Quality in Clinical Trials –
A Resource-Limited Settings Perspective

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Angela De Pretto
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auf Antrag von

Prof. Christian Burri (Fakultätsverantwortlicher/Dissertationsleiter)

Prof. Bernhards Ogutu (Korreferent)

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Prof. Dr. Martin Spiess

Dekan

To My Family

"Quality – you know what it is, yet you don't know what it is."

– Robert M. Pirsig, Zen and the Art of Motorcycle Maintenance

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List of abbreviations

CIOMS	Council for International Organizations of Medical Sciences
CONSORT	CONsolidated Standards Of Reporting Trials
COREQ	Consolidated Criteria for Reporting Qualitative research
CT	Clinical Trial
CTTI	Clinical Trial Transformation Initiative
DoH	Declaration of Helsinki
EDCTP	European and Developing Countries Clinical Trials Partnership
EKNZ	Ethikkomission Nordwest-und Zentralschweiz
GCP/GCLP/GMP	Good Clinical Practice/Good Clinical Laboratory Practice/Good Manufacturing Practice
IC	Informed Consent
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICTRP	International Clinical Trial Registry Platform
IIT	Investigator-Initiated Trial
INQUIRE	INcreasing QUality In patient-oriented academic clinical REsearch
LAR	Legally Acceptable Representative
LMIC	Low- and Middle-Income Country
NTD	Neglected Tropical Diseases
PDP	Product Development Partnership
PPP	Public-Private Partnership
QbD	Quality by Design
REWARD	Reduce Research Waste and Reward Diligence
RLS	Resource-Limited Settings
SDG	Sustainability Development Goals
SOP	Standard Operating Procedure
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SSA	Sub-Saharan Africa
TGHN	The Global Health Network
WHO	World Health Organization

Summary

Background: Clinical trials have to follow strict standards in order to assure participant safety and data integrity. The development of these standards, however, did not include the perspective from resource-limited settings, hence, leading to operational challenges when applied in these settings. Over the past decades, the conduct of clinical trials was characterised by inefficiency and waste, questioning in how far adherence to the existing standards reflects "quality". A common and broadly accepted understanding of the concept of "quality" in clinical research has never been defined, potentially leading to wasteful, as well as undervalued clinical trial activities. An academic framework was developed to fill this gap; however, it did not consider the perspective of resource-limited settings. This thesis, therefore, sought to provide insight about particular needs in clinical trial guidance encountered in resource-limited settings and to contribute to the perception of "clinical trial quality" from a resource-limited perspective.

Methods: We used a qualitative design, including semi-structured interviews with clinical trial stakeholders comprising investigators, sponsors, and monitors. 46 interviews were conducted with stakeholders having experience in 27 countries in sub-Saharan Africa. Framework analysis was performed to identify themes with respect to the entire clinical trial scope and build a clinical trial quality concept. We used MAXQDA software for the analysis.

We additionally performed a systematic literature review to address the lack of guidance in the case of informed consent management for paediatric participants with minor parents. We searched PubMed/MEDLINE, Embase, CINAHL, and Google Scholar for articles published up to March 2019. In total, 4382 articles were screened, and two analyses were performed based on these articles. In the first analysis, 16 articles met our inclusion criteria. Various study types addressing informed consent in clinical trials involving children with minor parents in sub-Saharan Africa were included. We performed descriptive and qualitative framework analyses. In the second analysis, 44 articles met our inclusion criteria. We included publications of clinical trials that potentially included children with minor parents in sub-Saharan Africa and addressed informed consent. A descriptive analysis was performed.

Results: Clinical trial quality definitions resulted in 11 elements, summarised into a clinical trial quality concept, consisting of two components: clinical trial quality-building factors (Scientific factors and Moral factors) and -promoting factors (Context adaptation; Infrastructure; Partnership; Operational excellence; Quality system). 12 resource-limited settings specific themes were identified, which could be categorised under the promoting factors "Context adaptation", "Infrastructure", and "Partnership".

