the number of clinical trials carried out in these settings is rising (59, 64) while funding and the number of qualified health staff remain limited. In the past years, a number of non-governmental institutions have funded research activities, such as the Wellcome Trust and the Bill and Melinda Gates Foundation. However, in 2014, the total annual funds available for neglected disease medicines development was USD 3,377 million in (65); in the same year, the estimated cost to the pharmaceutical industry of developing one new prescription medicine to the point of marketing approval was USD 2,558 million (55). Increased efficiency in trials would allow more trials to be conducted with these limited funds available. This, in turn, has important implications for public health in resource-limited settings, where trials are urgently needed to develop new safe and effective health interventions (9).

As discussed previously there is little scientific evidence to show that the procedures for clinical trials are carried out in an efficient and cost-effective manner (21), and compared to the North even less research is available on trial practice in SSA. Yet, there are a number of initiatives to strengthen clinical research in SSA the most prominent ones are 1) Global Health Trials Network; an interactive global resource where useful information for running a clinical research project is available, and knowledge and experience can be shared 2) The European & Developing Countries Clinical Trials

Partnership (EDCTP); they aim to accelerate the development of new or improved drugs, vaccines, microbicides and diagnostics against HIV/AIDS, tuberculosis and malaria as well as other poverty-related and neglected infectious diseases in SSA 3) Malaria Clinical Trials Alliance (MCTA), their objective is to facilitate the timely development of a network of centres in Africa with the capacity to conduct clinical trials of malaria vaccines and drugs and to support, strengthen and mentor the centres in the network to facilitate their progression towards self-sustaining clinical research centres 4) African Medicines Regulatory Harmonisation Programme (AMRH); their objective is to establish and improve standards and requirements related to the regulation of and access to safe, high-quality medicines for the African population.

Additionally, in the last two decades a number of African-owned research institutions, so-called centres of excellence, have been established. Examples are the Kenya Medical Research Institute (KEMRI), the Malaria Research and Training Centre of Mali (MRTC) or the Center of Medical Research Lambaréné (CERMEL), in Gabon. These centres have been involved in multiple trials and collected substantial experience in conducting GCP-compliant clinical trials.

When this PhD program started there were only few research papers published on clinical trial practices in SSA. In the meantime interest in the topic has increased. However, these few publications addressing the trial conduct in SSA are mostly reflections on past trials and are not based on a research-based approach. Concrete recommendations for solutions within the conduct of trials in SSA are still scarce (29, 57).

1.6. Methods and study setting

1.6.1. Methods

This thesis applied an exploratory mixed methods design which is an ideal approach to exploring a topic for which little research has been carried out so far (66). The purpose of mixing quantitative and qualitative methods is to benefit from the specific strength of each type of method. Moreover, the combination of the two methods provides a better understanding of a research question than either method alone (66). We started with a literature review and preliminary interviews with clinical research professionals working in the pharmaceutical industry, in academia and in resource-limited settings (figure 1). Further, we piloted the interview guide in a Tanzanian clinical research centre. This was followed by the main part of the PhD project which was qualitative interviews. It is the nature of the exploratory mixed methods design that the qualitative part is usually the main part (66). Key informant interviews allowed us to explore experiences, perceptions, and attitudes of clinical trial staff working in SSA. The openness of the qualitative approach is very suitable for fields where little research exists. The third part was a quantitative online survey. In the survey we further investigated the most important variables in relation to protocol suitability, which we identified in the qualitative interviews. The online survey targeting trial staff in SSA allowed us to quantify, increase generalizability and explore correlations between variables.

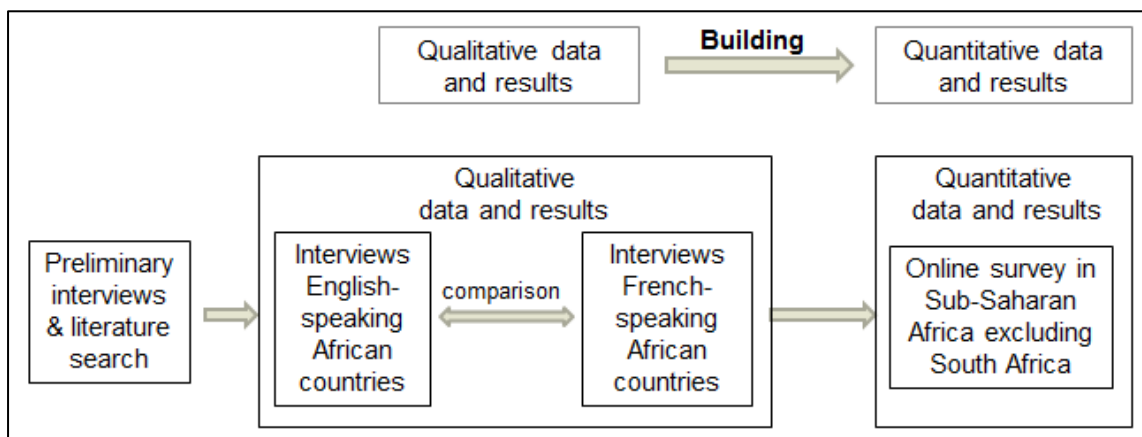


Figure 1 Exploratory mixed methods design

1.6.2. Study setting

All data for this thesis was collected in SSA. In the qualitative part English-speaking African countries (Kenya, Ghana) were visited followed by French-speaking African countries (Burkina Faso and Senegal). These four countries were selected to compare results between different language (English and French-speaking countries) and geographical (West and East Africa) regions, which had the advantage of covering different parts of SSA (Figure 2). The listed countries were selected as they contribute substantially to health research activities in SSA (67). In addition, in all four countries a minimum of three established clinical research centres (centres of excellence) are present. We deliberately conducted all our interviews with trial staff working in established clinical research centres. The reason for this was that trial staff in these centres have more experience in conducting clinical trials and were considered a better source of information, compared to remote trial sites for neglected diseases research, which might only have little experience to share. In order to cover two countries in East Africa, we collected qualitative data also in Tanzania, but had to exclude Tanzania finally as in one of the two visited centres we conducted the pilot run and were not able to include this data.

The quantitative survey was targeting all countries in SSA to provide a bigger sample size and enable results representing all of SSA. As clinical research is more established in South Africa and not exactly comparable with other SSA-countries we excluded South Africa from our study (68). Although we did not reach our target sample size of 200, the distribution of survey participants across countries reflected the different countries' number of clinical trials conducted (69), only Malawi, Zimbabwe and Nigeria were underrepresented in our survey.



Figure 2 Case-countries for qualitative data collection (Kenya, Ghana, Burkina Faso and Senegal)

1.6.3. Ethics

Ethical review exemption was obtained from the Ethics Committee of North-western and Central Switzerland (EKNZ) and from the Pharmacy and Poisons Board in Kenya (Ref. No. PPB/ECCT/Misc/2015(79)), based on the reasoning that the research project did not involve access to or collect private, sensitive or health-related data or materials. The ethics committees in Ghana, Burkina Faso and Senegal were asked to grant an ethical exemption but their statutes do not allow for such exemptions. Therefore, we applied for and received full ethical clearance from the Ghana Health Service Ethical Review Committee (GHS-ERC: 18/09/14), the Comité d'Éthique sur la Recherche en Santé in Burkina Faso (N 2014-11-131) and the Comité National d'Éthique pour la Recherche en Santé in Senegal (n12/MSAS/DPRS/CNERS).

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2. Hypothesis and objectives

The goal of the project is to contribute to increase the efficiency in the conduct of clinical trials in sub-Saharan Africa while maintaining high quality

Hypothesis

The ICH-E6 GCP guideline is intended to be subject of varying interpretation and it allows considerable flexibility in the implementation. However, this flexibility is not adequately used. A practical and appropriate interpretation of guidelines enables the efficient trial implementation also in low-resource settings

Objectives

1. To identify the main operational challenges in clinical trials in sub-Saharan Africa in an evidence-based approach and to develop the most appropriate solutions
2. To compare challenges from French- and English-speaking countries and develop solutions respectively
3. To investigate advantages and challenges of working with the ICH-Good Clinical Practice (GCP) guideline and its interpretation for clinical trials in sub-Saharan Africa?
4. To identify how the suitability of the trial protocol could be increased for clinical trials in sub-Saharan Africa

3. The GCP guideline and its interpretation – perceptions of clinical trial teams in sub-Saharan Africa

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3.1. Abstract

Objectives

To explore the advantages and challenges of working with the Good Clinical Practice (GCP) ICH E6 guideline and its interpretation from the perspective of clinical trial teams based in sub-Saharan Africa.

Methods

We conducted 60 key informant interviews with clinical trial staff at different levels in two clinical research centres in Kenya, Ghana, Burkina Faso and Senegal, respectively, and performed thematic analysis on the responses.

Results

Clinical trial teams perceived working with ICH-GCP as highly advantageous and regarded ICH-GCP as applicable to their setting and efficiently applied. Only for informed consent did some clinical trial staff (one third) perceive the guideline as insufficiently applicable. Specific challenges included meeting the requirements for written and individual consent, conditions for impartial witnesses for illiterates or legally acceptable representatives for children, guaranteeing voluntary participation and ensuring full understanding of the consent given. It was deemed important to have ICH-GCP compliance monitored by relevant ethics committees and regulatory authorities, without having guidelines applied overcautiously.

Conclusion

Clinical trial teams in sub-Saharan Africa perceived GCP as a helpful guideline, despite having been developed by Northern organisations and despite the high administrative burden of implementing the guideline. To mitigate consent challenges, we suggest applying GCP in an adapted manner and making use of the flexibility offered by the guideline.

3.2. Introduction

Clinical trials in sub-Saharan Africa (SSA) are critically important to improving the health of local populations. Guidelines ensure that ethical and scientific quality standards are met in clinical trials (CTs) involving humans. History has shown the need for guidelines to protect the trial participants (1). Having the appropriate guideline for scientific and procedural rigor in CTs is crucial because of its potential impact on health policy or on new medicines registration.

The E6-Good Clinical Practice (GCP) guideline developed by the International Conference of Harmonization (ICH), consisting of the USA, EU, and Japan, is the internationally accepted gold standard by which to perform CTs (2). The guideline was developed emphasizing on trials targeting medicines registration and without input from resource-limited countries (RLCs) (2).

The ICH-GCP aims to protect the rights, safety and well-being of trial subjects and to ensure the quality and integrity of data from clinical testing. Today, many other guidelines regulate quality, efficacy, safety, and multidisciplinary topics beyond the ICH-GCP document. Other agencies have issued various guidances and position papers as well (3, 4).

In industrialised countries, ICH-GCP itself is rarely criticised (5-8). Instead, criticism is directed towards the interpretation of the guideline (9-11), such as the over-interpretation which leads to inflated administration and costs. Due to the limited validity of patents, the pharmaceutical industry reportedly prioritizes faster trials and regulatory compliance over cost savings, risk-adaptation and reducing of complexity (12). In contrast, ICH-GCP states in nine instances that the guideline should be implemented according to the risk of the trial (2); this risk-based notion becomes even more prominent in the E6 Integrated Addendum to ICH-GCP, which is currently undergoing consultation (13).

Additional challenges arise when applying ICH-GCP in RLCs. First, these international standards seemed to have been imported without considering cultural and socio-economic contexts (14, 15). Second, CT teams in RLCs often have to overcome deficits in infrastructure, human resources and health systems.

An appropriate interpretation of ICH-GCP for RLCs is missing and some researchers fear the enforcement of the mentioned industry standards in RLCs as they are becoming the globally accepted practice (12, 14, 16-19). However, most authors think that ICH-GCP is the right guideline for CTs in RLCs and that full adherence to ICH-GCP (20) or at least to its core elements (19, 21) is appropriate and should be preserved. Some authors claim that ICH-GCP's administrative requirements distract attention away from the participant and are not feasible for CT teams in RLCs (17, 21). Along with the ethical challenges, the guidelines need an appropriate interpretation in these settings (14, 17).

A reason for not applying ICH-GCP in an adapted manner in RLCs could be that sometimes the mostly Northern sponsors (10) demand that trials in RLCs meet all conceivable expectations of their Northern regulatory authorities in terms of guidance interpretations. Authors criticizing the current trial practices in RLCs underline that an appropriate, adapted application of the guidelines does not equate to substandard conduct of trials compared to wealthier countries (14, 16, 19). These authors argue that a risk-adapted approach is urgently needed and possible without compromising quality (17, 21). This debate is not supported by any systematic research but has been introduced largely by Northern expatriates working in RLCs.

Several initiatives have tried to tackle the lack of adequate CT standards in RLCs. WHO developed the WHO-GCP which promotes identical standards to ICH-GCP, while the African Vaccine Regulatory Forum (AVAREF) published a draft GCP-guideline specifically for vaccine trials in SSA. The AVAREF-GCP differs from ICH-GCP by including a chapter on 'Provisions and prerequisites for a clinical trial' that stresses the importance of risk-benefit considerations and ethical principles including references to ethics guidelines. A common platform for clinical researchers in RLCs, the "global health trials" community, hosts discussions about GCP application (22). Roundtable discussions concluded that ICH-GCP guidelines are "non-negotiable" and equally applicable in the North and South. They recommend to coherently establish ethical reviews in the sponsor's country and locally as well as Data

and Safety Monitoring Boards. Ethical challenges such as informed consent and standards of care, were also discussed (23, 24) whereas the development of general recommendations on this sensitive topic was regarded as being challenging (23). At a more detailed level, Hannah *et al.* developed quality indicators to assess ICH-GCP compliance in trials in RLCs (20), while Küpfer *et al.* listed minimal standards (25). Lang *et al.* highlighted where the guideline might be overcautiously applied (14) and Acosta *et al.* reported challenges of implementing the 13 principles of GCP in RLCs (18).

Nevertheless, guidance on risk- and context-adapted application of ICH-GCP in RLCs is still missing, prompting CT teams and sponsors to devise their own approaches. Our team has faced similar operational challenges over the past 20 years and we agree with Lang *et al.* that local CT teams must be involved in the debate on guideline application (16).

The study investigates advantages and challenges of working with ICH-GCP and examines whether the guideline is being applied in an RLC-adapted and efficient manner in the perception and experience of trial staff working in RLCs in SSA. Among the wealth of regulations, ICH-GCP is the accepted gold standard in most SSA-countries although the extent to which it has been integrated into national laws varies. In the remainder of the document, “guideline” and “GCP” always refers to ICH-GCP E6, while “authority” refers to regulatory authorities and ethics committees.

3.3. Methods

To compare different language regions in SSA, clinical research centres were chosen in two English-speaking (Kenya and Ghana) and two French-speaking African countries (Burkina Faso and Senegal). These four countries were selected as they contribute substantially to health research activities in SSA and cover Western and Eastern regions. (26). In each country we contacted all the major clinical research centres with a focus on poverty-related diseases and a track record of completed CTs (no more than four such centres could be identified per country). In every country we selected the first two research centres that agreed to our visit. In English-speaking Africa two rural, one semi-urban and one urban clinical research centres were visited and in French-speaking Africa three urban and one rural research centres were visited. Two of the urban centres frequently conducted trials in the rural area too. The names of the centres have been withheld to ensure anonymity of the interviewees. Interviews were open to all investigators, study coordinators, clinicians and professionals working in quality assurance in the centre with at least half a year experience in clinical research. In each centre the sample was drawn with the assistance of one clinical trial staff member, who approached eligible participants and informed them about the study.

Sixty key informant interviews were conducted (see table 1). The majority of the interviewees were exclusively working in clinical research without involvement in routine health care. For the interview guide development NV reviewed the literature and conducted preliminary interviews with clinical researchers working in RLCs and developed countries. Based on these results NV generated the interview guide together with three experienced clinical researchers and a social scientist. We selected the interview questions which best encouraged interviewees to openly speak about applicability and efficiency of guideline implementation. The interview guide was pre-tested and developed iteratively as data emerged. It consisted of general questions about quality, guidelines, challenges, and perceived inefficiencies in CTs. In Kenya and Ghana, interviews were conducted in English. The interview guide was then translated into French, which included a back-translation and review of terminologies. Subsequently, interviews in Burkina Faso and Senegal were conducted in French.

Table 1 Characteristics of interviewed clinical trial staff

	Kenya (n = 17)	Ghana (n = 13)	Burkina Faso (n = 16)	Senegal (n = 14)
Role in study				
Investigators (n = 28)	8	4	8	8
Study coordinators (n = 17)	5	6	3	3
Clinicians (n = 10)	3	2	3	2
Professionals working in QA (n = 5)	1	1	2	1
Gender				
Female	9	4	3	4
Male	8	9	13	10
Clinical research experience [years]				
0 - 2	1	4	2	1
3 - 5	2	3	4	2
6 - 8	6	0	5	3
9 and more	8	6	5	8
Study Phase				
Phase I (a + b)	10	3	10	3
Phase II	12	3	13	4
Phase III	13	10	13	8
Phase IV	4	7	9	3
Type of trial				
Drug trial	15	8	16	11
Vaccine trial	14	10	13	9

After having explained the purpose of the study and informed the participants of their right to withdraw from the study at any given time, participants gave either oral consent (Kenya) or written consent (Ghana, Burkina Faso, and Senegal).

Between 13 and 17 interviews were conducted in each country between 2014 and 2015. After the first 11 interviews in each country, saturation of information was reached with few or no new concepts raised (27).

Interviews were tape-recorded and transcribed verbatim (by NV, AJ, SK, AK). Data were analysed in MAXQDA 11, using thematic analysis as per Braun and Clarke 2006 (28). NV and AJ coded independently, with a focus on guidelines, administration and inefficiencies in CTs. The coding framework was discussed before agreeing on a final version. Key themes were cross-tabulated to explore differences between countries and staff levels.

Ethical review exemptions were granted by the Ethics Committee of Northwest and Central Switzerland and the Pharmacy and Poisons Board in Kenya because the research project was not involving access to or collection of private or sensitive data. Ethical clearance was obtained in Ghana, Burkina Faso and Senegal as the statutes of the ethics committees in these countries do not foresee ethical review exemption. This study adhered to the qualitative research review guidelines (RATS) (29).

3.4. Results

Advantages of the guideline

All interviewees expressed that the guideline's advantages outweighed the disadvantages. They stressed its importance and usefulness as a means of ensuring trial participants' well-being, and data reliability and quality. Staff appreciated the guideline's framework while working in a challenging environment.

"There are advantages. All this allows us, firstly, to obtain quality data; secondly, to respect the welfare of study participants. So this is a necessary advantage, plus it permits data standardisation relative to other sites. To standardise the way people work across sites, well these are all advantages. Now there aren't any drawbacks! There are just constraints."

Investigator, male, Burkina Faso, centre five

Staff (55/60) across countries and professional positions could not think of a single disadvantage or unnecessary step in working according to the guideline. CT work is laborious and time-consuming but no time is lost due to guideline-related unnecessary administration or repetitive steps.

The entire administration process was regarded as an essential element of trials and indispensable for quality. Some investigators (11/60), mainly from English-speaking countries, mentioned the high demand for documentation; 10 described it as a nuisance. However, all but one agreed that nothing should be minimised or skipped in practice. The following quotation is a representative experience of documentation and repetition in clinical trials

"What happens, human as we are or practical as the work may be, what happens if that result could not be traced again? (...) when you see how important what you would have thought was just too much work becomes very useful. So yes, I sometimes, I will agree with you that you would see some of the work you are going over again and again and it appears being repeated but generally, I think at the close of the day, as much as you document the better."

Quality Assurance professional, male, Ghana, centre three

Three principal investigators and one clinician favoured a risk-based approach, particularly for phase IV trials; however, too few interviewed staff was involved in phase IV trials to permit further investigation of this topic.

"Well time is definitely being lost on various things but I guess deciding whether that is unnecessary is the difficult thing. I mean, I think that there needs to be a risk-based approach to the conduct of trials if one is doing a new vaccine trial. You know vaccine is never been given to people before (...) But on the other hand, if one is doing a phase IV trial of medications that are already in use and one wants to determine non-inferiority of a simpler regime, for instance, then it would not be appropriate to apply exactly the same rigor. And I think that this view is starting to come into trials in Europe that one can take a risk-based approach."

Investigator, male, Kenya, centre one

Over-interpretation was never raised as an issue. However the importance of training and experience in working with the guideline was emphasised.

The informed consent procedure

A third (18/60) of the interviewees, independent of country, position and language-region, mentioned actively that the guideline's requirements for the informed consent (IC) are unimplementable and too

restrictive. Interviewees (25/60) referred to major difficulties with IC, including obtaining written and individual consent, finding impartial witnesses for illiterates or legally acceptable representatives for children, and guaranteeing voluntariness and full understanding of the consent given.

In the perception of interviewees GCP requires written consent from a trial participant which is difficult to apply to a population with a high illiteracy rate and an oral culture, where one's word is highly valued and signatures or thumb prints are associated with police punishment.

"I think the first thing is that we have an oral tradition. And when I have to see someone to ask if he wants to participate in my study, he says 'yes', I say 'okay yes' this is not enough, 'read this paper, and sign it'. I think that this is not traditional for us. It can even happen that this brings trust issues because he doesn't understand why he must sign something he has already agreed. So obviously, this would have to be put back on the table and discussed again one day or another."

Investigator, male, Burkina Faso, centre six

Trial participants in SSA are often shaped culturally by a sense of collectivity. The importance of first obtaining community consent from community and religious leaders was repeatedly stressed.

Fulfilling the GCP requirement of having an impartial witness present for consent of illiterate trial participants can be challenging when too few literate individuals are available or willing to serve as impartial witnesses. This issue was mainly raised in Burkina Faso. To guarantee impartiality, no payment is involved and an eligible impartial witness may be required to serve for several trial participants, potentially jeopardising the independence of the witness.

Moreover, in SSA, documents confirming a child's legally acceptable representative, as required by GCP, may not be available. It is common for relatives to care for a child in place of the biological parents, thus, trial staff struggle to include such children.

According to GCP, IC must be given voluntarily and in full understanding of the benefits and risks of the trial. Ensuring this is challenging when the language of the IC form is highly technical and certain scientific words cannot be translated into local languages. Interviewees suggested treating consent as a continuous task whereby essential information is repeated throughout the trial. The high workload associated with this process, however, caused interviewees to simultaneously question the feasibility of doing so. Trial staff also cautioned that lengthy IC forms reduce comprehension among participants. A few staff members felt that IC served more to protect the sponsor than to inform the trial participant.

"Yes, we must alleviate [the informed consent] because, in practice, we see that all this administration is not for the people, it is for the sponsor. The sponsor does it to be safe, to be within his rights, in case problems happen. So I, personally, say that, the informed consent all that, that's really for the sponsor or investigator, if there is a problem he could say in court, 'I have made this sign, that I will do this!'"

Investigator, male, Senegal, centre eight

Yet, interviewees stressed the importance of IC and asked for clear and applicable guidance in both language-regions. They perceived that GCP does not clarify how to deal with listed IC issues and called them grey areas.

"Is there a better way we can do it? Can we use pictures, can we use diagrams to convey the same message yes, and meet all the essential elements for the consent without having a 20 page document. Is there a better way to do it?"

Investigator, male, Kenya, centre two

While discussing IC difficulties often the role of GCP was addressed. Due to the consent difficulties three interviewees from French-speaking countries wanted a GCP designed especially for Africa to outline a more relevant and realistic IC process. However, most interviewees preferred using ICH-GCP as the globally applied guideline.

