

# The Good Clinical Practice guideline and its interpretation – perceptions of clinical trial teams in sub-Saharan Africa

N. Vischer<sup>1,2</sup>, C. Pfeiffer<sup>1,2</sup>, A. Joller<sup>1,2</sup>, I. Klingmann<sup>3</sup>, A. Ka<sup>4</sup>, S. K. Kpormegbe<sup>5</sup> and C. Burri<sup>1,2</sup>

<sup>1</sup> Swiss Tropical and Public Health Institute, Basel, Switzerland

<sup>2</sup> University of Basel, Basel, Switzerland

<sup>3</sup> European Forum for Good Clinical Practice, Brussels, Belgium

<sup>4</sup> Département de Sociologie, Université Cheikh Anta Diop de Dakar, Dakar, Senegal

<sup>5</sup> Department of Sociology, University of Ghana, Legon, Ghana

## Abstract

**OBJECTIVES** To explore the advantages and challenges of working with the Good Clinical Practice (GCP)-International Conference of Harmonization (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 clinical research centres in Kenya, Ghana, Burkina Faso and Senegal and thematically analysed 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 it. To mitigate consent challenges, we suggest adapting GCP and making use of the flexibility it offers.

**keywords** clinical trials, Africa South of the Sahara, good clinical practice, qualitative research, guideline

## 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 rigour 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, the EU and Japan, is the internationally accepted gold standard by which to perform CTs [2]. The guideline was developed emphasising

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 also issued various guidances and position papers [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 that leads to inflated administration and costs. Due to the limited validity of patents, the pharmaceutical industry reportedly prioritises faster trials and regulatory compliance over cost savings, risk

adaptation and reducing 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 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 from the participant and are not feasible for CT teams in RLCs [17, 21]. Along with the ethical challenges, the guidelines need 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 criticising the current trial practices in RLCs underline that an appropriate, adapted application of the guidelines does not equate to substandard conduct of trials compared with 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 *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]. 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 and standards of care were also discussed [23, 24], whereas the development of general recommendations on this sensitive topic was regarded as being difficult [23]. At a more detailed level, Hanna *et al.* [20] developed quality indicators to assess ICH-GCP compliance in trials in RLCs, while Kuepfer and Burri [25] listed minimal standards. Lang and Siribaddana [14] highlighted where the guideline might be overcautiously applied, and Acosta *et al.* [18] reported challenges of implementing the 13 principles of GCP in RLCs.

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.* [16] that local CT teams must be involved in the debate on guideline application.

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.

## 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 African countries, one semi-urban, one urban and two rural clinical research centres were visited, and in French-speaking African countries, one rural and three urban 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 (Table 1). The majority of the interviewees were exclusively working in clinical research without involvement in routine health care. To develop the interview guide, 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.

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 [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, as 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].

**Table 1** Characteristics of interviewed clinical trial staff

	Kenya ( <i>n</i> = 17)	Ghana ( <i>n</i> = 13)	Burkina Faso ( <i>n</i> = 16)	Senegal ( <i>n</i> = 14)
Role in study				
Investigators ( <i>n</i> = 28)	8	4	8	8
Study coordinators ( <i>n</i> = 17)	5	6	3	3
Clinicians ( <i>n</i> = 10)	3	2	3	2
Professionals working in QA ( <i>n</i> = 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

## 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 5

Ninety percent of 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 3

Three principal investigators and one clinician favoured a risk-based approach, particularly for phase IV trials; however, too few interviewed staff were 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 1

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

### **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 6

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, and 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 8

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 2

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 8

### Oversight of compliance with guidelines

The importance of oversight by national authorities was stressed; this topic came up less frequently than 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.