The systematic review showed that informed consent approaches for children with minor parents were variable and could involve either the minor parent, another representative or both. When individual consent by minor parents based on emancipation or "mature minor" status was applied, it lacked an evidence base in the context of research and mostly followed national laws on medical care. When no laws or guidance existed, an interpretation of the local decision-making culture, including community engagement and collaboration with local ethics committees, defined the informed consent approach. In the secondary analysis, there was no robust evidence on whether any recruited children had minor parents and how consent was obtained for them. Explicit descriptions of proxy decision-makers were rare and were mostly provided in referenced clinical trial registrations or protocols. Also, terminology describing proxy decision-makers was often used inconsistently.

Conclusions: A comprehensive clinical trial quality concept should be multidimensional, including quality-promoting factors in addition to scientific and ethical components. Consideration of resource-limited setting-specific aspects led to three clinical trial quality-promoting aspects as possible additions to the INQUIRE framework: 1) Clear communication of infrastructural disadvantages to funders, sponsors, and auditors, 2) Prevention of exploitation of research populations and workforce in resource-limited countries by following existing ethical frameworks, and 3) Context adaptation as an additional clinical trial quality promoter. Amending the INQUIRE framework by adding these aspects could be beneficial for proactive implementation of quality into clinical trials.

The systematic literature review emphasised that the implementation of informed consent for children with minor parents may be context-dependent and hampered by absent or ambiguous clinical trial regulations, as well as divergent local realities. We recommended a set of questions to be considered in the development of an ethically acceptable informed consent approach and proposed information to be integrated into international clinical trial guidelines.

The review further highlighted that CT reporting guidelines should require clinical trial publications to state or reference exceptional informed consent procedures applied for special population groups. Moreover, international clinical trial guidelines should provide harmonised definitions of proxy decision-maker types to facilitate correct and transparent informed consent for children and children with minor parents.

Overall, adopting practical guidance on exceptional, or context-dependent situations into general guiding documents or referencing such guidance in the respective area was considered beneficial. This would, on the one hand, give more attention to these situations and, on the other hand, give more recognition to the related efforts.

1 Introduction

1.1 The importance of clinical trials

Clinical trials (CTs) are controlled experiments on human subjects generating evidence on the safety and efficacy profiles of investigational products [1]. Therefore, CTs are an essential part of the development process of new medicines (i.e., drugs, vaccines or diagnostics), which first involves pre-clinical testing in tissue cultures and animal models typically followed by four clinical phases in humans. In the respective phases, CTs involve an increasing number of participants, and their focus moves from pure safety aspects to proof of concept to large scale confirmatory CTs being thus increasingly closer to real-life conditions [2, 3]. The data collected in CTs allow health authorities to decide on the investigational product's market authorisation [2]. Hence, CTs provide evidence-based knowledge that drives medical policymaking and advancement.

There is a continuous need for CTs to inform and improve global therapy standards: Some diseases lack effective treatments, or adverse drug reactions, as well as emerging drug resistance, may hinder the use of available treatments. Moreover, existing treatments are sometimes not affordable or accessible to all those in need and require suitable alternatives. CTs are further necessary to improve therapeutic knowledge about specific patient groups, including women, children, the elderly or people with a lower socioeconomic status, which were previously underrepresented in clinical research [4, 5].

In resource-limited countries, CTs are of particular importance. While the global burden of disease is dominated by non-communicable diseases, resource-limited countries bear an over proportional share of communicable diseases [4]. These communicable diseases include HIV/AIDS, malaria, tuberculosis, and the group of neglected tropical diseases (NTDs; e.g., Buruli ulcer, Leishmaniasis, etc.) [5], and are further referred to in this thesis as poverty-related diseases. As poverty-related diseases correlate with high rates of early mortality, targeted and sustainable treatment options are undeniably needed [6]. Affected countries often lack the capacity to address this health disparity on their own. Therefore, fighting these diseases has been acknowledged as a global responsibility and health priority, which is reflected in the sustainable development goals (SDGs) and facilitated through various global and international initiatives and funding strategies [7, 8]. In this thesis, we focus on CTs conducted in sub-Saharan Africa (SSA) which is a region significantly affected by poverty-related diseases and resource-limitation.