"No I do not agree. No. What? Adapted to the context? No. Research must be done the same way in Europe, the USA and Africa. We need to create the same conditions. Do you agree with me? You cannot contextualise GCP, no. That's not research."

Investigator, male, Senegal, centre eight

Oversight of compliance with guidelines

The importance of oversight by national authorities was stressed; this topic came up less frequently compared to informed consent challenges. This oversight seems to be missing according to mainly Burkinabe interviewees, who wished for well-functioning authorities. Some researchers experienced challenges meeting GCP reporting requirements as the local authorities' requirements were less comprehensive. Coherence between GCP and authority requirements was deemed important for increasing the guideline's usefulness.

"And since they [authorities] gave their approval and the study has started, we don't come back to them for information. They do not come to us either, so there is a follow up problem. So it would be good, if reports are made regularly. For them too, that they can follow all we do. It's good that you have given your approval, but you have to follow up. "

Investigator, male, Burkina Faso, centre five

In the English-speaking African countries, some interviewees complained about overcautious surveillance from authorities and having many authorities involved in one trial. Double ethical review from one national EC and from the EC in the sponsors' country was not challenged but interviewees criticized involving additional ECs as e.g. institutional review boards on top. All review committees have different reporting requirements, which can be laborious to navigate, while not adding to the trial quality. One principal investigator in Kenya compared the involvement of multiple ECs in a trial to wearing several bicycle helmets: more does not increase safety. Overcautious oversight also takes the form of overly stringent reporting requirements, e.g. the investigators have to report every serious adverse event (SAE) individually to all national ECs, although the GCP calls only for the sponsor to report suspected unexpected serious adverse reactions (SUSARs). Five interviewees claimed that the authorities would not spot the important issues and miss the big picture in all of the information collected. They perceived it important to align authority requirements with GCP.

3.5. Discussion

Overall, interviewed CT staff in SSA found the GCP guideline very helpful in guiding their daily work and ensuring an international standard (Figure 3). Staff did not complain about unnecessary administration, repetition or unnecessary details. We therefore conclude that GCP is not being applied overcautiously from the perspective of visited CT teams. This finding was observed consistently, independent of the country visited or the staff level of interviewees. The result supports the general opinion that GCP is an appropriate guideline for RLCs (12, 16, 18-20). It contradicts those authors claiming that an adequate and applicable interpretation of GCP was missing in RLCs (17, 19, 21). Indeed, trial staff worried that a more pragmatic interpretation of GCP would compromise quality.

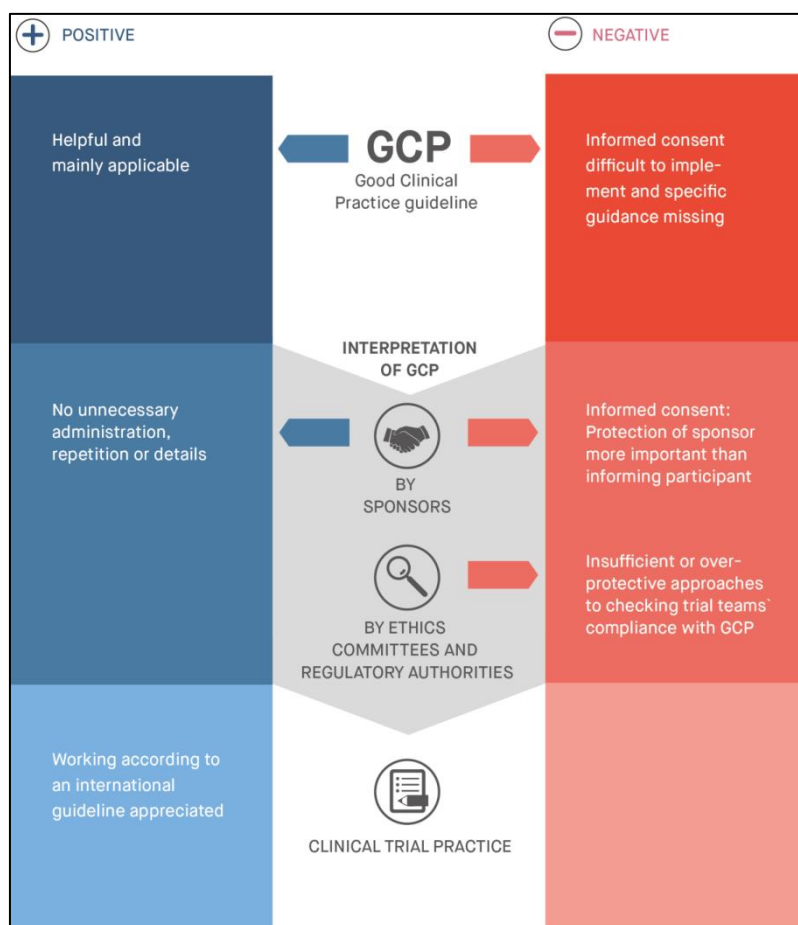


Figure 3 Summary of advantages and challenges of working with International Conference of Harmonization (ICH)-Good Clinical Practice (GCP) in the perspective of trial teams, ©evolve communication gmbh.

Several factors might account for trial teams' positive accounts of working with GCP. Due to limited resources and challenging working conditions, clinical research centres in RLCs may automatically take a more pragmatic approach to GCP implementation compared to Northern countries. In addition, with less exposure to Northern industrial interpretations of GCP, they might be less likely to adopt overprotective practices. Also CT staff might be used to administration and questioning administrative hurdles might not be a priority. Another explanation could be the high frequency of vaccine trials in SSA. Compared to drug trials, conducting vaccine trials is even more complex. Whereas trials in the North are conducted in hospitals and fully integrated into routine work, the interviewees in SSA work in specialised clinical research centres and might be more experienced and skilled in research and in applying the guidelines. Perhaps the guideline does not play an important role in staffs' CT routine; some spoke more about the protocol than the guideline. Health staff coping with high demands of guidelines in difficult working conditions might adopt informal practices in order to deal with their working realities (30). This phenomenon, known as "street-level bureaucracy", could be another reason why trial staff did not complain.

Despite an overall willingness to work with GCP, one third of the interviewees in both language-regions perceived GCP to be unsuitable for the IC process. It surprised us to learn that, in the staff's experience, IC challenges were more pertinent than the administrative requirements. Perhaps it is not so unexpected, as the guideline was developed according to different cultural and educational characteristics of trial participants than those found in SSA. IC difficulties are also mentioned repeatedly in the literature (20, 24, 31, 32). For example, Kalabuanga *et al.* suggest changing the guideline to permit trial-inclusion of children without a legally acceptable representative (33). The

length and technical language of the consent form is a highly debated topic in both the North and South, as is the view that its content serves mainly to protect sponsors (32, 34).

Based on the results and the discussion in the previous paragraph some interviewees seemed unaware that GCP as a guideline allows for an adapted application. For example, GCP does not explicitly require written consent. Hence, if the local law does not require written consent, deviation from the guideline is possible. Also GCP does not forbid providing the participant information by video, comic or tape. Deviations from the guideline for other processes are possible if they are thoroughly explained in the protocol.

Concrete guidance on how to best apply GCP in the face of consent challenges was perceived to be missing by interviewees. We had the impression that authorities were not able to assist trial teams in mitigating their consent challenges.. The forthcoming integrated addendum to the ICH-GCP E6-guideline (13) presents an opportunity to refine the wording here.

The IC chapters in both the AVAREF-GCP and the ICH-GCP are identical, however, in another chapter AVAREF-GCP stresses that IC should be obtained in accordance with national culture(s) and requirements. The South African GCP (the only country in SSA to have its own GCP-guideline) differs from ICH-GCP by requiring both written and verbal IC and by strongly recommending community involvement and consultation with community advisory groups. The South African ethics guideline allows caregivers to consent if the minor does not have a legally acceptable representative (35).

Some topics which were less frequently mentioned should nevertheless not be neglected as they have also been discussed in other publications discussing the applicability of GCP. To maximise GCP's helpfulness, interviewees suggested that national authorities provide adequate oversight and align their requirements with GCP. Authorities in some SSA countries were only recently established, thus capacity building efforts must be on-going and collaboration between sponsor and authorities prior to the study start is important (23). Authorities must be capable of making contextualized decisions (36).

Some trial staff perceived that authorities with substantial experience enforce GCP too rigorously and overprotective. For example, comprehensive reporting of SAEs to authorities is not required by GCP but according to interviewees required by the authorities, which leads to higher workloads for trial teams and an unmanageably amount of safety data for the ECs (37). J. Sing criticises the overprotective requirements of South African authorities and asserts that although authorities act with good intention, they end up punishing the trial participant (38). The lack of experience, resources and ability to decide on context-adapted application of these authorities could be the reason for this over-protectionism which is driven by the good intention of protecting the participant. An additional challenge for national authorities is that they must comply with health laws, which are often out-dated in SSA and may not include GCP. There are promising initiatives such as the African Medicines Regulatory Harmonization Program, which aims to harmonise medicines regulations (39).

There are some limitations to this study. Although our research covered various geographical and language regions, findings might not be true for all clinical research centres in SSA as the sample size was small due to the qualitative approach. Data was collected by a female, Swiss scientist, which might have contributed to a degree of bias, since monitoring and auditing visits are often carried out by foreigners. Another limitation is that we do not know the extent to which CT teams follow GCP in practice, since the study was interview-based and processes were not checked. We deliberately avoided testing the interviewees' GCP knowledge because we wanted to provide an environment conducive to open expression. These limitations are somewhat mitigated by the fact that all centres visited have long-standing experience and have been repeatedly monitored and audited.

3.6. Conclusion

According to the interviewed trial teams, GCP is a helpful and important guideline for working in challenging environments. One third of the interviewees found the application of GCP for informed consent to be challenging. Overall, GCP is perceived to be efficiently applied and appropriate. Applying GCP in an adapted manner and using the flexibility offered by the guideline might help to avoid consent challenges in future.

3.7. Acknowledgment

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4. “You can save time if...” - A qualitative study on internal factors slowing down clinical trials in Sub-Saharan Africa

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4.1. Abstract

The costs, complexity, legal requirements and number of amendments associated with clinical trials are rising constantly, which negatively affects the efficient conduct of trials. In Sub-Saharan Africa, this situation is exacerbated by capacity and funding limitations, which further increase the workload of clinical trialists. At the same time, trials are critically important for improving public health in these settings. The aim of this study was to identify the internal factors that slow down clinical trials in Sub-Saharan Africa. Here, factors are limited to those that exclusively relate to clinical trial teams and sponsors. These factors may be influenced independently of external conditions and may significantly increase trial efficiency if addressed by the respective teams.

We conducted sixty key informant interviews with clinical trial staff working in different positions in two clinical research centres in Kenya, Ghana, Burkina Faso and Senegal. The study covered English- and French-speaking, and Eastern and Western parts of Sub-Saharan Africa. We performed thematic analysis of the interview transcripts.

We found various internal factors associated with slowing down clinical trials; these were summarised into two broad themes, “planning” and “site organisation”. These themes were consistently mentioned across positions and countries. “Planning” factors related to budget feasibility, clear project ideas, realistic deadlines, understanding of trial processes, adaptation to the local context and involvement of site staff in planning. “Site organisation” factors covered staff turnover, employment conditions, career paths, workload, delegation and management. We found that internal factors slowing down clinical trials are of high importance to trial staff. Our data suggest that adequate and coherent planning, careful assessment of the setting, clear task allocation and management capacity strengthening may help to overcome the identified internal factors and allow clinical trials to proceed more efficiently.

4.2. Introduction

Clinical trials are essential for medical advances as they provide the highest degree of evidence to support new interventions and decisions about disease management. However, the conduct of clinical trials is very complex; people are exposed to potential health risks and vast quantities of data are collected. Professionals working in clinical trials are confronted with numerous regulations, ethical challenges, high workloads and administrative requirements. Over the years, the costs, complexity, legal requirements and documentation associated with clinical trials globally has risen constantly (1-3), however, the added value of these changes in terms of increasing the quality of clinical trials remains unknown (4). This trend stands in sharp contrast to current efforts to make health systems more productive.

Working conditions are even more complex for clinical trials conducted in resource-limited settings. This paper focuses on Sub-Saharan Africa (SSA), where limited infrastructure, human resources, experience and ethical challenges may especially affect the efficient conduct of clinical research. The topic of efficient trial execution is of particular importance in these settings as the number of clinical trials carried out in SSA is rising (5, 6) while funding and the number of qualified health staff remain limited. In 2014, the total annual funds available for neglected disease medicines development was USD 3,377 million in (7); in the same year, the estimated cost to the pharmaceutical industry of developing one new prescription medicine to the point of marketing approval was USD 2,558 million (8). Increasing efficiency in trials would allow more trials to be conducted with the limited funds available. This in turn has important implications for public health in resource-limited settings, where trials are urgently needed to develop new safe and effective health interventions (9).

Increased efficiency in clinical trials would not only reduce costs, but also lead to more productive work settings with manageable workloads and requiring less time to perform a trial. The International Conference of Harmonization's Good Clinical Practice (GCP) Guideline E6, the most widely accepted standard for the conduct of clinical trials, is currently being amended for the first time since its introduction in 1996. The main reason for the addendum in preparation is "the encouragement of implementation of more efficient approaches to clinical trial design, conduct, oversight, recording and reporting" (10). By increasing efficiency for clinical trials in SSA, we do not mean to lower the standard for these trials, but to identify and manage factors which are currently slowing down trials.

There is little scientific evidence to show that the procedures for clinical trials are carried out in an efficient and cost-effective way (11). The few publications addressing the conduct of clinical trials in resource-limited countries are mostly reflections on past trials. These publications are not directly reporting on factors slowing down clinical trials, but list general challenges. A particular challenge reportedly associated with clinical trial delays is the lengthy regulatory and ethical review process (2, 12-14). The complexity of the latter is compounded by multiple ethical reviews and communication gaps between the committees and authorities (12, 15). Promisingly there are developments towards a better collaboration and joint reviews between these bodies; the WHO-supported AVAREF (African Vaccine Regulatory Forum) platform was founded to support multi-national vaccine trials, but also was instrumental in the acceleration of clinical trials during the Ebola crisis (16). Other reported challenges include the often poor and/or illiterate study participants and differing cultural values and beliefs (6, 17). These populations, for whom research is an unfamiliar approach, may be highly sceptical about participating in a trial; for some, trials may offer the only access to treatment, which of course raises ethical questions (6, 18). Together, these factors can lead to recruitment, consent and follow up difficulties, which slow down trial progress (6, 15, 19). Inadequate infrastructure, particularly in rural areas, may affect clinical work, communication, access and the availability of basic refrigerated medicines, which together may also considerably slow down trials (19, 20). The aforementioned challenges can be categorised as external factors, as they are the given conditions of the framework in which clinical trials operate in these settings.

In this manuscript, we focus on those factors that slow down trial progress and that exclusively relate to clinical trial teams and sponsors, defined here as internal factors. Such factors may be influenced independently of the external conditions, if the challenges are known and the parties are aware of them. Only a few published reflection papers mention such internal factors affecting clinical trials in

SSA and most of the factors described were of general importance and not particularly targeted to the time component of trials. For example, brain drain and inadequate budgets were described as internal challenges in vaccine trials in Africa (6). The authors noted that investigators were often frustrated about their small scientific output and recommended more cooperation among stakeholders.

Experiences from the Gambia pneumococcal vaccine trial demonstrated that human resource management was very time consuming (21). The same authors identify lessons learned, citing the importance of a quality management plan, of documenting roles and responsibilities of collaborating groups and of on-site supervision including feedback to each staff member. They also stressed the need for senior staff to create a strong team spirit. Adequate planning, including assessments of available resources, was considered indispensable. To the best of our knowledge, apart from these reflection papers, there is only one research study on this topic. A qualitative study focusing uniquely on investigator-initiated trials in Ethiopia identified internal challenges such as limited learning opportunities (which negatively affects human resources), lack of recognition and career options, lack of experience, poor planning and problems with trial management (14). In other reflection papers, high administrative requirements resulting from a conservative interpretation of guidelines and regulations were blamed for increased duration and costs of trials (2, 22). In contrast, own research found that clinical trial teams in SSA do not perceive the administrative requirements as slowing down the trials but rather considered them essential for ensuring quality (Vischer *et al.* submitted).

A lack of data on the operational aspect of trials was stated in the literature (21, 23) and, to our knowledge, no publication has specifically investigated how efficiency could be increased internally in trials. By identifying internal factors that slow down clinical trial progress, we take a first step towards increasing efficiency and achieving more resource-effective trials. Compared to external factors, internal ones may be easier to influence, manage or eliminate. Trial teams have an important role in overall trial success and are faced with complex trial processes on a daily basis. Hence, they were considered an important source from which to gain valuable insights into the challenges to and opportunities for increasing the efficiency of trials. The aim of this study was to investigate internal factors slowing down clinical trials by giving a voice to trial teams in SSA. Our focus was strictly on clinical trials in SSA, excluding trials involving contract research organisations (CROs).

4.3. Methods

Study setting

Qualitative data were collected in clinical research centres in Kenya, Ghana, Burkina Faso and Senegal. These four countries were selected in order to compare results between different language and geographical regions. All four countries strongly contribute to health research in Africa. We contacted all major clinical research centres specialising in poverty-related diseases and with a track record of completed clinical trials (no more than four such centres could be identified per country). In each country, we conducted our study in the first two research centres to agree to our visit. We visited both rural and urban clinical research centres. The names and detailed locations of the centres have been purposely withheld to allow participants to remain anonymous.

Sampling

At the centres, interviews were open to all investigators, study coordinators, clinicians and quality assurance professionals with at least six months of experience in clinical research. The different organisational levels were selected to enable data triangulation. For each centre, the sample was drawn with the assistance of a senior clinical trial staff member, who approached eligible participants and informed them about the study. Nobody refused participation but six trial workers were unavailable for interview due to time constraints during our visit (see Fig 1). In one centre, six participants asked to be interviewed in groups of two. These interviews were conducted, transcribed verbatim and the findings were in line with the overall result but ultimately the data were excluded to avoid a possible bias.

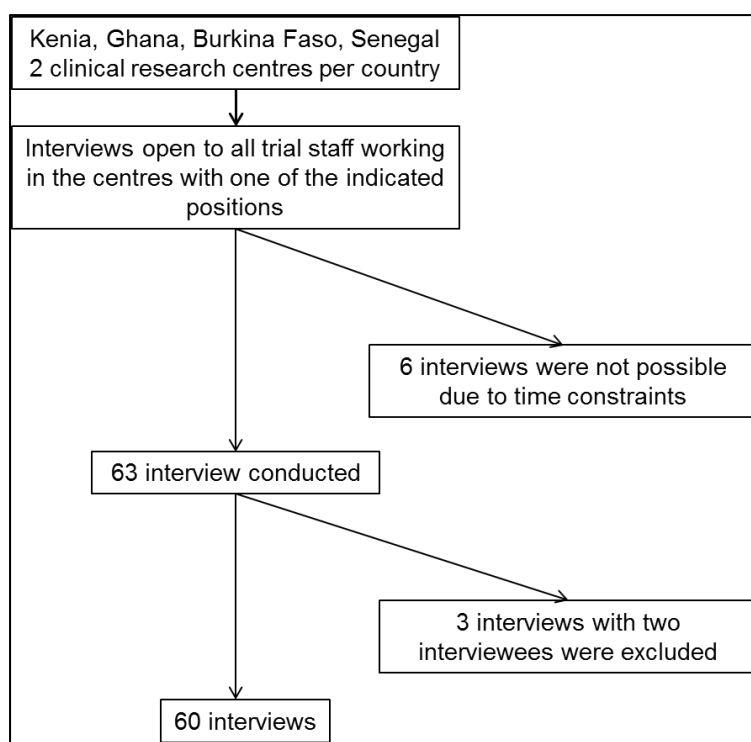


Figure 4 Sampling procedure

Interviews

A semi-structured interview guide (see S1 Text) with open-ended questions was used to encourage participants to describe their own understandings and opinions and to allow identification and exploration of themes and hypotheses that might not have been anticipated. The interview guide was developed by an interdisciplinary team based on a literature review and preliminary interviews with clinical research professionals. The interview guide was pre-tested outside the study area and later developed iteratively as data emerged. The guide was used with flexibility and included general questions about quality, challenges and perceived inefficiencies in clinical trials. Interview questions did not target experiences in a specific trial but rather the participant's trial experience in general. In Kenya and Ghana, interviews were conducted in English. After translating the guide into French (including back-translation and revision of terminologies), interviews were conducted in French in Burkina Faso and Senegal. Data were collected by NV alone in Ghana, together with ML in Kenya and together with AJ in Burkina Faso and Senegal, between April 2014 and September 2015. The interviews took place in a private room of the clinical research centre. Summaries and observations were written down by the interviewer directly after each interview. Saturation of information was reached when few or no new concepts were raised (24). Additional data, unstructured observations and informal conversations with external monitors, who were on-site during our visit, were collected and recorded in a field diary.

Data management and analysis

All interviews were transcribed verbatim. NV reviewed the English and AJ the French transcripts and original recordings. Data were grouped according to the interviewees' responsibilities and countries. Thematic analysis was conducted as per Braun and Clarke 2006 (25) using MAXQDA 11. English and French transcripts were analysed in their original language. After repeated readings of the transcripts, initial coding was performed. The analysis focused on internal factors perceived as slowing down clinical trials. Notes were taken during the analysis to ensure that analysis was reflective. Themes that emerged from the subsequent data interrogation were tested in further interview analyses. Similarities, differences and patterns were identified across the interviews before finally defining and naming themes.

Ethical considerations

Ethical review exemption was obtained from the Ethics Committee of North-western and Central Switzerland (EKNZ) and from the Pharmacy and Poisons Board in Kenya (Ref. No. PPB/ECCT/Misc/2015(79)), based on the reasoning that the research project did not involve access to or collect private, sensitive or health-related data or materials. The ethics committees in Ghana, Burkina Faso and Senegal were asked to grant an ethical exemption but their statutes do not allow for such exemptions. Therefore, we applied for and received full ethical clearance from the Ghana Health Service Ethical Review Committee (GHS-ERC: 18/09/14), the Comité d'Éthique sur la Recherche en Santé in Burkina Faso (N 2014-11-131) and the Comité National d'Éthique pour la Recherche en Santé in Senegal (n12/MSAS/DPRS/CNERS).

An information sheet about the study was given to the participants prior to the interview. We explained the objective and background of the research project and informed them of their right to leave the study any time. Anonymity and confidentiality were guaranteed, thus no study centres and names are disclosed in the paper. Written consent was obtained in Ghana, Burkina Faso and Senegal. In Kenya, audio recorded oral consent was sufficient as the study received ethical review exemption. A copy of the consent form, including contact details of the interviewer, was given to the participants. All participants agreed to be audio recorded during the interview, which averaged 45 minutes.

This study adhered to consolidated criteria for reporting qualitative research (COREQ) (26).

4.4. Results

Study participants

A total of 60 clinical trial staff participated in the key informant interviews. Thirteen to seventeen interviews were conducted in each country (see Table 2). Saturation of information was reached as little or no new concepts were raised after the first 11 interviews in each country.