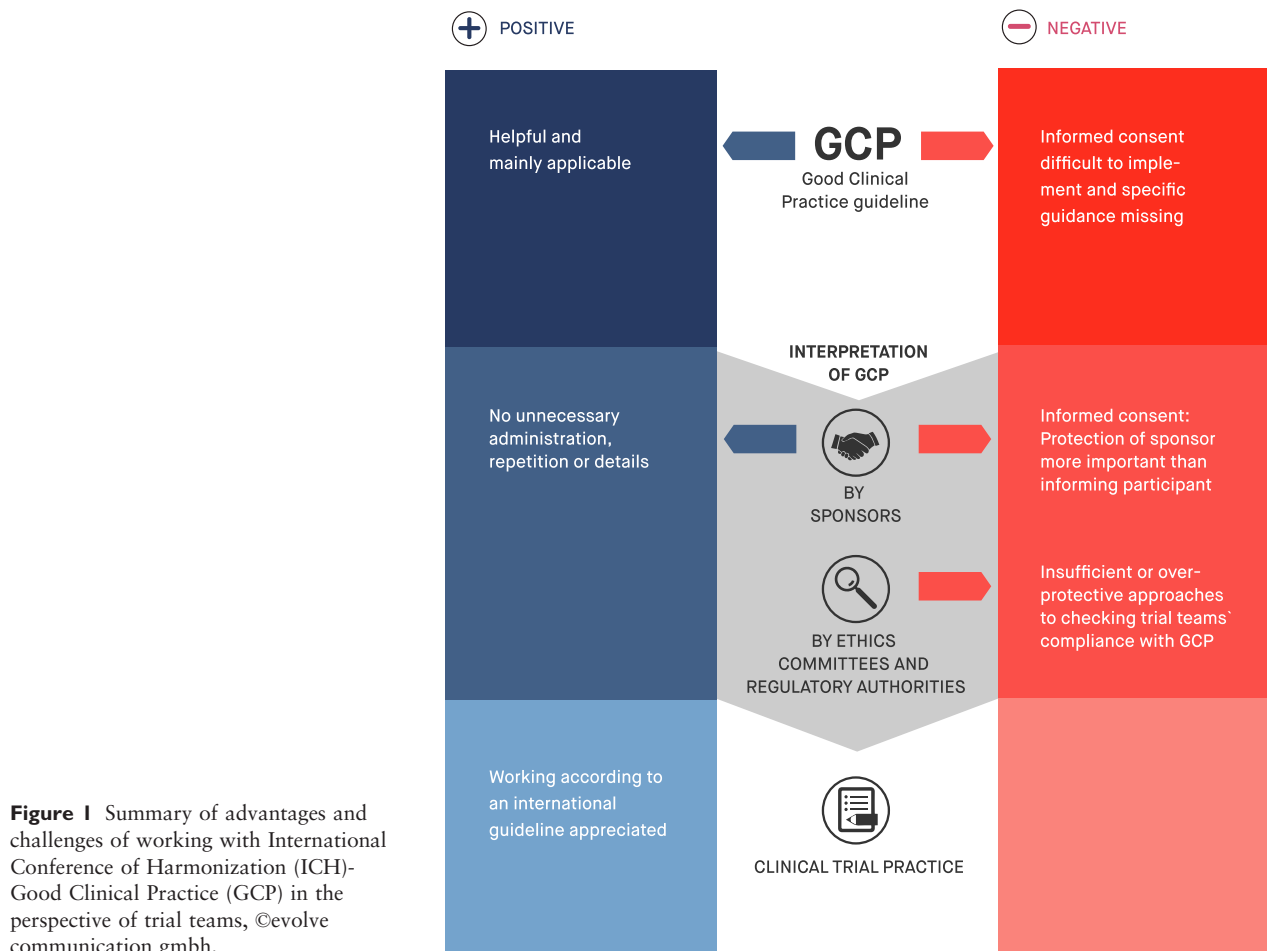
‘And since they [authorities] gave their approval and the study has started, we don’t come back to them for information. They do not come to us either, so there is a follow up problem. So it would be good, if reports are made regularly. For them too, that they can follow all we do. It’s good that you have given your approval, but you have to follow up’. Investigator, male, Burkina Faso, Centre 5

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 criticised involving additional ECs as, for example, 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 do not increase safety. Overcautious oversight also takes the form of overly stringent reporting requirements, for example 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.

### Discussion

Overall, interviewed CT staff in SSA found the GCP guideline very helpful in guiding their daily work and ensuring an international standard (Figure 1). 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.

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 than northern countries. 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. Conducting vaccine trials is even more complex than conducting drug trials. 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 whether the minor does not have a legally acceptable representative [35].

Some topics that 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 ongoing and collaboration between sponsor and authorities prior to the study start is important [23]. Authorities must be capable of making contextualised decisions [36].

Some trial staff perceived that authorities with substantial experience enforce GCP too rigorously and over-protective. 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 outdated 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 were collected by a female Swiss scientist, which might have contributed to a degree of bias, as 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, as 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.

## 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.

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**Corresponding Author** Nerina Vischer, Swiss Tropical and Public Health Institute, Socinstrasse 57, 4051 Basel, Switzerland.  
E-mail: [nerina.vischer@unibas.ch](mailto:nerina.vischer@unibas.ch)