1.2 The evolution of clinical trial guidelines

As CTs involve experiments with human participants, they must follow ethical standards. These standards have undergone a long historical evolution. Already around the beginning of the 20th century, national food and drug legislation was used. However, the first internationally established ethical code of conduct for research was the Nuremberg Code in 1947, which resulted from problematic medical experiments led by Nazi members during World War II [9]. The Code essentially requires investigators to have a sound scientific basis for their experiment and to assure the participants' safety and voluntary participation [10]. Further disasters in clinical research, such as the thalidomide tragedy in 1961, contributed to the need for more extensive ethical guidance (Appendix 6.1, Figure S1) [9]. Consequently, the Declaration of Helsinki (DoH) was introduced in 1964 by the World Medical Association defining universal ethical principles for medical research involving human participants [11].

In 1982, the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) introduced the International Ethical Guidelines for Health-Related Research Involving Humans to facilitate the implementation of existing ethical principles in research [12]. However, the implementation of CTs required additional standards, which led to a large variety of additional regulations. In order to achieve harmonisation in the conduct of CTs to promote the mutual recognition of CT data, a definition of common standards for CT became indispensable [9]. In 1996, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals[1] (ICH) published the Good Clinical Practice (GCP) guideline [13]. The growing demand from regulatory authorities, ethics committees, funders and medical publishers for CTs to be ICH-GCP compliant ultimately led to the ICH-GCP guideline being recognised as the international standard for the conduct of CTs [14-16].

However, while the ICH-GCP guideline is defined as "ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects" [1], it is unclear in how far adherence to this standard truly reflects the quality of CTs. Researchers argued that the guideline is not evidence-based, as it was built upon informal consensus, lacks references to literature or other systematic sources of information, and its benefits were not proven [17, 18]. Moreover, it was developed mainly by industry stakeholders

[1] Before October 2015: International Conference for Harmonisation of Technical Requirements for Pharmaceuticals

and regulators, whereas it should also be followed by non-commercial, academic trials [17, 19, 20].

A restrictive interpretation of the guideline, including, for example, extensive CT documentation and monitoring 100% of CT data, had contributed to an administrative burden that was disproportionate to the nature of many CTs [6, 17, 21]. At the same time, the heavy focus on assuring CT quality through "reactive" quality control measures, such as monitoring and auditing, led to increasingly complex CT protocols [22], which, in turn, fuelled the demand for "reactive" quality control measures and contributed to a significant increase in study costs [23]. High study costs for their part contributed to increased outsourcing of CT activities to countries with lower salary costs [16], which reinforced the need for restrictive supervision of the compliance with CT regulation [22].

As a countermeasure, a trend towards "proactive quality" has been followed over the past decade [22]. Risk-based quality management principles and adapted monitoring approaches were promoted by various initiatives to increase the efficiency of the conduct of CTs [24-27]. Risk-based quality management involves identification and continuous evaluation of risks inherent to the CT and prioritisation of quality measures according to the risk's potential impact. Adapted monitoring approaches include adjusting the monitoring intensity to the risk of a CT [28-30], as well as the possibility for remote or centralised monitoring with triggered monitoring visits [31]. These quality management principles were eventually adopted in a first amendment of the ICH-GCP guideline in 2016 [32].

Moreover, the concept of "Quality by Design" (QbD) was promoted by the Clinical Trial Transformation Initiative (CTTI), which is a US-based public-private-partnership between Duke University and the FDA formed in 2007 [16]. QbD aims for prospective identification of possible errors or "Critical to Quality Factors" [33]. Thereby, a CT should be designed in a way to prevent errors, instead of coping with them retrospectively [29, 30]. These considerations on QbD were adopted by the draft version of the ICH E8(R1) General Considerations for Clinical Trials guideline (ICH-E8(R1) guideline) [34] and are planned to be also considered in a complete renovation of the ICH-GCP guideline that is currently ongoing [35].