Table 2 Characteristics of participants

		Kenya (n = 17)	Ghana (n = 13)	Burkina Faso (n = 16)	Senegal (n= 14)
Role in trial	Investigators (n=28)	8	4	8	8
	Study coordinators (n=17)	5	6	3	3
	Clinicians (n=10)	3	2	3	2
	QA professionals (n=5)	1	1	2	1
Gender	Female (n=20)	9	4	3	4
	Male (n=40)	8	9	13	10

Most participants had been involved in commercial and non-commercial drug and vaccine trials (see Table 3). Participants had between 10 months and 15 years of working experience in clinical research.

Internal factors slowing down clinical trials

Table 3 Participants` experience of working in clinical trials

		Kenya	Ghana	Burkina Faso	Senegal
Clinical research experience	0 to 2 years	1	4	2	1
	3 to 5 years	2	3	4	2
	6 to 8 years	6	0	5	3
	9 or more years	8	6	5	8
Study phase	Phase I (a or b)	10	3	10	3
	Phase II	12	3	13	4
	Phase III	13	10	13	8
	Phase IV	4	7	9	3
Type of trial	Drug trial	15	8	16	11
	Vaccine trial	14	10	13	9

Themes

We identified several internal factors that are perceived to slow down clinical trials. The two overarching themes were:

- (1) planning (comprising the main issues poor planning and missing context-adaptation) and
- (2) site organisation (comprising mainly high staff turnover and workloads)

Planning

Clinical trial staff, independent of country and position, repeatedly stressed the importance of the planning phase for clinical trials. More than half of all respondents (41/60) stated that in order to be more efficient, enough time should be allowed for planning. In their experience, things that were not thought through in the planning phase led to lost time during the trial. Staff frequently mentioned that they lose time in their trials due to poor planning.

“Sometimes so much does not go into planning. If you really would spend so much time in planning, it would be a lot easier. So if you plan a lot regarding processes, procedures in the study then you wouldn’t have to rush or you wouldn’t have to make some mistakes because you have duly planned, so it is sometimes a bit challenging when you’ve not really planned so well. Then that is where much of the problem is.”

—Study coordinator, male, Ghana, centre two

Various planning sub-themes were frequently discussed such as budget feasibility, clear project ideas, realistic deadlines, understanding of trial processes, context adaptation and involvement of site staff in planning. They were mentioned to the same degree across the different professional levels interviewed.

Budget feasibility

Seventeen participants, mainly from the French-speaking countries, mentioned that budgets were not carefully developed in the planning phase and were based on unrealistic or incorrect assumptions. Interviewees said that trials in Africa are expensive due to additional associated costs like community engagement, electricity and the trial participants’ health care. Under-budgeting was perceived to slow down trials by either stopping the trial completely or by distracting site staff during the trial with budget discussions or with applications for new funding sources. According to the interviewees, diligent

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elaboration and thorough discussion of the budgets in the planning phase would help to save time once the trial is in process.

“Often people are mistaken in the estimate, because they have not budgeted these things, because they have not thought about this before. And often Europeans say, yes it’s expensive, you ask too many things. No, because the environment is different, this has to be considered.”

—Study coordinator, male, Senegal, centre one

Clear project idea

Five respondents from French-speaking Africa mentioned to lose time because of changes to the project by request of the sponsor during the project process or implementation phase. One Burkinabe clinician asserted that sponsors should develop a clear view of the project goals and approaches in partnership with the sites. Such an approach would avoid time losses due to amending the project according to the sponsors’ new ideas during the production phase.

Realistic deadlines

In nine interviews, participants suggested that unrealistic deadlines defined in the planning phase slowed down clinical trials. Trial staff mentioned that sponsors push to have the first trial participant enrolled as early as possible, although the deadline might be unrealistic. Starting a trial without being fully prepared increased the probability of making mistakes during the trial conduct. Such mistakes required adjustments to be made and were time consuming to resolve. Common pitfalls leading to misestimating timelines were ignoring the long approval process and being too optimistic when calculating recruitment rates (a phenomenon commonly known as Lasagna’s Law). Deadlines of great importance to the sponsors were often unrealistic to achieve and forced trial teams to rush during preparation, creating extra burdens.

“So it is that at some point you may, for example, start when you are not sure that everyone is ready. But you must start with the team and then train people in the study. This only lengthens the time of the study.”

—Investigator, male, Burkina Faso, centre one

According to interviewees, if the deadlines were realistic, the long waiting time before approval is granted could be used more efficiently. A study coordinator described the centre’s positive experience of using this long waiting time for diligent trial preparation. According to her, without making use of the waiting time before approval, the site would have experienced all sorts of problems later on. On a different level, two investigators complained that the negotiation processes to establish the contract between the trial site and the sponsor frequently delayed the trial start.

Understanding of trial processes

Providing sufficient time for every team member to understand the protocol, as well as their role and responsibility in the trial, was perceived to be crucial. The idea came up mainly in Kenya and Senegal (17/60). The importance of joint team meetings to go through every step in detail and anticipate possible challenges of the trial was also stressed. Interviewees reported that elements that had not been anticipated and pre-discussed in the preparatory phase would slow the trial down later. Five staff members shared with us the benefits they experienced from conducting a test run with a dummy participant to practice all trial steps and identify hiccups prior to the start of the study.

“I think we do not put people enough in the situation of a real life trial before starting a clinical trial. We think that because we are doctors, we will know how to do that. It is not that simple.”

—Study coordinator, female, Senegal, centre two

Context adaptation

Adapting the project to the setting was reported to be the single most important consideration that was often neglected during planning. The importance of context adaptation or the challenges of unadapted trials came up frequently (28/60) across different staff levels and countries, but was raised somewhat more frequently in the French-speaking countries. Staff defined adaptation as ‘adapting the project to the participants’ culture and values as well as to the health system, site specific procedures, seasonal conditions and the human and infrastructural resources available’. Respondents suggested checking, for example, if the equipment was available for certain lab tests or ensuring that the trial was as uninvasive as possible due to participants’ fear of having blood drawn. According to interviewees, unadapted studies were the result of Northern sponsors’ unfamiliarity with the local context. A frequent claim was that sponsors still assumed that all of Africa was the same and were not aware of the different realities in different countries or regions. This misperception resulted in great efforts during implementation to correct for, efforts which could have been saved if the project had been adapted to the setting from the outset (during the planning phase). In one respondent’s experience, protocols that are both unadapted and stringent were very difficult to implement and often resulted in multiple protocol deviations.

“I would tell you to try to really adapt to the realities of the countries. Because if you give us a typical European protocol that has to be reproduced here, I think we are going to have problems. We do not have the same manner of working. We do not have the same tools to work with. So it might be important to really see what is feasible in the country (...) If not, you will have many, many deviations afterwards, because we were not able to do that. We would need all the time to document why we were not able to do that because we did not have the lab to do this test or that test.”

—Study coordinator, female, Burkina Faso, centre five

“It is challenging working with people [when] they don’t have experience with this type of setting”

—Investigator, female, Kenya, centre two

Interviewees appreciated feedback meetings with sponsors to discuss challenges of previous trials to avoid repeating mistakes in upcoming trials. A Ghanaian clinician highlighted her positive experience of adapting the protocol to the site in a multicentre trial, a difficult task as all sites work along the same protocol, despite differing contexts.

“If there is a protocol for about seven different African countries to run a trial in every country it’s reviewed in (...) the scientific review committee (...) it’s also adapted to how we run our system, some parts are adapted. So what I know is that, in all the various countries we have one parent protocol but in the protocol we are allowed to make adaptations to suit our health system, then it becomes a workable protocol.”

—Clinician, female, Ghana, centre one

Involvement of site staff in planning

Involving local clinical trial staff in the planning process was, for many respondents (35/60), the best way to ensure that the trial is adapted to the local situation as local staff is most familiar with the context. The topic was raised across all staff levels but with higher frequency in the French-speaking countries.

One Burkinabe clinician stated that all the time spent adapting the trial to local practices and conditions could be saved if the trial staff were involved in the planning phase. Interviewees mentioned that local trial staff would help to identify unadapted processes as well as risks, difficulties and redundancies. Respondents suggested developing local risk management plans. For many interviewees, involving site staff in the planning also means involvement in protocol development. More details regarding site staff’s involvement in protocol development will be reported elsewhere (Vischer *et al.*, forthcoming). However, the notion as discussed here included planning and implementation in general.

Internal factors slowing down clinical trials

“There are studies (...) that people have designed together, people were involved in writing, it makes that this loss of time on the field is not felt. But when it is, like for example firms, I will not mention names, that send their protocol and say ' this is what we want, this is the information we want you to collect ', this is when the losses of time happen.”

—Clinician, male, Burkina Faso, centre two

In contrast to the statements above, six interviewees were satisfied with their degree of involvement in the trials` planning. They argued against more involvement as they perceived that it would be impossible to foresee every risk, even for trial staff, and that the involvement would add too much work. Three of the six interviewees were from the French-speaking countries and held high ranking positions. However, there was no consensus within the centres as other interviewees from the same centres complained about the lack of involvement.

Site organisation

The theme of site organisation incorporates topics such as staff turnover, employment conditions, career path, workload, delegation and management. All of these topics were mentioned as factors slowing down clinical trials.

Staff turnover

In 19 interviews, high staff turnover was mentioned as a major internal challenge contributing to losses of quality and time. All but two clinical research centres (in Senegal) perceived staff turnover as a limitation. Interviewees reported that former staff left for other clinical research centres, contract research organisation and positions abroad. Only one interviewee regarded circulation of staff as positive and healthy and said that employers had to accept that they train staff for others. The majority (33/60) stressed repeatedly the importance of experienced and qualified staff for guaranteeing good quality, avoiding mistakes and inefficiencies as well as for supervising inexperienced staff, indicating the negative influence of losing experienced staff. Finding qualified and experienced staff is challenging due to the lack of health professionals in SSA, according to respondents. As the conduct of clinical trials is not part of basic health professional training, great efforts are made to train new staff in research concepts and to prepare them for the strict working environment.

“In our daily practice, what makes us waste time is especially the repetition of staff training.”

—Investigator, male, Burkina Faso, centre one

“So when you have very experienced people leaving, that can cause a very great challenge.”

—Investigator, male, Kenya, centre two

Employment conditions

One stated reason for high staff turnover was that staff was hired temporarily and if there was no subsequent trial in the centre, the employee had to leave to find new employment.

“You recruit people, you train them for temporary employment (...) The drug trial, maybe it will not exceed eight months. After eight months, you are not sure if you keep the person (...) He goes somewhere else or he will look for something. You're going to work on another project; you will find other people who perhaps will be taken away elsewhere. And there is staff turnover. We, as such, we are in the institution, we are working for the institution, there is no problem. But the support staff is renewed all the time. And that doesn't help. If we had permanent staff, I think, with time they will acquire some experience and it will also allow them... there will be mistakes they won't make anymore.”

—Investigator, male, Burkina Faso, centre one

A few interviewees expressed dissatisfaction working in clinical trials because of the many routine tasks, the very strict working environment and the need to work under high pressure. The resulting low staff motivation prevented efficient trial conduct.

Career path

High staff turnover was also attributed to lack of recognition and career prospects in clinical research. A Kenyan investigator said that after having worked in a position for a while, you want a promotion, but instead you stay in the same position for many years. The need for a career path for clinical trial professionals came up in six interviews. Poor career prospects were seen as contributing to staff leaving for salary reasons as soon as they had gained enough experience. The better-paid jobs were often outside of SSA, contributing to brain drain. Due to the sensitivity of this topic, it was only mentioned when the interviewers actively asked participants in a follow-up question to give reasons for high staff turnover rates.

Workload

Related to site organisation, interviewees perceived high workloads as another major factor slowing down clinical trials. With a lot of emotion, respondents (23/60) reported that the high workload was an enormous challenge for them. Overloaded staff sadly reported that they had lost their social life, had not had holidays for five years, or were involved in eight studies at the same time, for example.

“That is to say, you can work 24 hours 7 days a week without even having time to eat or sleep. It is difficult, but I am used to it today. I’m used to it. Even at 2 am you wake me up, I’ll do what is required.”

—Investigator, female, Burkina Faso, centre one

Independent of their position, we interviewed overloaded and stressed staff members in each country. We identified them by their statements or by their difficulty of finding time for an interview while we were there. In contrast to the interviewees that were constantly overworked, other interviewees were not overloaded or less so, particularly in centres without on-going trials. A female Senegalese study coordinator summarised this situation as follows: “Sometimes there is a rush and sometimes there is not much going-on in the centre”.

Participants shared ideas for reducing the high workload and associated time losses. Firstly 10 interviewees, mainly from rural research centres, suggested hiring more staff in order to distribute the workload among more staff members. However, they knew that this was challenging due to a lack of qualified personnel and little interest in working in rural areas. Secondly, a few interviewees, mainly from one centre, suggested distributing the trials more evenly throughout the year instead of, for example, only focusing on malaria trials, which all take place during the rainy season. Thirdly, four interviewees suggested setting realistic deadlines to avoid a constant sense of urgency. Lastly, their strongest suggestion for reducing high workloads was to assign clear roles and responsibilities for everybody involved in the trial. They indicated that good trial coordination would enable fair sharing of the workload and ultimately save time. All interviewees shared the opinion that delegation helped to guarantee a manageable workload.

“So that’s it. There is the project manager, there is the research assistant and there is the technician of study. The work is divided. There is not a too high workload.”

—Clinician, male, Senegal, centre two

Interviewees mentioned that clinical trial responsibilities are concentrated among investigators in addition to their medical and scientific tasks, which adds work to their already overloaded schedules and consequently leads to delays. Hence, delegating tasks is particularly important to relieve investigators. This observation was reported mainly in the French-speaking countries. Table 4 shows that a study coordinator position (or similar role) hardly exists as a single role in these countries and, thus, investigators often have a double responsibility as study coordinators.

“You can save time if for each investigator you put a study technician who helps him. This is not done here.”

—Investigator, male, Senegal, centre two

Table 4 Additional or parallel roles in trials

	Kenya	Ghana	Burkina Faso	Senegal
Investigators (in addition): study coordinator (n=4)	-	-	3	1
Investigators (in parallel): lab manager (n=2)	-	-	2	-
Study coordinators (in parallel): lab manager (n=3)	-	-	1	2

Management

Interviewees reported that clinical research centres required management to avoid challenges associated with slowing down clinical trials. This overarching topic was not reported as frequently (7/60) as the more specific ones like high staff turnover and workload but good management was seen to influence and even prevent the latter ones. For example, the elimination of gaps between trials was considered to be a management task and would reduce staff turnover rates. This issue was particularly raised in centres focusing on seasonal illnesses like malaria. Other important managerial aspects mentioned were negotiating and budgeting skills. Particularly for discussions with the sponsors, such skills were regarded as essential to defend the budget, for example. Good coordination, including good staff coordination and the creation of a team spirit, was considered to be primarily a management task.

A few interviewees suggested having centre managers to facilitate trial conduct in a reasonable timeframe through responsibilities for acquiring new projects, ensuring staffing, maintaining budgets and communicating with the sponsor. One investigator compared her centre with another one as follows:

“They have a manager and you know that helps a lot. And for us, I see us going that way because the more you do many multiple studies at the same time you just can’t keep on doing it the way we have been doing it where the PI or the main physician is burdened with all those details.”

—Investigator, female, Kenya, centre two

Another idea for improving institutional management skills was to educate investigators in management.

“So that’s all these skills that you need to have, not only clinical expertise, lab competence, but also the competence of management.”

—Investigator, male, Senegal, centre one

The management topic was mainly raised by high ranking staff members working in the French-speaking countries.

4.5. Discussion

To the best of our knowledge, this is the first study to investigate internal factors slowing down clinical trials in SSA. The literature on the topic is scarce and mainly focuses on external challenges like the lengthy approval process, which is often described as a major cause for delays in clinical trials (2, 12). We identified several internal factors (factors only relating to clinical trial teams and sponsors) that were perceived to slow down clinical trials; we summarised them according to two themes, “planning” and “site organisation”. Based on our results, we argue that trial efficiency could be increased by tackling these internal factors.

It surprised us how clearly and consistently these two themes emerged from the interviews, independent of position and country, and also how often internal factors slowing down clinical trials were mentioned in general. The openness of the qualitative approach allowed for in-depth exploration and enabled respondents not only to list challenges but to elaborate on possible solutions as well. Interviewees presented several solutions which would not have been possible with a closed questioning format. Factors inhibiting efficiency were often associated with a decrease of quality, indicating that improving “planning” and “site organisation” might increase trial quality as well as efficiency.

It was striking to note the frequency with which poor planning came up in interviews as a factor slowing down clinical trials. In drug development, speed is considered imperative because of very high costs and frequent competition. As a result, sponsors and funders pressure teams to meet tight deadlines. However, trial teams see this practice as actually resulting in time losses, which contradicts the general view that applying pressure increases efficiency. Our observation is, however, in line with Senge’s Law of Systems Thinking, which states that “faster is slower”. Senge warns against the temptation to advance at full speed without caution, since every system has its own unique and optimal speed and a fast fix often leads to a slow cure (27). J. Brock-Utne reports on his clinical research experience and highlights that “before you embark on your question you must prepare well, which will take much longer than you think” (28). The result is further supported by literature stating that intense planning in clinical trials is particularly important in resource-limited settings (15, 23, 29). The process map available on the global health network webpage shows that planning clinical trials is important and lengthy (30). The forthcoming three process map steps are in line with our findings: I) the importance of having a clear project idea and one single question; II) the importance of realistic trial costing and secured financial support, additionally this point is supported by other authors who discuss the difficulty of predicting budgets due to unstable currency, for example, and who complain about the limited flexibility of sponsors over budget (6, 12, 23); and lastly III) the importance of meetings of study staff in order to understand and discuss every trial step before the trial. Our study participants requested very clear instructions and exchange. The GCP-guideline does not specifically require standard operating procedures (SOPs) for investigators, however, SOPs supported by study specific working instructions might mitigate this concern. In addition, we argue that having a checklist for every trial-specific step, once the trial participant is on site, would be useful for staff and ensure uniformity of how tasks are performed. The newer trend of assessing risks in preparation of a clinical trial (31) might be an ideal way to improve planning and to set more realistic timelines in such complex working environments.

Interviewees particularly stressed the importance of adapting the trial to the context during the planning phase. A possible explanation is that trials in SSA have often had Northern sponsors who might not be familiar with or ignore setting differences. The literature confirms trial staff opinions that adapting projects to the context prevents time-consuming errors and challenges along the way (6, 19, 32). Challenges of unadapted trials were reported more often in the French-speaking countries. This could be the result of increased language barriers, as protocols and communication with sponsors are often in English. Our data suggest that sponsors should thoroughly inform themselves about local contexts, carefully assess the framework and inquire about what went wrong in previous trials. We argue that this would allow sponsors to develop innovative strategies for the respective settings.

Respondents suggested involving the local staff in planning to increase trial suitability. It is a particularity of clinical trials that the investigator (i.e. the site) and the sponsor have clearly defined roles (33). The sponsor’s role is very prominent and limits the influence of the investigator / research site on decisions about the design and conduct of trials. In turn, the sponsor is expected to thoroughly understand the capacities, limitations and requirements of the site to carry out the project. There is evidence in the literature about the advantages of having involved local trials teams in SSA (15, 34). A recent publication on lessons learned in Ebola trials reports on the importance of having foreign researchers engage with appropriate local stakeholders at the earliest stage possible (35). Systems

thinking stresses that stakeholders will know what problems are most likely to arise and stakeholder should be involved from the beginning (27). The transboundary research principles of the Commission for Research Partnerships with Developing Countries (KFPE) recommend setting the agenda together with stakeholders and to interact with stakeholders (36). Particularly local staff's input on recruiting and following-up participants can potentially speed up trials (20) while adaptation to the site's procedures and routines accelerates the implementation of the trial. We are aware that extensive site staff involvement is not feasible for multicentre trials but we are of the opinion that having at least one staff member per site involved in the planning process is important to account for different settings (23, 37). It would then be the responsibility of this staff member to seek inputs from the rest of the team.

The second theme to emerge was "site organisation" and included staff turnover, employment conditions, career path, workload, delegation and management. Interviewees were highly affected on a personal level by human resource challenges like high staff turnover and workloads, which might explain the frequent reporting of this topic. Staff turnover is often a challenge where financial incentives (38) and lack of job security (15) are prevalent. Consistent with Angwenyi *et al.* interviewees perceived experienced staff as crucial for the supportive supervision of and as role models for the many inexperienced staff (29), indicating the challenges of losing experienced staff. Staff turnover is generally a challenge in health facilities in resource-limited settings as it is associated with increasing workloads, lowering the quality of services, reducing team efficiency and causing a loss of institutional knowledge (39). The missing career path of African clinical scientists is mentioned throughout the literature (5, 6, 11-13). In addition, clinical scientists do not have a high status (11), which discourages professionals from entering this career (5, 12, 14). Usually, only the principal investigator's name is visible and recognition of the rest of the trial team is absent (40). Whitworth *et al.* argue that the lack of career paths to attract and retain good researchers is the most serious impediment to health research in Africa (41).

A few interview partners directly mentioned the importance of management in order to save time in clinical trials. We argue, in turn, that all site organisation factors slowing down clinical trials are influenced by management. The WHO stresses the need for management in the health sector, including management of volume and coverage of services, resources (staff and budgets) and external relations and partners (42). Accordingly, building a portfolio, preferably going beyond a single disease, is crucial for the sustainability of a trial centre (15). This is a management task that could decrease staff turnover by guaranteeing permanent positions and a balanced workload. Cutts *et al.* confirmed the importance of management and noted that it takes up a large proportion of time in clinical trials (21). This opinion is shared by the 2014 report of the European and Developing Countries Clinical Trials Partnership (EDCTP) on capacity development for clinical research in SSA, which recommends to go beyond scientific issues and to address managerial skills (43). Whitworth *et al.* recommend providing institutional support for management of research centres (41) and the Council on Health Research for Development (COHRED) more specifically recommends improving the contract management capacity of these institutions (44). Our data suggest that management should focus on winning staff commitment, creating an area of expertise and using human resources optimally by allocating clear tasks to appropriately trained and suitably qualified professionals.

The issue is generalisable and lack of management has been described as a common challenge in health systems in resource-limited countries (42, 45). At the same time, increasing evidence shows that good management practices can generally improve health system performance by increasing institutional incomes and patient satisfaction levels, among other things (46, 47). Health professionals, including clinical researchers, are not trained in management and we support the implementation of management training to improve both institutional management skills as well as career prospects. To improve management, WHO recommends classroom or online training courses and the inclusion of basic management concepts in the training programmes of nursing and medical schools (42). Effective on-the-job methods for improving management also exist and include learning-by-doing and action-learning through regular supportive supervision of high level managers or twinning between similar

organisations in developed and developing countries, for example (42). Clinical trials and long-term partnerships may offer room for such training opportunities.

With the exception of quality management plans and documenting responsibilities of collaborating groups, neither of which came up in our interviews, our study confirms all of the factors slowing down clinical trials as mentioned in the few reflection papers on the topic.

We found that similar challenges in the conduct of trials exist in the North and South, such as high staff turnover (48), poor career prospects (49) and a lack of management (37). McMullen *et al.* explained differences in recruiting performance of sites conducting complex intervention trials in a Northern setting and yielded results similar to ours (50). They report that centres with good recruitment rates were characterised by strong leadership and by good relations between management and staff and among staff. Support and time for implementation, appropriate division of roles, stable staff, and consideration of site-specific characteristics and realities were deemed crucial.