1.3 The need to define clinical trial quality

In 2009, the Lancet provided striking evidence that 85% of CT investment was wasted [36]. A subsequent Lancet series entitled "Increasing Value and Reducing Waste" was published in 2014 and identified the following areas for improvement: proper selection of research questions; robust study design; conduct and analysis; risk-based CT regulation and management; published and accessible results; and complete and useful reporting [37]. In order to promote quality in these areas, the authors started a campaign called "Reduce Research Waste and Reward Diligence" (REWARD) in 2016 [38]. Thereby, standardised tools and processes were promoted, such as the performance of systematic literature reviews when defining research questions; the application of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement for CT protocol development [39]; the Consolidated Standards of Reporting Trials (CONSORT) statement for appropriate reporting of randomised controlled trials [40]; and the registration of CTs in official CT registries before their initiation [41, 42]. The various areas for improvement addressed by the Lancet series brought CT quality into a broader context. In addition to the requirement of proactive and risk-adjusted CT quality management, fundamental components of academic research (i.e., a scientifically sound methodology) must be fulfilled, as otherwise, the CT becomes worthless.

Since the overall perception of quality in CTs has been transitioning over the past decade, several CT quality definitions have been published to facilitate its management. For example, Switula explained CT quality according to ISO 9000:2015, which is an internationally recognised quality management standard for various industries [43]. The ISO 9000:2015[2] standard describes quality as "the degree to which a set of inherent characteristics of an object meets the requirements". Thereby, an object is defined as "anything perceivable or conceivable" (e.g., product, service, process, person, organisation, system, resource) and a requirement is defined as "a need or expectation that is stated, generally implied or mandatory" [44]. The CTTI also offered a perspective on CT quality, defining it as "the absence of errors that matter to decision making – i.e., errors that have a significant impact on the safety of study participants or the credibility of results (and thus on the care of future patients)" [45]. Moreover, the current draft of the ICH-E8(R1) guideline contains another CTTI-inspired definition of CT quality and considers it to be "fitness for purpose". Thereby, the purpose of a CT is to "generate

[2] In the paper by Switula ISO 9000:2001 was referenced, which used a slightly different phrasing for the quality definition and was superseded by the ISO 9000:2015. For the purposes of this thesis, the most recent definition was used.

reliable information to answer key questions and support decision-making while protecting trial participants" [34].

However, a recent systematic literature review emphasised that there has been no generally recognised common definition of CT quality [46], which may be a potential source for wasteful as well as undervalued activities in CT management. Therefore, the authors developed a quality framework for academic research "INcreasing QUality In patient-oriented academic clinical REsearch (INQUIRE)" that provides an overview combining established quality tools and guidelines [47]. Nevertheless, the framework was developed based on a review and compilation of existing quality aspects and, therefore, did not allow CT stakeholders to openly formulate a definition of CT quality, which may have added new perspectives. Moreover, the INQUIRE framework designed to consider the needs of non-commercial trials only involved experts from developed countries.

1.4 The need to consider a resource-limited settings perspective

The following sections describe sensitivities and circumstances in resource-limited settings (RLS) that might influence perceptions of clinical trial quality:

First, clinical researchers in resource-limited countries face particular challenges: Primarily, widespread poverty increases the vulnerability of the potential research population, as a lack of money, nutrition, health care and education can unduly influence individuals towards a CT participation [1]. Further, the frequently limited capacity of national ethics committees and regulatory authorities can affect the CT overview and slow down approval processes [48-50]. In addition, there is a lack of education and career opportunities in the area of clinical research, which can affect the availability of qualified CT staff [19, 51]. Moreover, poverty-related diseases often affect remote areas where health facilities are inadequately equipped for research and difficult to access [52-54]. Legal frameworks for the conduct of CTs may also be missing or inconsistent [55], leaving certain CT aspects undefined (e.g., investigator qualifications, storage of the investigational product, informed consent and its documentation, essential documents, notification of serious adverse events, and participant insurance and compensation). Also, studies can be affected by external factors such as climatic conditions or unstable local political situations [52-54]. Despite such challenges, CTs must meet the same quality standards as developed countries, in order to get regulatory approval. However, when the ICH-GCP guideline was developed, the conditions in resource-limited countries were not taken into account [14, 15, 50]. The need to adapt the ICH-GCP guideline to some common challenges in

resource-limited countries was debated in the past decade [15, 50]. Still, no respective adaptations have yet been implemented.

Second, several additional recommendations have been published in the meantime to support CTs in resource-limited countries. Among the most prominent examples are Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries, published in 2001 by the National Bioethics Advisory Commission, The Ethics of Research Related to Health Care in Developing Countries and its follow-up Discussion Paper by the Nuffield Council on Bioethics, published in 2002 [56] and 2005 [57], and The Ethical Principles for Clinical Research in Developing Countries by Emanuel et al. in 2004. These recommendations have never been updated since their implementation. However, in 2017, a CIOMS working group started to develop a new guideline. It aims to reach a consensus on "pragmatic recommendations for environmental improvements and good practices for the social acceptance, planning, evaluation, implementation and interpretation of randomised controlled clinical trials in resource-constrained environments (RLS)" [58]. As the CIOMS recommendations are still under development, a perspective on CT quality arising from this thesis may provide additional input.

Third, in sub-Saharan Africa, the conduct of CTs has been increasingly evolving in the past decades, and various Networks of Excellence have been established, promoted by international initiatives, including the European and Developing Countries Clinical Trial Partnership (EDCTP) and The Global Health Network (TGHN) [59]. In addition, special partnership models have been established to facilitate the implementation of CTs in RLS, such as public-private partnerships (PPPs), product development partnerships (PDPs) or consortia [52, 60]. Hence, this accumulated expertise in conducting successful CTs while having limited resources can potentially contribute to an understanding of critical contributors to CT quality.

Fourth, Lang et al. emphasised that in sub-Saharan Africa, CTs often have different characteristics than in Europe, and include larger proportions of infectious diseases, children, and non-commercial financing [19]. As these characteristics might contribute to the way CTs are implemented, they may have a potential impact on the perception of CT quality and should be considered.

While there are previous studies that have considered quality indicators, and monitoring aspects specific to RLS [61, 62], we are not aware of studies that have developed a CT quality definition with particular focus on these settings. Therefore, the goal of Manuscript I (Defining clinical trial quality from the perspective of resource-limited settings: A qualitative study based on interviews with investigators, sponsors, and monitors conducting clinical trials in sub-Sa-

haran Africa) was to contribute to the recent trends in increasing awareness about the meaning of quality in CTs to help understanding how quality and efficiency in the conduct of CTs may be maximised.

1.5 Specific challenges with informed consent in resource-limited countries

Informed consent (IC) is a critical step in clinical research. It is the only way to allow the enrolment of participants into research. Disregarding IC leads to a violation of human rights [11]. Only emergencies may justify a consent waiver or deferral if there is a clear indication of a potential benefit for the patient by the investigational medical product [63]. For a consent to be valid, it has to fulfil three elements: it has to be understood, voluntary and provided by a competent person, defined as someone who has the ability to understand the information provided about the research [56]. However, in resource-limited countries, a number of challenges are faced, when considering these elements of IC validity:

First, the understanding of potential CT participants might be hampered by limited school education, substantial illiteracy rates and a large variety of national languages, which may not exist in written. There is a strong dependence on literate impartial witnesses, who need to be available [53]. Also, additional efforts may be needed to establish a basic knowledge about the concept of research [56].

Second, the participants' voluntariness may be influenced by hierarchical social structures. Some communities make important decisions collectively, baring the risk of potentially pressuring individuals into CT participation [50, 64]. Also, local customs may require an initial agreement by a village chief, community leader or other family members in addition to an autonomous consent by individuals. Still, the participants need to be made aware of their individual right to refuse or withdraw CT participation [65, 66].