Our study must be considered in light of a few limitations. We only investigated the perception of trial site staff without comparing it to the sponsor's perception. Trial staff might not have been keen on talking about weaknesses in trial conduct with the interviewer, who was a female, Swiss scientist. In order to deal with this, staff members were encouraged prior to the interview to speak openly and anonymity was ensured multiple times. In turn, we gained confidence about the evidence presented as we consistently identified the same two main themes independent of country and staff level.

Qualitative research is constrained in terms of its generalisability; to mitigate this shortcoming we conducted the study in four countries and two languages of sub-Saharan Africa.

This study is intended to start a debate about efficient processes in clinical trials. We argue that study optimisation and future research should not only consider external but also internal challenges to conducting clinical trials. Particular topics of interests are how to improve the planning process, how to involve clinical trial staff in planning in a feasible way and what are quality criteria in clinical trials conducted in resource-limited settings. Further, we encourage future research to investigate how to make clinical research careers more attractive. We found that the experiences of local trial staff are a valuable source of information to identify challenges and solutions but are rarely acknowledged in the scientific literature.

4.6. Conclusions

This study investigated internal factors slowing down clinical trials, defined as those factors relating to clinical trials teams and sponsors only. In interviews with clinical trial staff working in research centres in SSA, we identified several such factors, which can be categorized broadly into the two themes "planning" and "site organisation". We found that these internal factors are of high importance to trial staff, inhibit efficiency and may be addressed more easily as they are independent of external conditions. We argue that adequate and coherent planning, careful assessment of the context, performing dummy runs and clear task allocation may eliminate important internal factors that tend to slow down clinical trials. In the long run, strengthening management capacities may lead to improved portfolios, balanced workloads, reliable staffing and increased career options for trialists.

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5. Increasing protocol suitability for clinical trials in sub-Saharan Africa: A mixed methods study

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5.1. Abstract

Background

The trial protocol is the most important document for clinical trials and describes not only the design and methodology of a study, but also all practical aspects. The suitability of the protocol has a direct impact on the execution and results of the trial. However, suitability is rarely addressed in trial practice and research. The aim of our study was to investigate protocol suitability and to identify suitability-enhancing measures for trials in sub-Saharan Africa.

Methods

We used an exploratory mixed methods design. First, we interviewed 38 trial staff at different organisational levels in Ghana, Burkina Faso and Senegal. Second, we conducted an online survey among trial staff in sub-Saharan Africa to investigate trial protocol suitability based on the main themes distilled from the interviews.

Results

Protocol suitability surfaced as a prominent topic in interviews with trial staff, critiqued for its lack of clarity, implementability and adaptation to trial participants as well as to the workforce and infrastructure available. Both qualitative and quantitative investigations identified local site staff involvement in protocol development as the most helpful mean of increasing protocol suitability. Careful assessment of the local context, capacity and cultures, and ensuring that staff understand the protocol were also cited as helpful measures.

Conclusions

Our data suggests that protocol suitability can be increased by discussing and reviewing the protocol with trial staff in advance. Involving operationally experienced staff would be most useful. For multicentre trials, we suggest that at least one trial staff member from each of the sites with the highest expected recruitment rates be involved in developing the protocol. Carefully assessing the context prior to study start is indispensable to ensuring protocol suitability and should particularly focus on the workforce and infrastructure available, as well as the needs and availability of trial participants. To allow for protocol suitability enhancing measures, planners must allocate enough time for trial preparation and solicit feedback and information on context at an early stage. Such prospective planning would increase implementability, efficiency and quality of trials in the long run.

5.2. Introduction

Clinical trials are essential for developing new medicines and for improving disease management. From a public health perspective, clinical trials in sub-Saharan Africa (SSA), where high burdens of disease exist, are of particular importance. Trials conducted in this region face particular setting-specific challenges like deficits in infrastructure and skilled workforce, in addition to the already complex task of performing a trial. Specific additional challenges derive from the difficulties of getting patient information and consent [1] and the frequent involvement of children.

The most important document in a clinical trial is the trial protocol, the key document for planning, conducting, externally reviewing, overseeing and interpreting a study [2]. The trial protocol provides a rationale for the trial, defines trial goals, processes and analysis methods and enables scientific and ethical review. A well-designed protocol is paramount for a successful clinical trial for several reasons. First, the study design described in the protocol significantly affects the costs of conducting the trial [3]. Second, protocol deficiencies may lead to amendments [2] and protocol deviations, which trigger queries and add to already heavy workloads. Protocol amendments are costly [4], may jeopardize data integrity [5] and trial participants' safety, and cause delays and disruptions of the trial [4]. One study found that nearly half of all amendments may be avoidable [6]. Third, the length and complexity of protocols have increased dramatically over the past decades. Higher protocol complexity is directly associated with a greater number of amendments, lower levels of study performance [3, 7] and increases chances of non-adherence and, hence, of risk and low quality. The frequency of procedures per protocol has also increased at an annual rate of 8.7%, which adds to on-site work burdens [8]. The number of protocol deviations is one of the key measures for trial quality [9] and protocols are the most important instrument for quality risk management. In summary, the protocol largely determines quality, outcomes, efficiency and potential challenges in clinical trials. Getz *et al.* state that protocol design may hold the key to achieving higher levels of efficiency [8]. Despite the challenges mentioned above and the apparent importance of the protocol, there is little research on how to optimize the conduct of trials in the North as well as in resource-limited countries [10, 11]. Gheorghide *et al.* criticise the limited data available to support best trial practices and that we only rely on experience and judgment [12].

To standardise the content and ensure the quality of trial protocols, the ICH E6 guideline "Good Clinical Practice" contains a full chapter on trial protocols [13]. The SPIRIT 2013 Statement (Standard Protocol Items: Recommendations for Interventional Trials) is a more comprehensive checklist of recommended items to include in a trial protocol [2]. This checklist was developed based on the argument that high-quality protocols facilitate proper conduct, reporting and external review of clinical trials, and that the completeness of trial protocols was often inadequate. In addition, the World Health Organisation's website offers instructions for designing and formatting a research protocol [14]. TransCelerate Biopharma Inc. developed the freely available "Common Protocol Template" to improve consistency across the increasingly complex protocols [15]. Other free protocol templates are available on the web [16, 17]; selecting the correct template depends on local laws, regulations and the sponsor. All efforts described above mainly focus on the scientific part of the protocol, which is of most interest to researchers and reflects their training.

However, a trial protocol goes beyond describing the research design. It also serves as an operational manual and must satisfy experts from different backgrounds and disciplines [18]. To date, little emphasis has been placed on protocol operationalization. Getz and Campo state that protocol authors often transfer out-dated and unnecessary procedures into next study designs because they are routinely carried over from long-standing protocol templates and operating policies [7].

A key aspect of operationalization is protocol feasibility, which is customarily assessed after the protocol has been finalised by the sponsor. It is currently common practice in clinical trials to have a site feasibility assessment and/or a pre-study visit. During both visits, facilities are commonly assessed

using a standard template in a checklist format that is often used across studies and is not tailored to the specific operational requirements of the trial protocol. On the global health trials webpage, such a protocol feasibility checklist is freely available [19]. To the best of our knowledge, there is only one study covering this topic [3]. This study highlights that protocol design feasibility is a topic of increasing interest to sponsor organizations and recommends more flexible and adaptive trial designs as well as more rigorous upfront planning and simulation.

In contrast to “feasible”, which is defined as achievable and possible, “suitable” is defined as fit for purpose. [20]. Protocol suitability goes beyond feasibility and addresses not only technical aspects of the protocol but also considers settings, environments and culture, as well as effectiveness and efficiency of execution. These are of particular importance, as the protocol serves as a manual for health care providers [18]. Protocols that cannot be effectively executed may result in protocol deviations, amendments, quality issues and safety problems. While feasibility of trial sites is routinely assessed, protocol suitability is a new concept and rarely considered. Meeker-O`Connell *et al.* stress that improving protocol design, trial planning and quality oversight has a direct impact on inefficiencies like high costs and unsustainability [21]. With the rising complexity of trial protocols and the intense pressure on sponsors to accelerate development cycle times, suitability is becoming more important to alleviate execution burdens and ultimately improve trial conduct efficiency [8].

The study presented here covers protocol suitability for clinical trials in SSA that investigate poverty-related diseases. Ensuring protocol suitability is particularly difficult in these regions due to the geographical separation between sponsors and trial teams. To the best of our knowledge, this is the first study investigating trial protocol suitability in SSA. As clinical research is more established in South Africa and not exactly comparable with other SSA-countries, we excluded South Africa from our study [22].

Clinical trial staff in SSA implements the trial protocols in practice and can provide valuable insights regarding protocol suitability. Nevertheless, the experience of trial staff is rarely acknowledged in scientific publications. Furthermore, Cullati *et al.* stressed that more research on trial protocols using qualitative methods could shed light on the factors that facilitate the conduct of clinical research [23]. Hence, we assessed trial staffs’ perspectives by using an exploratory mixed methods approach, combining qualitative and quantitative methods. Mixing two methods has the capacity to strengthen results and conclusions [24]. The aim of our study was to identify how protocol suitability could be improved for clinical trials in SSA.

5.3. Methods

Study design

We used an exploratory mixed methods design, which is an ideal approach to exploring a topic for which no research has been carried out so far [24]. We started with a qualitative part, conducting key informant interviews with clinical trial staff working in SSA, to identify important variables of protocol suitability. In order to quantify identified variables, increase generalizability and explore correlations between variables, we followed up with a quantitative part comprising an online survey targeting trial staff. We used the connection approach, deriving major themes from the qualitative interviews and using them to develop and formulate the questions and answer options in the quantitative survey [25].

Ethical review exemption for the whole project was granted by the Ethics Committee of North-Western and Central Switzerland (EKNZ), based on the rationale that the research project did not involve access to or collect private, sensitive or health-related data or materials. For the qualitative study, we received full ethical clearance from the Ghana Health Service Ethical Review Committee (GHS-ERC: 18/09/14), the Comité d`Éthique sur la Recherche en Santé in Burkina Faso (N 2014-11-131) and the Comité National d`Éthique pour la Recherche en Santé in Senegal (n12/MSAS/DPRS/CNERS).

Qualitative methods

We visited clinical research centres in Ghana, Burkina Faso and Senegal as they significantly contribute to public health activities in SSA and because the Swiss Tropical and Public Health Institute (Swiss TPH) has contacts with clinical research centres in these countries. In all three countries, we contacted the major clinical research centres that focus on poverty-related diseases and have a track record of completed clinical trials (no more than four such centres could be identified per country). In every country, we selected the first two research centres that agreed to our visit and ultimately conducted interviews in six centres, four of which were located in an urban setting and two in a rural setting. To ensure anonymity of interviewees, neither the names nor the exact locations of the clinical research centres are mentioned here. Interviews were open to all centre investigators, study coordinators, clinicians and quality assurance professionals with at least six months of experience in clinical research. In each centre, the sample was drawn with the assistance of a clinical researcher working in the centre, who approached eligible participants and acquainted them with this study.

Building on the literature and through pre-test with trial personnel working in SSA, we finalized the interview guide in an interdisciplinary team. Among other aspects, the guide consisted of the following questions:

- In your experience what is important for a good study protocol that is easy to implement?
- Could trial protocols be improved? If yes how and where?
- What is the influence of the study protocol on the trial?
- Who is writing the protocols you are working with?

All interviews were conducted by the first author of this paper. In Ghana, key informant interviews were conducted in English in December 2014. After translating the interview guide into French (including back-translation and terminology review), we conducted interviews in Burkina Faso and Senegal in March and April 2015. In each country, we considered having reached saturation of information in the number of interviews conducted when few or no new concepts were raised [26]. Unstructured observations, reflections during interviews and informal conversations with external monitors (who were on-site during our visit) were collected and documented in a field diary.

After explaining the purpose of the study and informing the participants of their right to withdraw from the study at any given time, participants gave written consent. Interviews were tape-recorded, transcribed verbatim and analysed using thematic analysis as per Braun and Clarke 2006 [27]. After repeated reading of the transcripts, initial coding was performed in MAXQDA 11. The analysis focused on the suitability of trial protocols. To ensure the analysis was reflective, notes were taken. We tested emerging themes from the data interrogation in further interview analyses. Themes were cross-tabulated to explore differences between countries and staff levels before finally defining and naming themes. This study adhered to consolidated criteria for reporting qualitative research (COREQ) [28].

Quantitative methods

The survey was based on the key themes that emerged from the qualitative interviews, namely protocol characteristics, context adaptation and involvement of site staff. We developed the survey in a team that included clinical researchers, a statistician and a social scientist and discussed it with and received input from the European & Developing Countries Clinical Trials Partnership (EDCTP), a funder of investigator-initiated trials and active in SSA since 2003. The resulting survey (Appendix 1 and 2) consisted of single and multiple selection questions and ranking of table lists related to the following topics: protocol characteristics, adaptation of procedures and practical aspects in the protocol, measures to increase protocol suitability, and current and most helpful involvement in protocol development. The survey also captured the experience of participants and the degree to which measures were implemented. The survey was deployed using a web-based survey tool developed for researchers at the University of Basel (FlexiForm[®]).

Increasing protocol suitability

The survey was piloted among 12 participants who had varying positions in the field of clinical research in SSA. As the relevance of the questions had already been tested in the qualitative interviews, the pilot run focused on the comprehensibility and clarity of questions.

In addition to covering the organisational levels reflected in the qualitative interviews, the survey also targeted pharmacists, lab coordinators and nurses working in clinical trials in order to consider a variety of perspectives and provide a bigger sample size. The English-language survey was translated into French, including back-translation and revision of terminologies. Invitations to participate were sent via email and contained the link to the English and French versions of the survey. Data collection took place from August 2015 until January 2016. A total of 294 survey requests were sent out by different organizations (Table 5) and all contained the appeal to forward the survey to team members.

Table 5 Survey distribution

Organisation distributing the survey	Number of trial staff in SSA receiving the survey by email
European and Developing Countries Clinical Trials Partnership (EDCTP)	80 investigators who had previously coordinated an EDCTP grant
Swiss Tropical and Public Health Institute	109 trial staff who worked on the RTS,S malaria vaccine trials in SSA 40 trial staff contacts from Swiss TPH
Two pharmaceutical companies	43 trial staff
European Federation of Pharmaceutical Industries and Associations (EFPIA)	22 trial staff

In the introductory text, we informed respondents that by filling in and pressing the “send” button they were giving consent to participate in the survey. In addition, respondents were assured of their anonymity and that it would not be possible to link the answers to their email-addresses. Respondents were informed that if they could not give a general answer, they should answer the question with reference to an on-going or most recent trial.

Categorical variables were described using absolute and relative frequencies and percentages. Explorative factor analysis (based on principal component analysis) with oblique rotation was performed on the survey items to identify leading dimensions of protocol quality. The resulting factor scores were then regressed on personal characteristics of the respondents. Independent variables for the regression analyses were selected based on prior knowledge and experience; other potential covariates were screened but did not improve the model. A p-value smaller than 0.05 was considered statistically significant. Data were analysed using the statistical software STATA 14.

5.4. Results

Qualitative results

Participants

Thirty-eight clinical trial staff participated in the key informant interviews (Table 6). Through open questions about efficiency, challenges and quality in the conduct of trials, protocol suitability emerged as a topic in the first five interviews in Ghana. To follow up on this topic, we added questions about protocol suitability to the remaining eight interviews in Ghana (no more than 13 trial staff were available for interviews in the two clinical research centres in Ghana). Qualitative research is centred on flexibility and the exploratory approach of the study enabled adjustments to follow up on an emerging topic [29]. We asked the questions on protocol suitability in clinical research centres in Burkina Faso and Senegal, as well.

Table 6 Role and experience of interviewees

		Ghana (n = 8)	Burkina Faso (n = 16)	Senegal (n= 12)
Role in trial	Investigators (n=16)	2	8	6
	Study coordinators (n=10)	4	3	3
	Clinicians (n=6)	1	3	2
	QA professionals (n=4)	1	2	1
Clinical research experience	0 to 1 year	0	1	1
	2 to 4 years	2	5	2
	5 to 7 years	1	0	1
	More than 7 years	5	10	8
Study Phase	Phase I (a or b)	2	10	2
	Phase II	2	13	3
	Phase III	6	13	6
	Phase IV	5	9	3
Type of trial	Drug trial	4	16	9
	Vaccine trial	7	13	7

Findings

Protocol characteristics

With high frequency, interviewees reported that a suitable trial protocol has to be clear to avoid methodological and procedural uncertainties that leave room for interpretation. Trial staff emphasized the importance of making protocols understandable for everyone on site, including less skilled staff like field workers, and consistent to avoid ambiguities and contradictions. A bit less frequently, interviewees mentioned the need to make protocols easy to implement, i.e. avoiding too many measurements at the same time. In addition, a few interviewees claimed that a logical flow was sometimes missing and called for well-structured protocols.

A few individuals preferred detailed protocols, citing an approved ability to understand and carry out procedures. Others favoured short protocols to facilitate work, without providing too many details that would only lead to amendments and non-adherence to protocol procedures. If protocols are too long, staff only read the section relevant to the work they have to execute.

“A long document to read can cause a problem. Ideally, summarised protocols that get to the essential points could be better for both the researcher and the ethics committee. This facilitates understanding and implementation on the ground. So that’s important.”

— Study coordinator, male, Burkina Faso, centre two

Interviewees from French-speaking countries stated the need to translate the protocol into French, as technical staff are unlikely to understand English. According to interviewees, protocol translations were often of bad quality, leading to errors and ambiguities.

Importance of context adaptation

The importance of context adaptation came up in half of the interviews, independent of country and organisational level. One third of participants reported recently working with protocols that were not fully adapted to the setting.

“I would tell you to try to really adapt to the realities of the countries. If you give us a typical European protocol that has to be reproduced here, I think we are going to have problems. We do not have the same manner of working. We do not have the same tools to work with. So it might be important to really see what is feasible in the country (...) If not, you will have many, many deviations afterwards, because we were not able to do that.”

— Study coordinator, female, Burkina Faso, centre two

Interviewees gave various examples of missing context adaptation. First, their biggest concern was the needs of trial participants, which protocols sometimes failed to consider. Protocols should seek to burden trial participants as little as possible. For example, interviewees in all three countries asserted that trial participants felt uncomfortable with blood drawings; one Senegalese investigator said participants would rather accept four small tubes instead of one big tube hence, it is important to ensure that trials are as non-invasive as possible and to discuss limitations in advance. Another example referred to the heavy agricultural workload of local populations during the rainy season; many trials deliberately take place in this season due to high disease prevalence of malaria, for example. Thus, trial procedures should adapt to the time constraints of its participants. Second, interviewees found that socio-cultural norms and values were sometimes not respected in the protocol. Interviewees gave various examples of this, like asking trial participants about death or sexuality, which are taboo subjects in these settings. A few interviewees mentioned that trial participants would not answer these questions honestly. Other examples included performing HIV tests or pregnancy tests on minors or asking the name of neonates when neonates are not given names in their first seven days of life. One interviewee stressed the importance of having a male and a female area for clinical trials in Muslim environments. Interviewees believed that better adaptation to possibilities and attitudes of trial participants would also improve participants' adherence to trial protocols and decrease losses to follow-up. Third, a few interviewees reported poor or no adaptation to local capacities, systems and/or the structure of the national health system. Staff experiences revealed that certain laboratory tests or the amount of workforce or expertise (e.g. presence of a psychologist) may not be available on site but were required by the protocol. A few interviewees claimed that the protocol timelines given for patient flow were written for ideal settings and circumstances, but not feasible in practice. Respondents were aware that full adaptation to the site was not possible for multicentre trials. However, they reported that for certain multicentre trials, they were allowed to adapt some sections or details to their setting, such as adapting the formulation of questions, which increased protocol suitability.

According to interviewees, protocols were not adapted to local realities because the ones who elaborated the protocol did not know the context. Hence, some procedures in the protocols were difficult to put into practice. Interviewee experiences revealed that it was best to adapt the protocol to the setting in the development phase, as it is far more challenging to adapt a finalized protocol.

Ideas for improving protocol suitability

Across countries and positions, interviewees' strongest suggestion for increasing protocol suitability was to involve trial-site staff in the protocol development phase. This idea was raised by the majority of interviewees, often in an emotional manner.

“So I think that involving the researcher in writing the protocol allows one to avoid challenges in the field. Because it is him [the researcher] who knows his setting well.”

—Investigator, male, Burkina Faso, centre one

Interviewees had different suggestions on how best to involve the trial team in protocol development. A few participants proposed holding discussions with relevant stakeholders prior to writing the protocol, while others suggested writing the protocol together with the sponsor. A few recommended

asking clinical trial staff to review the first draft of the protocol, with the aim of checking trial feasibility and providing added feedback. A few others preferred to wait until the protocol was finalized and then discuss the implementation of the trial in practice with the sponsor. For all trial staff, the objective of their involvement would be to ensure that the trial respected the realities of the setting and centre. Additionally, a few mentioned that their input regarding recruitment was of particular importance and would potentially accelerate recruitment rates.

At the time of the interviews, half of the interviewed trial staff was not involved in protocol development. Of the other half, most were involved only insofar as they received a draft protocol and corrected for coherency and applicability.

“There have been protocol meetings on many studies, but it is not all the studies that you get the opportunity to be part of the protocol development and you find out that in instances when you are not part of which and where, you know a training did not trickle down well to the end-users, myself included, there may be errors caused.”

— Study coordinator, male, Ghana, centre one

One Burkinabe investigator stated that participation in protocol development depended on the sponsor: if it was a pharmaceutical company, trial staff were not involved; if it was a university, the sponsor and the site staff developed the protocol together. A few Senegalese staff reported that only recently, they were asked to provide inputs before a protocol was finalized and submitted for ethical review. Most of the principle investigators (PIs) interviewed were allowed to give inputs during protocol development. One interviewee shared his opinion that these PIs should solicit input from the team.

“One the PIs should have it [the protocol]. And the PI also has the responsibility of sub-delegate (...) if you were the PI, it doesn't necessarily mean you are the technical person in some of the areas. So it is not enough for the PI to just look at it and say 'oh the science is ok', you need the technical people to look at it and then they advise 'ok this way'.”

— Quality assurance professional, male, Ghana centre one

The majority of trial staff agreed that not only the PI but also technical staff, like statisticians and trial nurses, should be involved in protocol development. Others expressed the following sentiment:

“When we work with a pharmaceutical company, it's difficult to get everyone involved. But at least the PI may be involved.”

— Investigator, male, Burkina Faso, centre two

Trial staff cited additional benefits of their involvement to trial efficiency. According to interviewees, their involvement would decrease the number of amendments, help to find redundancies in the trial processes and improve the preparation of staff for the trial. They were dissatisfied with only executing protocols and claimed that collaboration was missing. Trial staff was also of the opinion that staff motivation would increase if they were allowed more influence on the protocol.

Finally, two interviewees mentioned that protocols should be written by investigators and sponsors together, so that the investigators could learn protocol writing skills.

“When the monitors come for the training, we go through documents and we say when such things in our setting cannot be done like that. Then we have to go back again. This is what I have criticized sometimes. We must amend, go back, start again. Because if you amend, we have to resubmit and so on. Whereas, if maybe we could tolerate that for some studies, you can select the site first and the whole protocol development process is done together with the site. This will allow one to take into account many aspects and once we start the process, we won't need to go backwards anymore.”

— Quality assurance professional, male, Burkina Faso, centre two

Other ideas for increasing protocol suitability were also presented with some frequency. One such idea included conducting a test run with a dummy participant to identify and tackle difficulties in advance, coordinate activities and ensure that everyone knows their responsibility before recruitment starts.

“Then we realized that the test run was our secret. That was our success because we had virtually identified all the possible problems, looked at how they could be resolved before the real test.”

— Quality assurance professional, male, Ghana, centre two

A few interviewees suggested including trial participants’ perspectives in the protocol development, as patient challenges occur very frequently, e.g. during informed consent and follow-up. Involving trial participants in discussions and knowing their perspectives would help to increase protocol adherence, according to interviewees. Having “lessons learned” meetings after trial completion and providing sponsors with information about what went wrong was also deemed to have a positive influence on future trials. According to interviewees, identifying weak spots and finding solutions prior to writing the next protocol would avoid repeating the same mistakes and allow staff to profit from experience.

Quantitative results

Participants

The final survey sample size was 110. Eleven records were excluded because these respondents indicated a country outside SSA as their main work place. Characteristics of the respondents are presented in Table 7. There were high proportions of PIs (26.4%) and trial staff with more than seven years of clinical research experience (49.1%). The majority of respondents worked in clinical research centres (71.8%) and 53.2% spent more than 75% of their working time on clinical trials. The distribution of survey participants across countries (Table 8) reflected the number of clinical trials conducted in different countries [30]. Only Malawi, Zimbabwe and Nigeria were underrepresented in our survey. We asked survey participants to forward the survey to colleagues working in clinical research, thus the total number of surveys distributed is unknown and we cannot calculate a response rate.

Table 7 Role and experience of survey participants

Recent primary role in clinical research	Number of participants, <i>n</i> (%)
Principle investigator	29 (26.4)
Sponsor-investigator	11 (10.0)
Investigator	16 (14.6)
Clinician	14 (12.7)
Quality assurance professional	7 (6.4)
Study coordinator	22 (20.0)
Pharmacist	3 (2.7)
Lab coordinator	7 (6.4)
Trial nurse	1 (0.9)
Institution	
Centre	79 (71.8)
Hospital	12 (10.9)
Field site	7 (6.4)
University	4 (3.6)
Other	6 (5.5)
Missing	2 (1.8)

Increasing protocol suitability

Experience in clinical research	
0 to 1 year	4 (3.6)
2 to 4 years	20 (18.2)
5 to 7 years	32 (29.1)
More than 7 years	54 (49.1)
Experience in drug trials	91 (82.7)
Experience in vaccine trials	63 (57.3)
Sponsor	
Pharma companies	40 (36.4)
Other than pharma companies	29 (26.4)
Mixed	40 (36.4)
I do not know	1 (0.9)

Table 8 Distribution of survey participants per country

Country	Number of participants, <i>n</i> (%)
Kenya	23 (20.9)
Burkina Faso	18 (16.4)
Tanzania	13 (11.8)
Ghana	7 (6.4)
Uganda	7 (6.4)
Cameroun	6 (5.5)
Mali	6 (5.5)
Gabon	4 (3.6)
Mozambique	4 (3.6)
Gambia	3 (2.7)
Zimbabwe	3 (2.7)
Botswana	2 (1.8)
Ethiopia	2 (1.8)
Senegal	2 (1.8)
Benin	1 (0.9)
Congo	1 (0.9)
Zambia	1 (0.9)
Several countries in SSA	7 (6.4)
Total	110 (100)

Increasing protocol suitability

Findings

Characteristics and context-adaptation of protocols

Protocol characteristics are presented in Table 9. Only one third (38.2%) of all respondents considered protocols as being easy to implement. About half of the survey participants rated trial protocols as being completely understandable, clear and consistent.

Table 9 Protocol characteristics

Protocol characteristics	not at all [%]	partially [%]	completely [%]	missing [%]	no opinion [%]
Understandable (for all staff levels)	3.6	43.6	51.8	0.9	-
Easy to implement	6.4	53.6	38.2	1.8	-
Clear (no uncertainties)	7.3	39.1	45.5	6.4	1.8
Well structured	1.8	22.7	71.8	2.7	0.9
Complex	15.5	50.9	29.1	2.7	1.8
Consistent (e.g. no ambiguities)	4.6	39.1	51.8	4.6	-
Well translated	6.4	21.8	40.9	10.9	20

Of the respondents, 65.1% considered the follow-up procedure described in the trial protocol to be well adapted to the setting, while 58.7% considered the inclusion and exclusion criteria to be well adapted (Table 10). Only about one third rated workforce availability (30.9%), daily clinical practice (32.1%) and available infrastructure (35.8%) as well adapted to the protocol requirements; thus, these elements were rated as having the lowest degree of context-adaptation. Some 13.6% considered participant incentives and 10% considered availability and needs of trial participants as marginally adapted to the context.

Table 10 Adaptation of protocol procedures and in-protocol required resources to the setting

	marginally adapted [%]	partially adapted [%]	well adapted [%]	no opinion [%]
Informed consent procedure	3.6	39.1	56.4	0.9
Inclusion and exclusion criteria	3.7	36.7	58.7	0.9
Participant incentives for participation	13.6	45.5	36.4	4.6
Recruitment procedure	3.6	46.4	50.0	-
Data and information to be collected	4.6	36.7	57.8	0.9
Medical interventions	8.2	35.5	52.7	3.6
Medical procedures and decisions	7.3	39.5	51.4	1.8
Safety reporting and management	4.6	39.1	54.6	1.8
Follow-up procedure	2.8	30.3	65.1	1.8
Amount of workforce available	13.6	53.6	30.9	1.8
Infrastructure available	13.8	48.6	35.8	1.8
Availability and needs of trial participants	10.0	50.9	38.2	0.9
Daily clinical practice	8.3	56.9	32.1	2.8
Ethics committee system	8.2	46.4	44.6	0.9
Drug regulatory authority system	9.1	42.7	45.5	2.7

The majority of respondents (56%) mentioned that protocols were amended an average of three to five times per trial; 7.3% mentioned more than five protocol amendments per trial.

Increasing protocol suitability

Measures to increase protocol suitability

When asked what measures would increase protocol suitability, involvement of local staff in the study planning and protocol development was rated as the most helpful option by respondents (61.8%) (Figure 5).

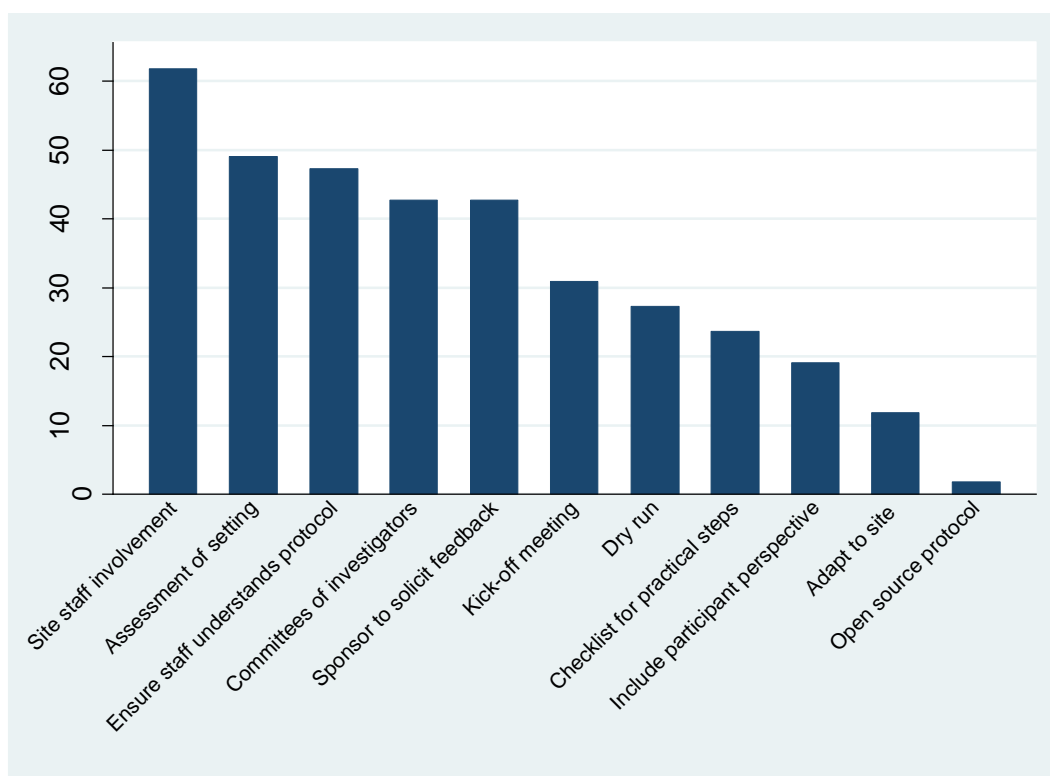


Figure 5 Measures to increase protocol suitability

This result was consistent across countries and positions. A related frequently selected approach to increase protocol suitability was to have committees of investigators in multicentre trials (42.7%), consisting of investigators from all participating sites. On average, respondents were more frequently working on multicentre trials than on single centre trials (77% spent at least 50% of their work time in multicentre trials). The second most helpful option mentioned was careful assessment of local context, capacity and culture by sponsors (49.1%). However, the adaptation of the protocol to site and health care specific systems in a single centre trial (11.8%) was only rarely selected. Overall almost half (47.3%) rated ensuring that everybody understands the protocol and knows his/her role and responsibility in the trial as one of the most helpful options, while the more concrete measures of having a kick-off meeting or a dry run were less frequently chosen (30.9% and 27.3%). Almost half (41.3%) reported to have had a kick-off meeting for all of their trials. Dry runs were less frequently implemented; 24.8% never had dry runs in any trial and 21.1% had dry runs in all trials. Soliciting feedback from the site on what went wrong in previous trials by sponsors was another popular option for respondents (42.7%) to increase protocol suitability. However, 40.4% had never had any “lessons learnt meetings”. Only 1.8% considered that the use of the open source protocol development technique would increase protocol suitability, but 73.4% had never heard of this technique.

Respondents were asked to tick the three options they considered most helpful for increasing protocol suitability. Because multiple selection was possible, 13.6% ticked more than three options. Percentages of answers from those that chose more than three options were compared with the answers of respondents who correctly filled in the survey; the ones that chose more than three options ranked checklist for practical steps, assessment of setting, inclusion of trial participants` perspective and adaptation to site as slightly higher. However, including the ones that chose more than three

Increasing protocol suitability

options did not change the measures' ranking order and, due to the small sample size, we included all answers in the final results and figures.

The qualitative interviews suggested that trial teams would consider their involvement in protocol development as highly important. Figure 6 shows that one quarter (26.4%) of trialists were not involved in protocol development at all; most were clinicians or study coordinators and only a few investigators and PIs. Reviewing the protocol was the most frequent manner of involvement (47.3%).

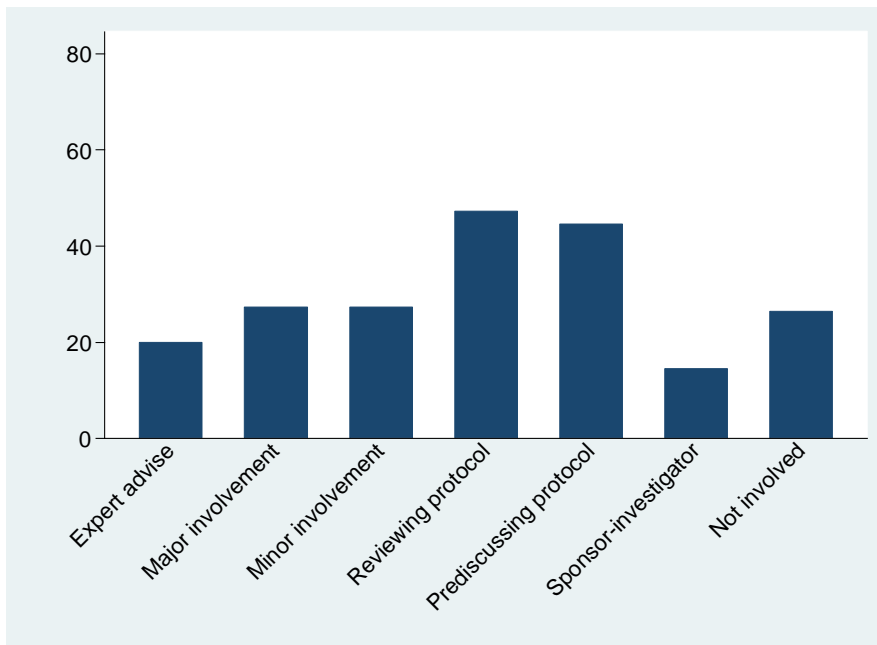


Figure 6 Present involvement of site staff

Almost half (45.5%) indicated that it would be most helpful if they were heavily involved (major involvement) in protocol writing. However, as shown in Figure 7; the majority considered reviewing protocols and participating in pre-discussions of protocols (both 66.4%) as optimal.

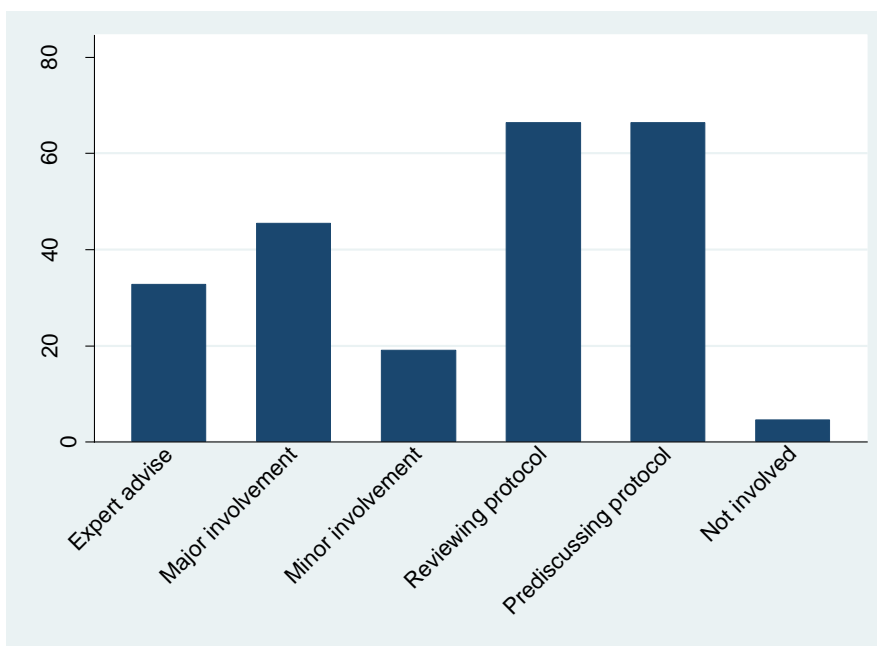


Figure 7 Most helpful involvement of site staff

Factor analysis of the different assessment variables was performed to assess potential associations between protocol quality and personal characteristics. The third factor score was most strongly related to personal characteristics of the study participants and described the degree of implementability, understandability, clarity and structure of the trial protocol. The only statistically significant association found was the professional role of survey participants. Compared to other professional roles, the third factor score was on average significantly higher for PIs (difference=0.43, 95%-confidence interval=0.04 to 0.83, $p=0.033$) and significantly lower for sponsor-investigators (difference=-1.10, 95%-confidence interval=-1.85 to -0.35, $p=0.005$) and quality assurance professionals (difference=-1.22, 95%-confidence interval=-2.02 to -0.42, $p=0.003$).

5.5. Discussion

This study identified perceived deficits of protocol suitability and yielded several measures to enhance protocol suitability, as put forward by trial staff. According to trial staff, protocol suitability constraints included ambiguity, complexity and poor understandability for all staff levels. Staff mentioned lack of clarity in procedural descriptions and imprecise wording in protocols. Only one third of the survey respondents rated protocols as easy to implement. While context adaptation was a main theme in the qualitative interviews, survey respondents rated most trial aspects as rather well adapted, particularly inclusion and exclusion criteria and follow-up procedures. This finding surprised us and is inconsistent with the literature, which cites follow-up as a challenge [31-33]. The differences in the findings might be explained by the different methodologies used as literature findings base on authors' personal reflections. In turn, respondents cited poor context adaptation of the protocol to the availability and needs of trial participants as a constraint. The importance of adapting projects to research participants' cultural norms and values has been described elsewhere [1, 33, 34]. Staff perceived protocols as being too rigid for their settings. An example that was mentioned frequently in interviews was the importance of minimising blood draws. Trial participants in SSA are commonly scared of giving blood as blood is considered sacred, blood sampling is thought to make children ill and there are local rumours surrounding "blood stealing" and "blood selling" [1, 35, 36].

According to trial staff, visit windows and patient flow should also consider trial participants' obligations, e.g. that harvesting takes place at the end of the rainy season. The lack of protocol adaptation to available site workforce and to daily clinical practice of particular importance in hospital settings where trial activities are added to routine care, indicates that the work burden of trial implementation was underestimated by protocol developers.

The literature also stresses the importance of context adaptation for easy translation of protocol procedures into practice [37, 38]. Alsumidaie states that, "The sponsors design clinical trials expecting them to fit into study site operational infrastructures which leads to challenges like study procedures that are incompatible with how study sites operate" [39].

Context adaptation is more challenging in multicentre trials, as procedures must be uniform across sites to enable the required pooled data analysis. However, Thomason *et al.* state that standardisation of procedures across all sites within a trial in SSA is not always possible due to the differences in resources [33]. We argue that, for multicentre trials, the degree of adaptation to the context has to be considered carefully to avoid protocols that are overly site specific but that consider the cultural, social, economic and political differences between the sites involved. We suggest identifying commonalities among the sites involved and accounting for differing socio-cultural norms, but we acknowledge that this is difficult.

Measures to improve protocol suitability

Site staff identified a number of measures to improve the suitability of protocols, described below (Figure 8).

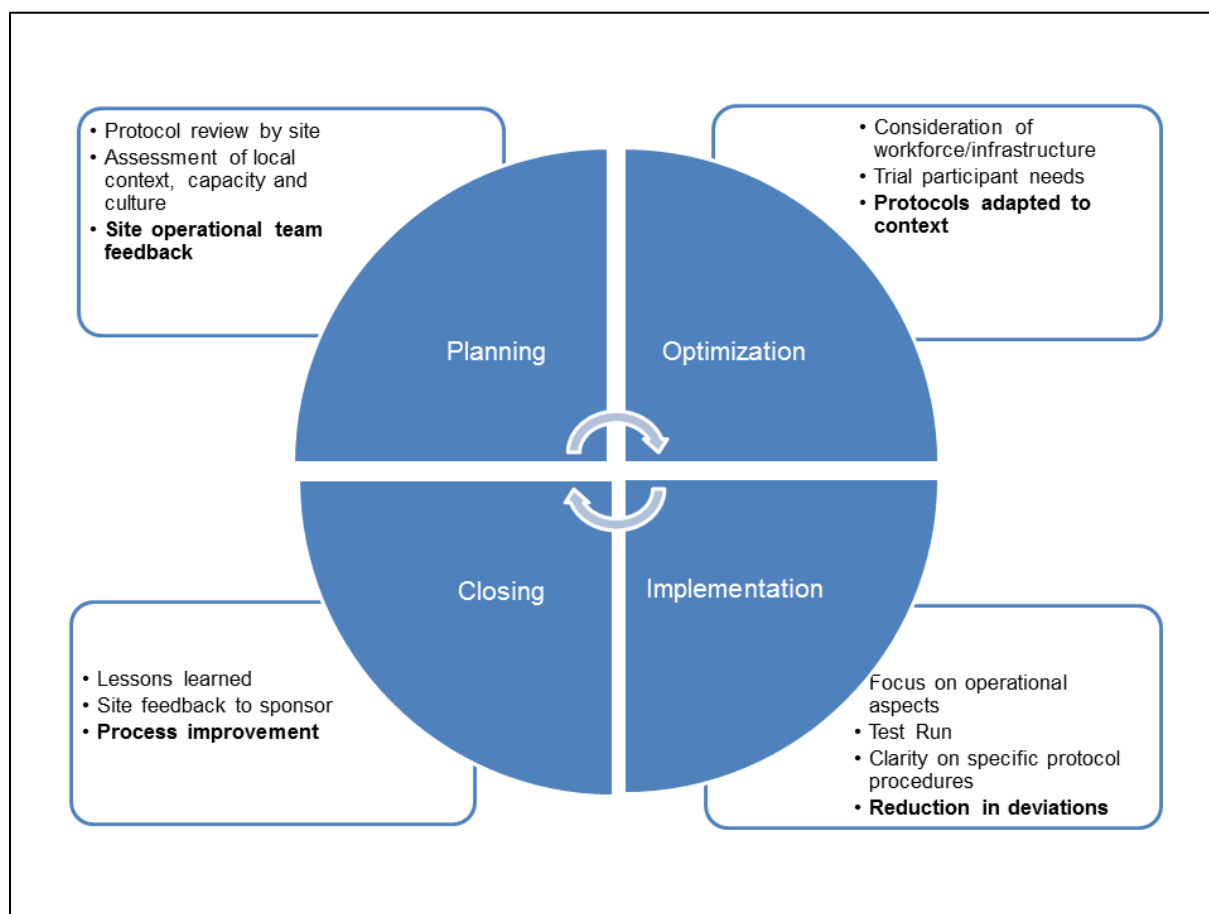


Figure 8 Implementation of measures to increase protocol suitability

Involvement of site staff in protocol development

In both qualitative and quantitative results, local trial staff involvement in developing the protocol came up and was rated as the most helpful option for increasing protocol suitability. The importance of site staff involvement in trial planning has also been stressed in the literature [11, 21, 32, 39]. Eastabrook et al. state, “Given the important role of site staff for overall trial success it is critical to understand their preferences and experiences” [40], while Alsumidaie promotes trial site involvement to create clinical trials that work operationally while reducing risks [39].

Half of the interviewees and three-quarters of survey respondents (half of survey respondents were investigators) had been previously involved in protocol development in some manner. It is important to carefully choose the composition of the trial team involved in this process. While key opinion leaders may give detailed scientific input, they are often not the ones carrying out the work on site. We agree with the respondents who suggested involving operationally experienced staff as particularly useful to increase suitability. Ideally, technical staff from various functional areas (investigator/ clinician, study coordinator, pharmacist, lab coordinator and data manager) should be involved, though this might not be possible for all sites in a multicentre trial. A popular option to increase protocol suitability for multicentre trials, as revealed in the survey, was to form protocol writing committees consisting of one investigator from each site. Indeed, involving an operationally experienced investigator who solicits feedback from his/her team and communicates the outcome to the sponsor would lead to optimized protocols. Multicentre trials on poverty-related diseases do not usually involve an extensive number of

trial sites, hence, it should be possible to solicit feedback from all sites in the planning phase of such trials. In cases where it is not possible to involve one investigator from each site, at least the sites expected to have a high enrolment rate should be involved in protocol development. Mbuagbaw et al. recommend selecting national coordinators to participate in the conception of multicentre trials [11]. The assistance of a social scientist would also help to inform protocol development by identifying context specificities. In line with this, Cooper et al. also suggest the use of qualitative research to identify the acceptability of the trial protocol among other things [41]. The meningitis vaccine project shares a positive experience of bringing trial teams together at meetings in the preparatory phase, which empowered the team and fostered communication between sites [32]. In addition, this approach enabled planners to anticipate and resolve operational issues and minimize the number of protocol deviations.

Trial staff rated reviewing and pre-discussing the protocol as the most helpful way to participate in protocol development. This is in line with Alsumidaie, who states that involvement is mainly about obtaining feedback on how to better operate the study [39]. As the sponsor is responsible for the research question and scientific aspects of the protocol, the trial team could provide valuable input in terms of protocol clarity, implementability and adaptation to trial participant needs. The latter is in line with literature stating that staff input would be particularly important for recruitment and follow-up of trial participants [32] as well as feasibility of scheduled study visits [42]. We consider it essential, that the site, in turn, is transparent and realistic in terms of their capacities.

In addition to increasing protocol suitability, trial staff mentioned several additional advantages of being involved in the protocol preparation process. First, developing an appropriate protocol is a discipline that requires training [31] and, according to interviewees and the literature, involving local trial staff in this process builds capacity and confidence [31, 43]. As there are only a small number of locally initiated trials [44] and limited career perspectives in clinical research [1, 45], this is a crucial skill for investigators to acquire. Second, staff saw being involved in protocol development as a way of improving their preparedness for the trial. Third, having an influence on the project would increase trial staff's motivation, as opposed to having a project forced upon them. In contrast to a top-down approach, a participatory approach fosters ownership of the trial [38, 43] and is also recommended by the transboundary research principles of the Commission for Research Partnerships with Developing Countries (KFPE) [46]. Experiences from the meningitis vaccine project also show that working closely with study staff can be empowering, strengthen team spirit, boost staff motivation and increase everyone's commitment [32]. Fourth, it has been stated that mobilising collective intelligence of various people for research protocols is a great benefit for research [47].

Assessment of the context and setting

More careful assessment of the local context, capacity, and culture by the sponsor was rated as the second most helpful measure to increase protocol suitability. Experiences from a trial in the Gambia are in line with this; the authors state that baseline situation assessments are required as each trial and site is unique [48]. For this purpose site assessments and pre-study-visits are commonly performed by sponsors or contract research organizations. While it is common practice to use standard templates (checklists), information collected this way is of limited value. Instead, the questions should be tailored to the trial and the setting. This includes, for example, a more thorough assessment of the socio-cultural context, local laws and customs where the trial will be conducted and identification of risks and needs upfront. This is in line with current trends toward risk-based approaches, including risk assessments in clinical development [49].

Our data suggest specific focus on the workforce and infrastructure (e.g. equipment) available, as well as on needs and availability of trial participants during assessments. Some established clinical research centres in SSA have community advisory boards (CABs) for community engagement and to inform the community appropriately about the study [50]. In view of our findings, it might be helpful to involve the CAB at the conception stage of a trial, to allow for socio-cultural adaptation. Additionally,

we found that engaging key staff from different organizational levels during the visits was beneficial. It is important to allocate enough time for such visits and ensure that they are conducted at an early project stage, where changes can still be incorporated. Moreover, it is important that the monitors performing these visits are well qualified, having both the requisite therapeutic knowledge and cultural sensitivity on top of the generally required knowledge of processes, protocols, regulations, laboratories and experience in clinical research.

Good understanding of trial protocols

Making sure that everyone understands the protocol and knows his/her role and responsibility in the trial is an important factor, as put forward by trial staff and the literature [51]. However, it is challenging in practice, as often staff in SSA, particularly in trials on neglected diseases, have neither a medical background nor prior experience in clinical research [10]. A survey on site initiation visits confirmed our findings, as protocol specific training emerged as a main request by trial staff [40]. The initiation visit presents an ideal opportunity for the site staff to go through each trial procedure in detail and discuss the operationalization of the protocol with the monitor. To coach the team, ensure compliance with the trial protocol and help to correct practices, ideally, the monitor should remain on site during the first few days of recruitment or re-visit the site shortly after recruitment has started. Similarly, Tinto et al. suggested that the Good Clinical Practice trainer supports the trial team in resource-limited settings during trial start [52].

Advantages of prospective planning

We are aware that the suggestions presented here to increase protocol suitability involve costs and might cause study start delays. However, a recent study by CTTI (Clinical Trials Transformation Initiative) confirmed that to overcome inefficiencies, an approach that emphasizes error prevention over remediation should be the norm [21]. Currently, the intense monitoring, auditing and inspecting processes test for errors during the trial rather than prospectively identifying, preventing and correcting them. In their quality by design project, the CTTI authors suggest, in line with our findings, that protocol issues should be identified early to minimize their impact and to describe the infrastructure, resources and training needs of the site [53]. Another study showed that to ensure data integrity, training and motivating sites is much more cost-effective compared to 100% source data verification [54]. To ensure quality, CTTI encourages critical thinking, addressing implementation challenges proactively and incorporating lessons learned into other trials as a means of continuous improvement. Protocol suitability-enhancing measures may also reduce the number of amendments, minimizing its negative impact on costs, duration, and quality of trials — particularly important given that the majority of survey respondents indicated three to five amendments, on average, per protocol.

Despite the intense pressure on sponsors to accelerate drug development [8], realistic timelines and sufficient time for trial preparation is important for implementing protocol suitability enhancing measures. This is in line with CTTI's assertion that, "Rewarding trial teams who minimize the time to first patient enrolled may serve as a disincentive to devoting time to identifying and preventing errors that matter through trial design" [42].

To ensure that site staff involvement does not delay protocol development and that the process is as efficient as possible, it is important that one person leads the process on the sponsor side and that the protocol development process is clearly defined. The global health trials webpage offers a concept protocol template that provides a format for recording discussions and for presenting a protocol to stakeholders at an early stage [19]. Another promising tool for cost-effective and efficient involvement of stakeholders in protocol development is SWOG, a web-based protocol writing system with integrated support for collaborative reviewing and editing [55]. This tool enables sponsors and trial teams to see each other's comments and reactions immediately, despite the geographical separation, which is particularly large for clinical trials in SSA [18]. The objective of the software developer was to increase the natural collaborative protocol writing process and facilitate interactions and communications among protocol writers [55].

Internal validity

Due to time restrictions in this investigation, we covered the site teams' perspective without incorporating the sponsors' view. The interviewer of the qualitative interviews is a female Swiss scientist, which may have biased interviewees towards giving a positive answer. The survey sample is a convenience sample, as it is impossible to eliminate nonresponse bias in online surveys. However, by providing the characteristics of survey respondents, we decreased the bias of nonresponses. Triangulation of perspectives through the mixed methods approach further decreased the bias. As EDCTP, pharmaceutical companies and Swiss TPH sent out the survey and are simultaneously potential sponsors or funders, survey respondents might have had a tendency to answer questions in a manner that would be viewed favourably by these organisations. However, we tried to mitigate this concern by ensuring anonymity in the survey's introductory text. Another limitation was incomplete responses received for a few questions. Lastly, we acknowledge that according to the sample size calculation, 200 survey answers would have been required, but despite many efforts we only received 110 answers. Possible reasons were poor internet connectivity and time constraints of trial staff. However, one should consider that the total number of clinical research staff working in SSA is likewise relatively small and we believe that our results are representative for established clinical research centres in SSA.

External validity

We speculate that many of our findings are also applicable for Northern settings. Due to the lack of literature on the topic in general and particularly in SSA, the majority of literature cited in this manuscript is based on the Northern setting and is mostly in line with our findings. An example that is equally true for Northern and Southern settings is the practice of sponsors designing clinical trials, expecting them to fit to the trial site [39]. Based on trial experiences in Northern settings, Farrell *et al.* recommend that differing clinical practices, working environments, and governance regulations should be taken into account [38] and CTTI recommends involving different levels of site staff to increase the quality of the trial [56].

To the best of our knowledge, this is the first study on trial protocol suitability for clinical trials in SSA. We encourage further research on trial protocols and their non-scientific parts, in particular. We promote the exploratory mixed methods methodology in the context where little is known about the research topic, as this approach allows new and important themes to emerge and provides the flexibility to adapt to these themes in subsequent steps.

5.6. Conclusions

By applying an exploratory mixed methods approach, we identified a lack of clarity, implementability and adaptation to trial participants, workforce and infrastructure as the main constraints of protocol suitability. We found that site staff involvement in protocol development, careful assessment of local context, capacity and culture as well as ensuring that staff understands the protocol are the most helpful measures towards increasing protocol suitability, according to trial teams. Considering and involving the site's input at an early stage of protocol development was deemed the best way to increase involvement, as the majority of trial staff did not seek major involvement in protocol development. Our data suggests that the measures presented increase implementability, efficiency and quality of trials in the long run, although it might slightly prolong the protocol development phase. We consider such an approach as particularly useful for clinical trials in SSA, as the protocols are mostly developed by Northern sponsors who might not be familiar with the setting.

5.7. List of abbreviations

SSA, Sub-Saharan Africa; Swiss TPH, Swiss Tropical and Public Health Institute; EDCTP, European & Developing Countries Clinical Trials Partnership; PI, Principle investigator; CRO, Contract research organization; CAB, Community advisory board; CTTI, Clinical Trials Transformation Initiative

5.8. Additional files

Additional file 1: Text S1. Survey-trial protocol, English.pdf

Additional file 2: Text S2. Survey-trial protocol, French.pdf

Additional file 3: Data S3. Data survey protocol.csv

Additional file 4: Table S4. Code book, survey protocol.pdf

5.9. Declarations

Consent for publication

Not applicable.

Availability of data and materials

All quantitative data collected during this study are included in this published article and its supplementary information files (Appendix 3 and 4).

Short interview excerpts and the interview guide are available within the text. Qualitative data cannot be made publicly available as study participants consented to interviews with the understanding that their data would remain anonymous and confidential. Further excerpts of study data are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors` contributions

The study was designed by NV, CB, CP. The data were analyzed and interpreted by NV, CB, CP, JK. Manuscript preparation was done by NV, CB, CP, JK. All authors contributed critically and significantly to drafting a final manuscript. All authors read and approved the final manuscript.

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6. Discussion and conclusions

This thesis investigated challenges in clinical trials in the perception of clinical trial teams in SSA. The main aim was to identify, how efficiency in clinical trials could be improved while maintaining or if possible increasing the level of quality. A specific focus was put on the advantages and challenges of working with the GCP-guideline, as literature states that this guideline's interpretation is a main hindrance of efficiency in trial conduct. In this chapter, first, the main results are summarized and discussed which is followed by a discussion on methodological issues and internal/external validity. Finally, the implications for research and practice are formulated based on the results of the thesis.

6.1. Summary and discussion of main results

In interviews with trial staff it was remarkable how clearly and consistently internal factors emerged as a challenge and as a cause for slowing down clinical trials in SSA. We defined internal factors as exclusively relating to clinical trial teams and sponsors independent of external conditions. We then summarised internal factors that were identified according to two themes, "planning" and "site organisation".

6.1.1. Planning

Trial staff considered rushing through the planning phase would lead to poor trial preparation as a main source for losing time during trial conduct. This is consistent with observations made in the Medicines Research Department of Swiss TPH. In drug development, fast progress is considered to be imperative due to very high costs and frequent competition. For example, Ganju states "the timelines for achieving certain milestones following the completion of phase 2 or 3 trial are very aggressive as the stakes are high" (1). As a result, sponsors and funders pressure teams to meet tight deadlines. However, in the perception of trial teams, this practice results in time losses, which contradicts the general assumption that the application of pressure leads to an increase in efficiency. The result, however, is supported by literature stating that intense planning in clinical trials is particularly important in resource-limited settings (2-4). Observations in our Department confirm high pressure during the planning phase and unrealistic deadlines for milestones. An additional challenge for a contract research organisation (CRO) is the long waiting time for the final contract between CROs and the sponsor. This practice leaves CROs to deal with financial uncertainties as they have to carefully balance how much to invest in the trial during the waiting time. In reference to short planning phases, Jon Ward, Chief Executive Officer at Aspen Clinical Research, recently asked: "Why is everyone rushing to try and get their study out there first rather than actually putting the time in to do it right the first time?" (5) Viewed from the outside it is obvious that it takes a lot of planning for big and complex projects such as clinical trials, and that budget feasibility and a clear project idea are indispensable prerequisites.

Adaptation to the context

Interviewees particularly stressed the importance of adapting the trial to the context in the planning phase. A trial that is suitable for the setting encounters fewer challenges and is more efficiently executable. Literature confirms trial staff's opinion that adapting projects to the context prevents time-consuming errors and challenges along the way (6-8). "Each trial is unique, therefore what works for one trial may not work for another, just as what works for one site may not work for another" states Eastabrook *et al.* (9). A possible explanation for unadapted trial projects is that trials in SSA often have Northern sponsors who might not be familiar with or ignore setting differences.

In interviews the missing context adaptation and the low degree of implementability of trials were raised particularly often in relation to the trial protocol. In an online survey we followed up on protocols`

context-adaptation. We found that compared to qualitative interviews most trial staff rated trial aspects as rather well adapted, particularly inclusion and exclusion criteria and follow-up procedures, which surprised us as in literature follow-up is described as a challenge (8, 10, 11). These differences in findings might be explained by the different methodologies used. The degree of adaptation to availability and needs of trial participants, in turn, was rated as low in our online survey which is in line with qualitative interviews. For example visit windows and patient flow should take into account trial participants' obligations and their fear of taking blood. The importance of adapting projects to research participants' cultural norms and values has often been described (6, 8, 11). We consider community advisory boards (CABs), which exist in some established clinical research centres, as a useful entity as they are directly in touch with communities. In trials CABs are mainly responsible for community engagement and for appropriately informing the community about a respective study (12). However, in light of our findings, we suggest already involving the CAB at the conception stage of the trial and thereby assisting sponsors in gathering information on the environment, culture, and values of trial participants. In addition, protocol's adaptation to the available site workforce and daily clinical practice was rated as poor in the survey. Our data suggests that sponsors should carefully assess the framework and inquire about what went wrong in previous trials.

Involvement of trial site staff

A majority of interviewees suggested involving local staff in planning to increase trial suitability and efficiency. Local trial staff know their setting and might have valuable experiences to share. The investigator (i.e. the site) and the sponsor have clearly defined roles in trials. While in academic trials investigators would take the role of both, investigators and sponsors, in most trials in SSA the sponsor and the site / investigator are separate entities. The sponsor's role is very prominent and limits the influence of the investigator / research site, which is a particularity of clinical trials. Yet, there is the saying that "the people on the spot know where the shoe pinches", which refers to the practical site (i.e. the local trial team) having the best source of information in regard to creating a project that is adapted to the context and considers capacities, limitations, and requirements as well as efficient execution. In addition, there is evidence in literature about the advantages of involving local trials teams in SSA (2, 13). Particularly local staff's input on recruiting and follow-up of participants can conceivably speed up trials (11). Furthermore, adjustments to the site's procedures and routines can accelerate the implementation of the trial. We consider the involvement of local staff from established clinical research centres as particularly helpful thanks to their perennial experience. Due to the often lacking trial experience of staff working in neglected disease trials in remote areas, their involvement might be less useful but their knowledge of the context can nonetheless be helpful. The importance of collaboration from the start on has also been emphasised in the transboundary research principles of the Commission for Research Partnerships with Developing Countries (KFPE). They recommend to set the agenda together with stakeholders and to interact with stakeholders (14). Finally, the following African proverb is also in line with our findings: "If you want to go quickly, go alone. If you want to go far, go together."

Interviewees regarded their involvement as particularly important for informing the trial protocol which serves as the manual for the trial. In our online survey involvement of local staff in study planning/ protocol development was rated as the most helpful measure to increase protocol suitability. We followed this up and investigated what kind of involvement would be most helpful. We found that trial staff rated participating in prediscussions of a protocol and reviewing the protocol as most helpful. Involved personnel would ideally be operationally experienced. Moreover, to have a trial protocol that is effectively implementable at each site we suggest to not have too many details in the protocol and instead have working instructions per site, while ensuring that all sites still measure the same. In addition, trial teams stressed that their experience should be solicited at an early stage, where meaningful input can still be incorporated by sponsors. In addition to involvement of trial staff, a few interviewees also recommended getting in touch with ECs and DRAs in the protocol development phase, which is consistent with literature (15). These authorities' input might help avoiding negative review during the approval process prospectively.

6.1.2. Site organisation

The second emerging theme was “site organisation” and included staff turnover, employment conditions, career path, workload, delegation, and management. We found high staff-turnover-rates in visited centres (except the two centres in Senegal) which is confirmed by literature (2, 4, 16). Reasons for the high turnover are; first, a lack of human resources, second that working in the centre is a springboard for a career abroad or in another field, and third, that the working environment of trials requires details, rigor, and a lot of administration, which might not suit every personality. Interviewees and literature perceived experienced staff as crucial for the supportive supervision of and as role models for the many inexperienced staff (4), indicating the challenges of losing experienced staff. Staff turnover is generally a challenge in health facilities in resource-limited settings as it is associated with increasing workloads, lowering the quality of services, reducing team productivity, and leading to a loss of institutional knowledge (17). Our data suggest that better career paths for clinical researchers would increase retention of staff. Options to increase the status of clinical scientists are creation of a career structure with perspectives of promotion and involvement in trial planning instead of only executing projects for others. In addition to the missing career path, recognition for clinical researchers is generally limited. Often society does not recognize the value of clinical trials as an indispensable part of developing new medicines that can potentially save lives and increase quality of life. This discourages staff from entering this career path. Moreover, clinical research has only limited recognition from the science community. In science the emphasis is on publications and as trial staff members are rarely authors of publications, their efforts are valued to a limited extent. Moreover, this already limited recognition often goes solely to the principle investigator instead of the whole trial team (18).

A few interview partners directly mentioned the importance of management in order to save time in clinical trials. Furthermore, we argue that all site organisational factors slowing down clinical trials are influenced by management. The WHO stresses the need for management in the health sector and Greg Martin, chief administrator and community director at careersinpublichealth.net, states that management is the competency that is most thoroughly missing in public health organizations. He particularly recommends knowledge on gant-chart, business process mapping notation, incentives, feedback, budgets, and balanced score cards. Meanwhile our data suggests that management should focus on winning staff commitment, creating an area of expertise and using human resources optimally by allocating clear tasks to appropriately trained as well as suitably qualified professionals. In addition, good institutional organization and building a portfolio, preferably going beyond a single disease, is indispensable for the sustainability of a trial centre (2). Cutts *et al.* confirmed the significance of management and noted that it takes up a large amount of time in clinical trials (19).

6.1.3. Differences in English- and French-speaking African countries

Main differences in the results from English- and French-speaking countries were that collaboration with the sponsor was more challenging and unadapted trials were reported more often in French-speaking countries. This could be the result of increased language barriers, as protocols and communication with sponsors are often in English. The challenges of language barriers have been described in the literature as well (20). Another difference was that the position of the study coordinator did not exist in French-speaking African countries and investigators could not delegate administrative tasks, but rather these tasks came in addition to the already high workload. In addition, the missing management was also mainly raised by high-ranking staff members working in French-speaking countries and less frequently reported in English-speaking countries.

6.1.4. External factors contributing to decreases in efficiency

In addition to the described internal themes, “planning” and “site organization”, two external themes emerged in interviews, which contributed to losses in time and challenges. “Patient management” was an external theme as the respective patients for a trial are a given part of the setting. Difficulties with

patients involved that they were often not familiar with the concept of research which might lead to misunderstandings and rumours. In addition, interviewees described that a lack of sufficient and appropriate community and patient information, as well as difficulties with identification of balanced incentives led to fears and rumours. This contributed to inadequate recruitment or losses to follow-up which slowed down trials. Interviewees pointed to the importance of community engagement and sensitisation. The second external theme was “lengthy approval procedures”. The waiting time for approvals from DRAs and ECs was a frequently mentioned cause for lost time by trial staff. Some interviewees mentioned that ECs and DRAs have only recently been established and are inexperienced. As a reason for lengthy approval processes, interviewees mentioned for example that these authorities would not have enough meetings where they decide on approvals.

6.1.5. Research on trial practices in sub-Saharan Africa

There are only a few papers available describing experiences, perspectives, challenges, and opportunities in conducting clinical trials in SSA (2, 3, 6, 7, 11, 15, 16, 19, 21-23). Most of them were published during the first two years of the thesis in 2013 and 2014 and there is a growing body of literature about the experiences performing clinical trials in SSA (4). The few manuscripts tie in with our findings generally. Findings that were mentioned in several publications were the importance of clear monitoring plans, that includes sufficient budget for monitoring activities (6, 11, 21), challenges in the follow-up procedures and adherence to study protocol (2, 11). Regulatory bottlenecks are also mentioned especially the lengthy approval time (16, 22), as well as the necessity of a harmonized ethical review process where the roles of the various ECs are rather complementary than duplicative (2, 21). That free medical care presents an incentive to participate in the trial, was the most frequently described ethical issue (6, 10). Other topics were more correlated to human resources and the importance of managing human resources well (19, 22). More specifically these publications stressed the importance and challenges of training (7, 11). As an example the experience of a poliomyelitis vaccine trial shows that in-house, targeted and systematic training programs worked best (7). Missing career paths (6, 23) and brain drain of trial staff (16, 19) were further challenges identified in case-studies and are fully in line with our findings. Additional findings are also consistent with our study and have been cited when presenting results in the previous paragraphs.

However, the main differences to our study are that existing literature mainly focuses on describing challenges and opportunities of external conditions which we defined as the given conditions of the framework in which clinical trials operate in these settings. In our study interviewees extensively mentioned issues related to internal conditions. A reason for this could be the different methodology used as all but one manuscript base their findings on personal opinions of the authors and are not applying any research methodology. Authors of these papers usually consist of high-ranked staff and/or Northern expatriates who worked in the trial. The one exception is the study by Franzen *et al.* applying qualitative methodology (22).

6.1.6. Quality of clinical trials

So far the focus of this discussion was on efficiency and not on quality. During setting up the PhD project we had various discussions on how to measure the quality of clinical trials for this project, however, no suitable measuring method could be identified. An elaborated method for measuring quality in clinical trials does not exist and research on the topic is needed. We therefore decided it would be best to directly ask local trial staff about what is important concerning quality and how quality could be improved in their perspective. Interestingly, our findings show that factors inhibiting efficiency were often associated with a decrease of quality as well, indicating that improvements to “planning” and “site organisation” might increase trial quality on top of efficiency.

6.1.7. The Good Clinical Practice guideline

Based on the original literature, the main hypothesis in this PhD-project was that the way GCP is interpreted and applied in practice is a hindrance for efficient trial conduct in SSA. Hence, we explored the advantages and challenges of working with the GCP guideline and its interpretation in the perspective of clinical trial teams based in SSA. We found that interviewed clinical trial staff perceived the GCP guideline as very helpful in guiding their daily work and ensuring an international standard. Staff did not mention any unnecessary administration, repetition or details although we asked probing questions during interviews. This result was found consistently, independent of the country or the organizational level of interviewees. We concluded that GCP is not being applied overcautiously from the perspective of visited trial teams and not a hindrance of efficiency. The result supports the general opinion that GCP is an appropriate guideline for RLCs (23-27) and is consistent with Tominaga and Toshiyoshi stating “the ICH was a successful harmonization initiative” (28). It is, however, refuting our hypothesis as well as those authors that claim an adequate and applicable interpretation of GCP was missing for RLCs (26, 29, 30). Trial staff was concerned that a more pragmatic interpretation of GCP would compromise quality. To the best of our knowledge, this is the first study on the topic, the debate in literature is not supported by any systematic research but has been introduced largely by reflections of northern expatriates working in RLCs.

In her very recently published PhD-thesis, R. Ravinetto addresses the appropriateness of GCP for clinical trials in low and middle-income countries and gives several suggestions for points to add in GCP (31). Examples of such suggestions are that the international GCP codes should include the distinction between commercial sponsors and non-commercial sponsors (the later depends on external funding), that the qualifications, responsibilities and monitoring/supervision of clinical trials laboratories should be specified and double ethical review should be required for externally sponsored research. During the Geneva Health Forum 2016, the author organized a restricted workshop session on the GCP guideline in low and middle income countries. Participants agreed on the importance of her suggestions but there was no consensus of whether the suggestions should be included into GCP or rather be part of national laws in these countries. None of her suggestions for GCP came up in our interviews with trial staff in SSA. The majority of interviewed trial staff, however, expressed that they wanted the same guideline to be used worldwide. This topic is also debated in literature; Hanna *et al.* advocates full adherence to ICH-GCP (27) and others recommend that at least GCP’s core elements should be preserved (26, 30).

6.1.8. The informed consent procedure

Despite an overall willingness to work with GCP, one-third of the interviewees in both language regions perceived GCP to be unsuitable for the IC process. Although it surprised us to learn that in trial staff’s experience, IC challenges were more pertinent than the administrative requirements, it is perhaps not so unexpected, as the guideline was developed for different cultural and educational characteristics of trial participants than those found in SSA. Difficulties identified of the GCP requirements for the IC were 1) obtaining written and individual consent as communities in SSA have an oral tradition and are often shaped culturally by a sense of collectivity e.g. in some regions a child belongs to the whole community, hence, community consent is more important in these settings than individual consent 2) fulfilling the GCP requirement of having an impartial witness present for consent of illiterate trial participants can be challenging when too few literate individuals are available or willing to serve as truly impartial witnesses 3) documents confirming a child’s legally acceptable representative, as required by GCP, may not be available. At the same time, it is common for relatives to care for a child in place of the biological parents 4) guaranteeing voluntariness and full understanding of the consent given is challenging when the language of the IC form is highly technical as well as lengthy and certain scientific words are not existing in local languages. IC difficulties in SSA are also mentioned repeatedly in literature (6, 27, 32-34). There are additional IC difficulties described in literature for example that, the system is hierarchical and patriarchal which exacerbates complications of ensuring voluntariness of the IC procedure (35). Trial participants trust that the doctor

knows what is best for them. Furthermore, based on experiences from our Department it is unclear if the mother of a child can take the role of legally acceptable representatives if she is a minor. In some countries like Burkina Faso the age of majority is not clearly defined by law. Often times the birth certificate is missing and trial participants' majority cannot be checked. Based on the interview data and experiences from our Department clear answers for context-specific IC questions are often missing. We deem it important to find appropriate solutions for all listed difficulties as the IC is one of the main reasons why trials are stopped.

New technology has the potential to increase the understanding of the IC. For example Afolabi *et al.* tested a multimedia tool integrating video, animations, and audio narrations in Gambia and found that participants understood certain domains of the IC better compared to the traditional consent interview (36). In addition, he found that the multimedia tool was acceptable and easy to administer among low literacy participants. There are also simpler tools such as info sheets with pictures or graphical study flow charts, to assist the IC process. We had the impression that trial staff was unsure if and how technology could be incorporated and that supporting and clarifying guidance would be useful.

We consider that the root cause of IC challenges in reference to the GCP guideline is that legal requirements contradict cultural practices. In line with experts in the field we suggest to take the ethical rather than the legal way if in doubt. Compared to ICH-GCP AVAREF-GCP also states that IC has to be obtained in accordance with national culture(s) and requirements (37). However, this does not mean that cultural practices must be accepted uncritically (34). For example, only informing the patient's family but not the patient of a serious disease prohibits a consent to be informed.

On one hand, we had the impression that some trial staff seemed unaware that GCP as a guideline allows for an adapted application. For example, GCP does not explicitly require written consent. Hence, if the local law does not require written consent, deviation from the guideline is possible. Deviations from the guideline for other processes are possible if they are thoroughly explained in the protocol. On the other hand, such an approach requires that ECs and DRAs cooperate and assist in finding, accepting and finally approving such solutions that are not fully in line with the guideline. We generally had the impression that authorities were not able to assist trial teams in mitigating their consent challenges. Depending on the countries ECs and DRAs may be young, inexperienced, and sometimes struggling with limited resources and capacities which might limit their commitment and disposition to support. Finally, concrete guidance on how to best apply GCP in the face of consent challenges was perceived to be missing by interviewees. Neither seems the planned addendum for GCP to involve any changes or elaborations for the IC process, the published draft addendum mainly elaborates on the application of new technology and risk-based quality management and monitoring (38).

The length and technical language of the consent form is a highly debated topic in both the North and South, as well as the view that its content serves mainly to protect sponsors (33, 34, 39). Flynn *et al.* complain that ICs are filled with legal terms (40). Considering the need for strategies to enhance comprehension of the IC the Clinical Trials Transformation Initiative (CTTI) very recently published a list of recommendations based on a literature review, expert interviews and multi-stakeholder meetings (41). Authors stress that the research staff providing the IC needs to be well-trained, responsive and sensitive to participants' emotional disposition, culture, level of education and inquiries. Authors recommend that the IC form is used as a support document for the overall IC process rather than the primary focus. CTTI suggests the use of a tiered approach in developing the IC form. They recommend that the first part of the form only contains the basic elements of the IC that are required by law and are critical to the decision-making process. The second part of the IC form should contain additional information grouped in chapters. It would then be the trial participants' choice to select which further information is of interest to them. Moreover, the form should incorporate plain language principles and offer flexibility with approaches. We agree with CTTI that the implementation of new processes in clinical research is often challenging, but we consider these research-based recommendations as valuable for trials in SSA as well to increase understandability of the IC.

To mitigate IC challenges we deem it important that the purpose of the IC process (ensuring freely given consent and receipt of adequate information prior to decision-making) is at the forefront. GCP as a guideline is supposed to be a helpful tool for this process. If GCP-requirements are against cultural norms, deviations are allowed as it is a guideline and not a law. Despite our finding that GCP is not over-interpreted in the perspective of trial staff, there is a risk in trials of focusing mainly on compliance with the guideline instead of the ethical principles behind the guideline. We argue it is about taking the principle and not the letter and deem it essential to teach this in trainings.

6.1.9. The concept of efficiency

In the introduction, we explained why efficiency is important for clinical trials in SSA. In the light of our findings, the concept of efficiency as it stands may be questioned though. We found that efficiency is decreased because there is not enough effort put into planning. Yet, the reason why sponsors cut down the planning phase is their intention to speed up trials by starting recruitment as early as possible. The urge to increase efficiency thus lead to the unsustainable measure of shortening planning. This situation is even aggravated because of the often lengthy contracting processes in larger companies. We consider the concept of systems thinking to be useful as it teaches us about the inter-dependence of components within a system (42). As clinical trials are big projects that include multiple parts such as data collection, patient-, quality- and data management, we may consider a trial as a system. In systems thinking we learn that we carefully have to check the consequences of measures before their implementation as they may affect other parts of the system. For example, in health systems human resources are one out of six building blocks of the system which ties in with our finding that local trial staff needs to be considered during set-up.

Philosophically, one might even take this thoughts one step further and question the general concept of efficiency. In the book “Momo” Michael Ende teaches us that time cannot be saved and time-saving measures only lead to exhaustion and unhappiness (43). Moreover, when we asked a Senegalese study coordinator ‘how time could be saved in clinical trials?’, he referred to the concept of efficiency as a Western concept unsuitable for his setting.

« Il y-a-t-il des pertes de temps ? Pour nous Africains, il n’y a pas de pertes de temps mais pour vous Européens il y a perde des temps. Parce que le temps / pour nous le temps c’est différent que vous le voyez. En Europe tous est rapide. On fait des choses tac, tac, tac, tac c’est à dire les choses doivent être / voilà on ne perde pas de temps, on fait tel jour ceci, l’autre jour etc. C’est différent parce que l’environnement est différent. Ici il faut prendre le temps, il faut prendre son temps pour bien faire les choses. Les gens ne réagissent pas de la même manière et souvent c’est un problème entre les chercheurs Africains et les chercheurs Européens. »

Study coordinator, Senegal, m, centre one

On top of this criticism that Western efficiency enhancing concepts may not work in other settings, the obsession of managers on gaining efficiency as a current attitude in business is generally criticised (44). This obsession may prevent companies from achieving differentiation, sustainable growth and innovations for their business (44). The emphasis on efficiency is rooted in the belief that companies that work less efficiently than their competitors will be eliminated from the market. The author stresses that business managers rarely understand the exact meaning of efficiency and effectiveness and often ignore the latter. While efficiency stands for “doing things right”, effectiveness means “doing the right things” and focuses on results. We consider that this applies to drug development, too, and sponsors are tempted to make cuts to the planning phases and not involving site staff to increase efficiency. By doing so sponsors solely focus on efficiency whilst neglecting effectiveness. We deem it important to take a step back and be reminded of the overall goal and incorporate effectiveness while trying to increase efficiency.

6.2. Methodological issues

An exploratory mixed methods design that includes key informant interviews as well as an online survey was employed in this study. Having two different methods and conducting interviews in different settings allowed for triangulation of data and analysis of aims from different perspectives. The exploratory approach of the study design allowed us to follow up on emerging topics, which is useful in a field where it is not possible to build on previous research. The flexibility this approach offers proved to be useful for this thesis, as the main hypothesis, the way GCP is interpreted and applied in clinical trials is a main hindrance of efficiency, was not confirmed and therefore allowed us to follow up on more pertinent topics. In this thesis qualitative interviews made up the main part which is common for exploratory mixed methods designs. The openness of the qualitative approach allowed for in-depth exploration and enabled respondents to not only list challenges but also to elaborate on possible solutions as well. Interviewees presented several solutions which would not have been possible with a closed questioning format. Moreover, clinical trial conduct is a practical topic and such topics are generally difficult to investigate by collecting numbers.

All qualitative and quantitative data collected are experiences and perceptions of trial staff working in SSA. We found that experiences of local trial staff are a valuable source of information to identify challenges and develop solutions. Trial staff works in trial practice and is exposed to the challenges and inefficiencies in trials on a daily basis. Moreover, trial staff is critically important for the overall success of the trial. Interviewing different organisational levels of trial staff further allowed for triangulation of perspectives. So far, perceptions of trial staff are rarely acknowledged in scientific literature and we encourage future research involving trial staff's experiences. In another study authors recommended having an additional section in the case report form for trial staff to report their challenges (45). Authors state that this systematic collection of trial staff's experiences would assist in informing and improving practices of future trials.

Interviews are highly suitable for exploring and gaining an overview of a new topic but potential interviewer bias needs to be considered (46). Interviewees may protect their privacy and adapt their responses to what they think the interviewer would expect or like to hear. Data were collected by a female Swiss scientist and since monitoring and auditing visits are often carried out by foreigners this might have contributed to a degree of bias like influencing interviewees towards giving a positive answer and not mentioning difficulties. Moreover, we were not able to check discrepancies between what interviewees say and what processes they actually follow in everyday trial practice in the interview-based approach. This was particularly a concern for the study on advantages and challenges of working with the GCP-guideline as we did not know the extent to which clinical trial teams follow GCP in practice. However, we deliberately avoided testing interviewee's GCP knowledge as we wanted to provide an atmosphere conducive to open expression. Structured observations would have been a suitable approach to investigate processes in practice but permission for observing staff at their work place may not have been granted from the centres. In another study investigating complex intervention trials the researchers used an autoethnographic approach. In this study the researcher who conducted the interviews was at the same time member of the study team, which enabled observations of trial practice (47). We consider such an approach suitable for future research as it would allow collecting additional data of organizational culture and practices.

For our study we stayed on site for one week but we consider that longer stays on site would have helped to build up trust with interviewees, to limit interviewer bias and to gather more informal data. However, we announced our visits at least one month in advance and sent out an information sheet on the studies objectives, rationale and interview procedures in order to build up trust and openness with interviewees. On site we distributed this sheet as well before the interview and during the introduction of the interview we explained the study, ensured anonymity, explained what is going to happen with the results, gave the opportunity to ask questions and encouraged to speak openly. The

fact that we conducted the interviews with researchers also somewhat mitigated the limitations described, as trial staff understood the concept of research. Trust may have been built up more quickly as both the interviewer and the interviewee had a research as well as a medical background. In addition all visited research centres have long-standing experience in clinical research and have been repeatedly monitored and audited. Information gathered in informal conversations with trial teams and external monitors who were on site during our visit complemented artificial interview situations. Exchange and discussions with supervisors and professionals with extensive field-work experience helped to avoid misinterpretations due to cultural or hierarchical differences.

It is important to note that due to the focus of the work and time restrictions in this study we exclusively covered the site teams' perspective without incorporating the sponsors' view. As the site implements the trial we considered investigations of the site's perspective as most important for our research questions. However, as several findings are closely linked to the collaboration with sponsors our approach might have given an unbalanced view. To a certain extent we mitigated this concern by the attendance of the weekly team meeting of the Medicines Research Department. As a CRO the Department is taking over certain sponsor responsibilities for clinical trials in low-resource settings, predominantly SSA. By attending this meeting for 3.5 years the researcher got insights into sponsors' perceptions, concerns and responsibilities as well as the way sponsors, sites and CROs operate together. Moreover, the researcher had the opportunity to gain additional insights during two co-monitoring visits in SSA.

Based on the main findings from the qualitative interviews we developed an online survey on the emerging topic of protocol suitability to enable triangulation of perspectives and to provide a bigger sample size. With little effort online surveys can be distributed to a large number of participants in different geographical areas which enabled distribution across SSA. Limitations of online surveys are the poor response rates. In our survey we were not able to reach the target sample size, possible explanations are poor internet connectivity and time constraints of trial staff. Received answers of the online survey are a convenience sample as it is impossible to eliminate nonresponse bias in online surveys.

External validity

Qualitative research is constrained in terms of its generalizability due to small sample sizes (48). To increase the generalizability of our study across SSA we conducted interviews in four countries and different language and geographical regions of SSA. We deliberately chose to conduct all interviews in established clinical research centres with a focus on poverty-related diseases. We gained confidence about the evidence presented as we identified the same themes independent of the staff level and with only little variations between countries. Thus, we consider that findings might be generally applicable for established clinical research centres in SSA, so-called centres of excellence, with a focus on poverty-related diseases.

Trials investigating medicines for neglected tropical diseases in SSA are mostly conducted in remote field sites (due to the epidemiology of the disease) which often do not have previous experience in clinical research. Due to the lack of experience of these trial teams, we considered that trial staff in established research centres was the better source of information for our study. As our findings exclusively originate from established centres they might differ from the situation in neglected diseases trials in remote areas. For example, capacity building might be of higher importance for such trials. The available literature on trial conduct in the North and also feedbacks concerning study findings suggest that our results are also partly applicable for clinical research in Northern settings. As the GCP-guideline is the globally-accepted trial standard and the same steps and the same documents are applied in trials independent of the setting. Hence, similar challenges and inefficiencies may arise which is additionally supported by Hanna *et al.* stating "challenges identified in the process are not unique to RLCs: some of them have been confronted in wealthier countries" (27).

For example IC problems are also repeatedly mentioned in Northern settings (33, 39). While vulnerability and illiteracy are not predominant, particularly lacking consent understandability and the length of the IC form is criticized in the Northern settings as well (40). Other challenges present in Northern as well as Southern settings are uncertain career prospects (49) and a lack of management (37), Farrell et al state “science alone will not sufficient to successfully deliver a trial” (49). In a study in Northern settings on complex intervention trials authors particularly pointed to the importance of leadership, staff relations and role distributions (47). High staff turnover is also present in both settings, however, the lack of qualified and experienced health staff is more challenging in SSA (48). Consistent with our study Strong *et al.* found in a trial conducted in the North that working with the same members for a number of years was increasing the efficiency of the team (50). To invest in planning and prospectively avoid mistakes instead of only controlling for them in the end has also been stressed (51) and particular unrealistic deadlines are often mentioned (49, 51). Only one-third of trials recruited their original target number within the timeline originally set (49). In parallel to our finding authors state that the trial is owned by the team (52) and that the ownership will be fostered by involvement (49). Missing adaptation to the context, infrastructure and culture are, however, less prominent in Northern settings.

6.3. Implications for research

Not much literature is available on the topic of trial conduct in SSA (3, 19). Available manuscripts are seldom based on a research-approach but are more often either found to be personal reflections or case studies. To improve clinical trials in an evidence-based manner we encourage more studies on trial procedures in SSA.

As we applied an exploratory mixed methods design more research is needed to validate and strengthen our findings. While qualitative research methodology is very suitable for under-researched topics, it is constrained by its generalizability. The findings on internal factors slowing down trials and protocol suitability need to be further investigated on a larger scale as there are no other studies available on these specific topics. Study findings demonstrate that in the perception of trial staff the GCP guideline is applicable and appropriately applied in SSA. To investigate how GCP is applied in trials in SSA, further follow-up studies with longer stays on site are required including observations. Based on our findings, specific questions for future research are; how the planning process could be improved to avoid challenges and inefficiencies in trial processes and how attractiveness of clinical research careers could be enhanced. Additionally, we found that more research is needed to find solutions for identified uncertainties in the IC process. Future topics of interest to a certain extent included in our interview data and literature but less closely related to our findings are; the recruitment process, and how much and which data is to be collected in trials.

As health research is dominated by quantitative approaches we encourage more qualitative research including interviews, focus group discussions, and observations particularly for practical topics such as clinical trials. Local trial staff members proved to be a valuable source of information in this thesis.

In our study we exclusively investigated the perception of trial site staff without incorporating sponsor`s perception. To get more insights into collaborations and planning phases of trials we deem it important to additionally investigate sponsors` experiences as well as their interests to have data from both sides.

We conducted our study in established clinical research centres in SSA with a focus on poverty-related diseases. Trials on neglected tropical diseases, however, are usually conducted in remote field sites due to the epidemiology of the disease. It is unclear to which extent our findings apply to these trials. Studies on the conduct of neglected diseases trials are needed to develop specific recommendations for these settings.

In our view the findings may also be true for research in other settings such as the North. Clinical trials worldwide follow the GCP guideline and involve the same steps, the same documents, and people are trained in similar ways. It would therefore not be so surprising to find that the challenges faced are comparable. To that avail, we started a control-study in Europe to conduct the same interviews in European clinical research centres. Due to time restrictions, we were not able to finish this study meaning that further investigation of similarities and differences in the optimisation of trial processes in low-resource settings and the North is needed.

6.4. Implications for practice

Our study findings highlight the following recommendations for practice in clinical trials in SSA. Although most of the recommendations appear to be obvious, they have previously not been shown and investigated due to a lack of research in the field. Moreover, in the experience of our Department these recommendations are often violated. We deem it important that findings and recommendations are also incorporated in teaching practices. The first two recommendations concern internal challenges and opportunities, we argue that internal challenges can be tackled more easily as they are independent of external conditions which we defined as the given conditions of the framework in which clinical trials operate in these settings.

Importance of careful planning

This study found that good planning increases efficiency of clinical trials. In clinical trials the focus is generally on correction (e.g. monitoring and auditing) rather than mitigation. We advocate prospective planning instead of damage control as input (planning and preparations before trial start) equals output (efficient and effective trial procedures). Assessing feasibility of trials (i.e. is trial execution possible?) before full preparations start is important, however, our data suggests looking beyond feasibility and assessing suitability (i.e. is an effective and efficient trial execution possible?). For example, suitability considers socio-cultural aspects which we often found to be insufficiently addressed during trial planning, which can result in difficulties with trial participants. We deem suitability to be particularly important for trials in SSA where Northern sponsors mostly develop the trial project. We found that enhanced suitability increases efficiency, quality and implementability in the long run. We identified involvement of local site staff in planning as the most helpful measure to improve trial suitability. We are aware that involvement of site staff involves costs and might cause a delay to the start of the study but this can be minimized by a number of measures. For instance a clearly defined process, technology that allows for collaborative reviewing and editing, as well as one person leading the process on the sponsor side. In our opinion a minimal involvement for a multicentre trial would be to involve a technical trial team member from the sites with the highest expected recruitment rates in an early stage of trial planning. In addition, we suggest to prospectively involve the community advisory board (CAB) to assist in informing about trial participants needs, values, and cultural norms before the protocol development as part of a careful assessment of context, culture, and resources by sponsors. We advocate for prospective planning and argue that clinical trials should be seen as huge projects involving multiple parts which can learn from systems-thinking. We deem that the inter-dependence of components in trials has not been considered sufficiently. Finally while focusing on efficiency, effectiveness has to be incorporated by having the aim of the trial (to help patients by testing a medicine in an ethical trial that produces reliable data) always at the centre regardless of the component one is responsible for.

Management and leadership of trial sites/ centres

Scientists are not necessarily fond of management and are often lacking respective training and experience. However, our data stresses the importance of institutional management for an effective work environment. This finding is backed up by literature in other health domains (53, 54), however,

this has neither been acknowledged nor implemented sufficiently in our opinion. We found that management and leadership have a positive influence on site organizational challenges such as staff turnover, employment conditions, career path, workload, and delegation. Free massive open online courses (MOOCs) on management are available and we suggest that basic management concepts are already taught in medical and nursing school. Effective on-the-job methods for improving management also exist and incorporate learning-by-doing and action-learning through regular supportive supervision of high-level managers or twinning between similar organisations in developed and developing countries. Training in management would additionally improve the uncertain career prospects of a clinical researcher. On a lower level, study coordinators are of high importance in clinical trials as they relieve investigators to a certain extent from their administrative trial tasks. As we hardly found this position in French-speaking African countries we recommend clinical research centres in these countries to educate and hire study coordinators.

Guidance for the informed consent process (in addition to the GCP guideline)

This study found that no answers are available for several uncertainties concerning the informed consent (IC) process which leaves trial staff in doubt for instance in such situations: 1) How to include a child in a trial if the caregiver is not the parent and the paper confirming his/her status is missing? 2) What to do if the majority of trial participants are illiterate whilst only a few witnesses are available? 3) How to obtain written and individual consent in communities with oral tradition that are culturally shaped by a sense of collectivity 4) Who is the legally acceptable representative of a child whose mother is a minor? 5) How to guarantee voluntariness and full understanding of the consent given if the IC form is technical and scientific words cannot be translated into local languages? 6) How to use new technology to improve the IC process?

First, we argue that complementary guidance to GCP is needed to answer these questions. Such practical guidance for IC would assist trial staff and give them confidence in taking decisions in the IC process. In contrast to a guideline, guidance is not stipulated by rules and regulations but is a form of support and describes authorities' thoughts on issues. It would be useful if such guidance could elaborate on how deviations from the guideline for IC are possible. To ensure that guidance is accessible for everyone we suggest publishing it on the ICH-website. Some documents elaborate on the inclusion of children without legally acceptable representative; the South African ethics guideline allows caregivers to consent when the minor in question does not have a legally acceptable representative (55). Slack and Strode give specific guidance on what questions trial staff should ask in clinical trials in South Africa to identify the status of the child's accompanying adult (56). Bwakura-Dangarembizi *et al.* report having been allowed a waiver to the legal guardianship requirement by the Zimbabwean Ethics Committee if caregivers were recognized by the families (57). Ravinetto suggests changing the term legally acceptable representative into "ethically and culturally acceptable representative" (31). To increase understandability of the consent in RLCs The Nuffield Council on Bioethics recommends to organise meetings with participants, providing information through health workers rather than physicians and to test the level of understanding in a test (34). Further they encourage assent and involvement of communities in cultures where it is inappropriate for an individual to consent without the community. We consider that such research and local regulations form an ideal basis for the development of a guidance for the IC.

Second, we consider it important that sponsors are aware of IC challenges in SSA and assist in developing mitigation strategies prospectively in the planning phase. Such planning would incorporate good assessment and understanding of the setting to identify IC issues in advance. We consider the involvement of the community advisory board (CAB) as helpful as they are the link between the trial sites and the communities and would be ideal partners to consult communities and identify the suitability of approaches in the setting. In addition, to identify IC issues prospectively we suggest collecting information on past experiences and involving trial staff as they know their setting for the development of mitigation strategies. Moreover, we recommend soliciting local ECs as they have access to information on trials carried out in their region or country.

Thinking outside of the box to improve clinical trials

The current focus in non-academic clinical research is on regulatory compliance and speed, not necessarily on good processes. Moreover, there is hardly any research performed on trial conduct. Alsumidaie calls clinical research an antiquated system and mentions a natural hesitation towards changes in clinical trials (58). To improve processes in clinical trials we suggest consolidating other fields (in health or external), that are focusing on improving processes and whose idea could potentially be copied for clinical trials.

Within the health sector the measurement of the quality of care is the first example, WHO states that they are crucial to meet sustainable development goal 3 “to ensure healthy lives and promote well-being for all at all ages” (59). However, quality of care measurements face similar difficulties to trial quality measurements as quality involves multiple factors and is very subjective i.e. differs depending on the focus area. According to WHO, the best way to measure quality of care are clinical observations, however, they are expensive to collect. WHO suggests measuring quality for each dimension separately; infrastructure and staffing, technical quality and patient experience. However, current quality measures are not sufficiently validated and need to be feasible therefore WHO launched a call this spring for research on measuring quality of care in low- and middle-income countries (59).

Second, WHO has an expert group on evidence-based guideline development and adaptation in the region and they found that the variety of contexts and cultures across regions are a challenge for the uptake of globally WHO-developed guidelines (60). Authors stress the importance of discussing the needs of the end-users. We consider that such recommendations from expert groups of global guidelines could also help to inform clinical trial guidelines for low-resource settings.

We deem that clinical research can also learn from other fields like aviation where the demand for high safety and quality combined with great pressure are ubiquitous just as for clinical trials.

In conclusion, this thesis investigated the perceptions, experiences and interests of trial staff based in SSA. The findings of this study underline the importance of internal trial factors, which we defined as factors exclusively relating to trial teams and sponsors and may be influence independently of external conditions. The two main internal factors found were planning as well as site organisation and underline the importance of a careful assessment, appropriate and coherent planning, clear task allocation and management capacity strengthening. Considering and involving the study sites and their experiences during trial planning was perceived to be beneficial. This thesis hopes to contribute to a better understanding on how to increase efficiency, quality and implementability of clinical trials in SSA.

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7. Appendix

7.1. Interview guide

Demographic background

1. What kind of positions have you already had within clinical research?
2. What was tested in your trials: drugs, vaccines, diagnostics or medical devices?
3. In which phases of trials have you been involved in?
4. For how many years have you been working in clinical trials?

General questions

1. What is your opinion what is important for having a good quality in clinical trials? We defined quality as patient`s safety and rights and data integrity.
2. Do you think that quality could be improved in clinical trials for improving patient`s safety and rights and data integrity? If yes: how?
3. Is time being lost in the conduct of clinical trials for example with unnecessary repetition or by spending a lot of time for a small detail? If yes where?
4. If I ask the other way around, do you think it would be possible to save time in the conduct of clinical trials? If yes where?
5. Do you face any challenges in the trials?
6. What might be challenges in the future?

Questions about the Good Clinical Practice (GCP) guideline

7. Do you follow any guidelines in your clinical trial work?
8. What is your experience in working with Good Clinical Practice (GCP) guideline or other guidelines in your daily clinical trials work?
Are there any disadvantages or advantages?
9. Are there also some challenges linked to the GCP-guideline or other guidelines?
10. Are there any aspects in GCP or other guidelines which are not applicable?
11. Is there anything you would like to add to the interview? Maybe there is something important and I have not asked it.

7.2. English Information sheet for participants in semi-structured interviews



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Information sheet for participants in semi-structured interviews

Efficiency and quality in conducting clinical trials in low-resource settings

Introduction: My name is Nerina Vischer, I am PhD student at the Swiss Tropical and Public Health Institute. You can find all my contact details above.

Nature of research: This is a PhD project which is designed to gather information about the practical conduct of clinical trials in Sub-Saharan Africa. The workload and the administration are increasing in clinical trials and this is why I am interviewing professionals involved in clinical trials. I would like to get to know the challenges in clinical trials and to find out what would help you in your daily work in clinical trials.

Duration /what is involved: Participation involves being interviewed by Nerina Vischer. The interview will last approximately 45 minutes. The interview will start off with some general questions and then follow up on more detailed things later on. If permitted by you the interview will be recorded with a digital recorder. The reason for this is that I can follow exactly what you said. If you feel in any way uncomfortable by being recorded you can tell me any time and I will stop it. If you do not permit to record the interview, answers will be hand-written.

Potential risks: The interview does not involve any risk. The questions concern the practical conduct of clinical trials and do not ask for personal or medical information.

Benefits: There are no direct benefits but your participation is highly appreciated as you support the project which has the objective to improve the practical conduct of clinical trials in Sub-Saharan Africa.

Costs: The study does not involve any costs for you.

Compensation: There is no financial remuneration.

Confidentiality: The researcher will not identify you by name in any reports using information obtained from this interview, and your confidentiality as a participant in this study will remain secure. To protect the anonymity of you and your institution the interview files will be encrypted



Seite 2

and the list with the codes will be saved in a separate place from the interview files. The files will be stored on a password protected computer.

Voluntary participation/ withdrawal: Your participation in this project is voluntary. You are free not to answer any question and you have the right to withdraw from the study at any time. If you decline to participate or withdraw from the study, no one will be told. You have the right to ask questions any time and they have to be answered to your satisfaction.

Outcome and Feedback: The anonymised data will be analyzed according to standard qualitative data analysis and published in peer-reviewed journals, whereas the results will not be attributable to a center or organization. If you are interested in the study results, NV is going to give you regular updates on the project.

Funding information: The PhD project is funded by the Swiss Tropical and Public Health Institute.

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7.3. English consent for participants in semi-structured interviews



Efficiency and quality in conducting clinical trials in low-resource settings

PhD project Nerina Vischer

- The study has been explained to me in a language that I comprehend. All the questions I had about the study have been answered. I understand what will happen during the interview and what is expected of me.
- I have been informed that it is my right to refuse to take part in the interview today and that if I choose to refuse I do not have to give a reason
- I have been informed that anything I say during the interview today will remain completely confidential: my name will not be used nor any other information that could be used to identify me.

If you want any further information on the study you can contact the following persons:

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 Committee
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Circle response:

I agree to take part in the study:	Yes	No
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Signature of participant:

NAME	SIGNATURE	DATE OF SIGNATURE

Signature of Nerina Vischer taking consent:

I have discussed the study with the respondent named above, in a language he/she can comprehend.

I believe he/she has understood my explanation and agrees to take part in the interview.

NAME	SIGNATURE	DATE OF SIGNATURE



7.4. French information sheet for participants in semi-structured interviews



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Informations pour les participants aux interviews semi-structurés

Efficacité et qualité de la conduite d'études cliniques en Afrique subsaharienne

Project de doctorat de Nerina Vischer

Vous participez volontairement au projet de recherche mené par l'Institut Tropical et de Santé Publique Suisse. Le projet est conçu pour recueillir des informations sur la conduite pratique des études cliniques. La charge de travail et d'administration dans les études cliniques a augmenté et c'est pour cela que nous conduisons des interviews avec des professionnels qui sont impliqué directement dans des essais cliniques. Le but des interviews semi-structuré sera d'identifier les défis rencontrés dans les études cliniques et de trouver des solutions afin de faciliter le travail quotidien en études cliniques.

Votre participation à ce projet est volontaire et vous ne serez pas payé pour votre participation ; il n'y a pas de risques ni de bénéfices. Vous pouvez cesser de participer à tout moment. Si vous refusez de participer ou vous retirez de l'étude, personne n'en sera informé.

La participation implique d'être interviewé par Nerina Vischer, doctorante ou Anne-Sophie Joller, étudiante de Master à l'Institut Tropical et de Santé Publique Suisse. L'interview durera environ 45 minutes. Si vous le permettez l'interview sera enregistré avec un enregistreur numérique en raison de bien pouvoir suivre vos réponses. Si vous ne le permettez pas les réponses seront écrites à la main par l'intervieweur. Vous pouvez toujours décider que vous ne voulez pas répondre à une certaine question.

Vous comprenez que le chercheur ne vous identifie par votre nom dans aucun rapport concernant les informations obtenues dans cet interview, et que votre confidentialité dans cette étude restera sécurisée. L'utilisation ultérieure des documents et données sera soumise à des règles standards de l'utilisation des données qui protègent l'anonymat des individus et des institutions. Les données rendues anonymes seront publiées dans des revues révisées par des pairs, et les résultats ne seront pas attribuables à un centre ou une organisation donnés. Si vous êtes intéressés par les résultats de l'étude, NV vous donnera une mise à jour régulière.



7.5. French consent for participants in semi-structured interviews



Efficacité et qualité de la conduite d'études cliniques en Afrique subsaharienne

Project de doctorat Nerina Vischer

- J'ai reçu une explication concernant la nature, le but, la durée de l'interview et j'ai été informé(e) de ce qu'on attend de ma part. On m'a donné le temps et l'occasion de poser des questions sur l'interview et toutes mes questions ont reçu une réponse satisfaisante.
- J'accepte volontairement de participer à cette étude et je comprends que ma participation n'est pas obligatoire et que je peux stopper ma participation à tout moment sans avoir à me justifier ni encourir aucune responsabilité.
- Je comprends que les informations recueillies sont strictement confidentielles et j'ai été informé que mon identité n'apparaîtra dans aucun rapport ou publication.

Pour plus d'information concernant l'étude contactez :

<p>Nerina Vischer MPharm, Etudiante de doctorat Bureau: +41 61 284 89 74 Portable: +41 79 741 37 67 nerina.vischer@unibas.ch Socinstrasse 57, 4051 Basel, Switzerland</p>	<p>Anne-Sophie Joller Etudiante de Master en Pharmacie Portable : +41 79 759 47 74 a.joller@stud.unibas.ch Socinstrasse 57, 4051 Basel, Switzerland</p>
--	--

Veillez encercler votre réponse:

Je consents de mon plein gré à participer à cette étude :	Oui	Non
---	-----	-----

Signature du participant:

NOM	SIGNATURE	DATE DE LA SIGNATURE

Signature de Nerina Vischer / Anne-Sophie Joller prenant le consentement:

J'ai certifié que j'ai expliqué la nature et le but de l'étude avec la personne ci-dessus. Je crois qu'elle / il a bien compris ce que j'ai expliqué.

NOM	SIGNATURE	DATE DE LA SIGNATURE



7.6. English online survey about the trial protocols

Survey about clinical trial protocols

1. What was your most recent primary role in clinical research? ⓘ

- Sponsor-Investigator
- Principle Investigator
- Investigator
- Clinician
- Position in quality assurance
- Study coordinator
- Pharmacist
- Lab coordinator
- Clinical trial nurse

2. For how many years have you been working in clinical trials? ⓘ

- 0-1 year
- 2 - 4 years
- 5 - 7 years
- more than 7 years

3. In which diseases area are you working? (Please choose all that apply) ⓘ

- Malaria
- Tuberculosis
- HIV
- Other neglected tropical diseases
- Non communicable diseases
- Other:

4. In which kind of clinical trials are you involved in? (Please choose all that apply) ⓘ

- Vaccine trials
- Drug trials
- Other:

5. The protocols you have worked with are

	not at all	partially	completely	no opinion
understandable (for all staff levels involved)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
easy to implement	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
clear (no uncertainties)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
well structured	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
complex	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

- consistent (e.g. no ambiguities or contradictions)
- well translated (only for not english-speaking countries)

6. The protocols you have worked with are ⚠

- | | not at all | more or less | sufficiently | too much | no opinion |
|----------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| detailed | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| long | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

7. Optional field to comment on previous two questions:

8. How many amendments do you have in average per protocol?

- 0
- 1 - 2
- 3 - 5
- > 5
- I do not know
- Other:

9. How well are the study procedures described in the protocol adapted to your specific setting? (1=poorly adapted, 5=well adapted) ⚠

	1	2	3	4	5	no opinion
Informed consent procedure including documentation	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Inclusion and exclusion criteria	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Participants incentives to participate in the trial	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Recruitment procedure	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Data and information to be collected	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Medical interventions (e.g. ECG)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Medical procedures and decisions (e.g. administration of drugs, treatment of concomitant diseases and emergencies)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Safety reporting and management	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Follow-up procedure	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

10. How well are the protocols adapted to...? (1=poorly adapted, 5=well adapted) ⚠

	1	2	3	4	5	no opinion
Amount of workforce available	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Infrastructure available	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Availability and needs of trial participants	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Daily clinical practice	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ethics Committee system	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Drug Regulatory Authority system	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

11. Optional field to comment on previous two questions:

12. Are you involved in the study planning of the clinical trials you are working in? (Please choose all that apply) ⚠

- Stimulating the topic as an expert
- Major involvement in protocol writing
- Minor involvement in protocol writing
- Reviewing the protocol
- Participating in prediscussion of protocol
- As a sponsor-investigator
- Not involved
- Other:

13. In which role would your involvement be most helpful within the study planning of the clinical trials you are working in? (Please choose all that apply) ⚠

- Stimulating the topic as an expert
- Major involvement in protocol writing
- Minor involvement in protocol writing
- Reviewing the protocol
- Participating in prediscussion of protocol
- Not involved
- Other:


14. Have you ever heard about open source protocol development? ⚠


- Yes, I have heard about it
- Yes, I have heard about it and was participating in an open source protocol development
- No, I have never heard of it
- Other:

15. Please tick the top three options you think help or would help to increase the suitability of trial protocols? (Please tick three options) ⚠

- Sponsor to solicit feedback from site on what went wrong in previous trials
- More careful assessment of local context, capacity and culture by sponsor
- Include participant perspective in study planning
- Involvement of local staff in the study planning/ protocol development
- Use open source protocol development technique
- Single center trials: Adapt the protocol to site and health care specific systems
- Multi center trials: Having committees which consist of investigators from all involved research centres
- Making sure that everybody understands the protocol and knows his role and responsibility in the trial
- Having a kick-off meeting before the study start where issues can be discussed and detected
- Having a dry run before the enrolment of the first patient
- Having a checklist for all the practical steps of the trial

16. Optional field to comment on previous question:

17. In which country do you work most of the time? 

18. In what kind of institution are you working in? 

- Clinical research centre
- Hospital
- Field site
- Other:

19. What percentage of your working time is spent for work on clinical trials? 

- 0 - 25%
- 26 - 50%
- 51 - 75%
- 76 - 100%
- Other:

20. For which percentage of clinical trials have you had a dry run (definition: a practice of the trial activities with dummy participants before the enrolment of the first participant)?

- 0 %
- 25 %
- 50 %
- 75 %
- 100 %
- Other:

21. For which percentage of clinical trials have you had a kick off meeting where issues were detected and discussed before the start of the study?

- 0 %
- 25 %
- 50 %
- 75 %
- 100 %
- Other:


22. For which percentage of clinical trials have you had a lessons learnt meeting after the trial has ended?

- 0 %
- 25 %
- 50 %
- 75 %
- 100 %

Other:

23. Who was the sponsor of your study? 

- Mostly pharmaceutical companies
- Mostly other than pharmaceutical companies
- Mixed
- I do not know
- Other:

24. What percentage of your trials are multicenter trials? 

- 0 %
- 25 %
- 50 %
- 100 %
- Other:

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7.7. French online survey about the trial protocols

Enquête sur les protocoles d'essai clinique

1. Quel a été votre rôle principal le plus récent en recherche clinique? ⚠

- Promoteur-investigateur
- Investigateur principal
- Investigateur
- Clinicien
- Position en assurance qualité
- Coordinateur de l'étude
- Pharmacien
- Coordinateur de labo
- Infirmier d'un essai clinique

2. Depuis combien de temps travaillez-vous dans les essais cliniques? ⚠

- 0 - 1 an
- 2 - 4 ans
- 5 - 7 ans
- plus de 7 ans

3. Dans quelle aire thérapeutique travaillez-vous? (Plusieurs réponses possibles) ⚠

- Paludisme
- Tuberculose
- HIV
- Autres maladies tropicales négligées
- Maladies non transmissibles
- Autres (précisez):

4. Dans quel type d'essais cliniques êtes-vous impliqué? (Plusieurs réponses possibles) ⚠

- Essais de vaccins
- Essais de médicaments
- Autres (précisez):

5. Les protocoles sur lesquels vous avez travaillé sont

	pas du tout	en partie	complètement	pas d'opinion
compréhensibles (pour tous les niveaux de personnel impliqués)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
faciles à implémenter	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
clairs (aucune incertitude)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
bien structurés	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
complexes	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

cohérents (pas d'ambiguïtés ou contradictions)

bien traduits (seulement pour les pays non-anglophones)

6. Les protocoles sur lesquels vous avez travaillé sont ⚠

	pas du tout	plus ou moins	suffisamment	trop	pas d'opinion
détaillés	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
longs	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

7. Si nécessaire, ajoutez vos commentaires sur les deux questions précédents:

8. Combien d'amendements avez-vous eu par protocole (en moyenne)?

- 0
- 1 - 2
- 3 - 5
- > 5
- Je ne sais pas
- Autres (précisez):

9. Selon vous, les procédures d'étude suivantes décrites dans le protocole sont-elles adaptées à votre contexte spécifique? (1 = mal adaptées, 5 = bien adaptées) ⚠

	1	2	3	4	5	sans opinion
Procédure de consentement éclairé y compris la documentation	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Critères d'inclusion et d'exclusion	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Incitation des personnes à participer à l'essai	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Procédure de recrutement	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Données et informations à recueillir	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Interventions médicales (par exemple ECG)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Procédures médicales et décisions (par exemple, administration de médicaments, traitement des maladies concomitantes et urgences)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Rapports et gestion de la sécurité	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Procédure de suivi	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

10. Les protocoles sont-ils adaptés ...? (1 = mal adaptés, 5 = bien adaptés) ⚠

	1	2	3	4	5	sans opinic
à la disponibilité du personnel	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
à la disponibilité des infrastructures	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
à la disponibilité et aux besoins des participants	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
à la pratique clinique quotidienne	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
aux procédures des comités d'éthique	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
aux procédures des autorités de réglementation pharmaceutique	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

11. Si nécessaire, ajoutez vos commentaires sur les deux questions précédents:

12. A quel niveau êtes-vous impliqué dans la planification de l'étude des essais cliniques pour lesquels vous travaillez? (Plusieurs réponses possibles) ⚠

- Initiation du sujet en tant qu'expert
- Implication majeure dans l'écriture de protocole
- Participation mineure dans l'écriture de protocole
- Révision du protocole
- Participation aux pré-discussions sur le protocole
- En tant que promoteur-investigateur
- Pas impliqué
- Autres:

13. Dans quel rôle votre implication serait-elle très utile au sein de la planification de l'étude des essais cliniques pour lesquels vous travaillez? (Plusieurs réponses possibles) ⚠

- Initiation du sujet en tant qu'expert
- Implication majeure dans l'écriture de protocole
- Participation mineure dans l'écriture de protocole
- Révision du protocole
- Participation aux pré-discussions sur le protocole
- Pas impliqué
- Autres (précisez):

14. Avez-vous déjà entendu parler de l'élaboration de protocole en open source? ⚠


- Oui, j'en ai entendu parler
- Oui, j'en ai entendu parler et j'ai participé à un développement protocole en open source
- Non, je n'en ai jamais entendu parler
- Autres (précisez):


15. S'il vous plaît, cochez les trois meilleures options qui, selon vous, aident ou aideraient à augmenter la facilité de la mise en œuvre des protocoles d'essais? (3 champs obligatoires) ⚠

- Que le promoteur sollicite des commentaires du site sur ce qui s'est mal passé lors des essais précédents
- Évaluation plus minutieuse de la culture, des capacités et des contextes locaux par le promoteur
- Inclure les perspectives du participant dans la planification de l'étude
- Implication du personnel local dans la planification de l'étude / le développement de protocoles
- Utiliser des techniques de développement de protocole en open source
- Pour les essais unicentriques: adapter le protocole aux procédures du site et au système de soin
- Pour les essais multicentriques: avoir des comités qui se composent d'investigateurs de tous les centres de recherche impliqués
- Faire en sorte que tout le monde comprenne le protocole et connaisse son rôle et sa responsabilité dans l'essai
- Avoir une réunion de lancement avant l'étude commence où les problèmes peuvent être détectés et discutés
- Faire un entraînement aux activités de l'essai clinique avec des participants factices avant l'inscription du premier participant


- Avoir une liste de contrôle pour toutes les étapes pratiques de l'essai

16. Si nécessaire, ajoutez vos commentaires sur la question précédente:

17. Dans quel pays travaillez-vous la plupart du temps? 

18. Dans quel genre d'établissement travaillez-vous? 

- Centre de recherche clinique
- Hôpital
- Site d'étude
- Autres (précisez):

19. Quel pourcentage de votre temps de travail est consacré au travail pour les essais cliniques? 

- 0 - 25%
- 26 - 50%
- 51 - 75%
- 76 - 100%
- Other:

20. Pour quel pourcentage des essais cliniques auxquels vous avez participé, avez-vous fait un entraînement aux activités de l'essai clinique avec des participants factices avant l'inscription du premier participant?

- 0 %
- 25 %
- 50 %
- 75 %
- 100 %
- Other:

21. Pour quel pourcentage des essais cliniques auxquels vous avez participé, avez-vous eu une réunion de lancement de l'étude où les problèmes ont été détectés et discutés avant le début de l'étude?

- 0 %
- 25 %
- 50 %
- 75 %
- 100 %
- Other:

22. Pour quel pourcentage des essais cliniques auxquels vous avez participé avez-vous eu une réunion sur les leçons tirées après la fin de l'essai?

- 0 %
- 25 %
- 50 %

- 75 %
- 100 %
- Other: - saisir ici -

23. Qui était le promoteur de votre étude? ⓘ

- Principalement des entreprises pharmaceutiques
- Principalement autre que les entreprises pharmaceutiques
- Mélangé
- Je ne sais pas
- Autres: - saisir ici -

24. Quel pourcentage de vos essais était des essais multicentriques? ⓘ

- 0 %
- 25 %
- 50 %
- 100 %
- Other: - saisir ici -

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