Third, when individuals are considered incompetent to provide consent, a legally acceptable representative (LAR) must be available to consent on their behalf. As minors are generally considered incompetent, IC has to be provided by their parent(s) or a legal guardian[3] [56]. In

[3] The terminology defining such proxy decision-makers may be variable across guidelines as discussed in more detail in chapter 4.5.2 Transparency on proxy decision-makers and in the appendix 6.14 Examples and interpretations of proxy decision-maker definitions.

addition to this, children can provide assent according to their decision-making capacity (i.e., intellectual maturity). With growing age and maturity, children's decision-making capacity increases. Hence, the information provided and the assent process should be adapted accordingly [67]. While infants depend entirely on the consent by a LAR, adolescents may become emancipated or "mature minors" and provide autonomous consent [68]. Such cases include CTs in sensitive areas (e.g., sexual health-related research), where adolescents represent a significant proportion of the target population [69]. However, CTs involving such a vulnerable population should be generally of low risk and have a prospect of direct benefit [70]. The age of consent (i.e., the legal age of majority), the age of assent, as well as criteria for emancipation or "mature minor" status are thereby subject to national legislation, which may be variable and difficult to define.

Also, the identification of the appropriate LAR to provide consent for the child may pose challenges. Persons accompanying children to medical facilities are not always the biological parents, as in some cultures, it is common to assign this duty to caregivers. As legal documentation may not always be available, it might be difficult to determine the appropriate person to consent for these children, particularly when their home is kilometres away from the research site [50, 71, 72]. Further, a shared decision-making culture, such as provided by assent next to parental consent, might not be accepted in societies that follow strict hierarchical decision-making structures [73]. Gender dynamics (e.g., in a male-dominated society) may also complicate the IC process for children: Mothers might not be authorised to consent for their children without consulting their husbands or other family members [56]. Such consent may be subsequently revoked or silently refused by not showing up to visits [74]. Hence, a careful assessment of socioeconomic, linguistic, and cultural variations is essential to the development of appropriate paediatric IC processes [75].

1.6 The need to evaluate informed consent approaches for children with minor parents in sub-Saharan Africa

Due to high child morbidity [76-78], as well as high teenage pregnancy rates in SSA [79], it is probable for children recruited in clinical research in SSA to have minor parents. This situation raises the question of who should decide about CT participation on behalf of the child. According to international guidelines, becoming a parent may grant "emancipated" or "mature minor" status, and authorise minors to consent autonomously [12, 80]. However, it remains unclear whether they are also allowed to consent on behalf of their children. While national guidance

may exist on the subject in some countries [81], it may be variable, missing, or in contradiction to local customs in others, which complicates the enrolment of such children in CTs [82].

There are three possible options for addressing the issue of IC for participation in CTs with children of minor parents (Figure 1):

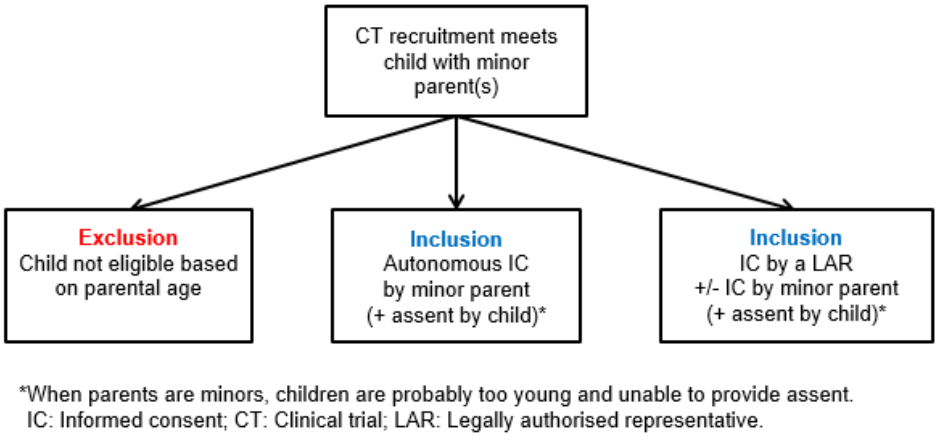

Figure 1: Informed consent possibilities for children of minor parents.

1) Exclusion of the child. Why should children of minor parents be included, when there are enough children with adult parents? However, such children would also be excluded from potential benefits provided, e.g., the continuous access to health care during the involvement in a CT. Also, a recent systematic literature review concluded that the most motivating factors for parents and children to participate in clinical research were: health benefit and altruism [83]. Therefore, preventing children from research based on the age of their parents would be unethical when they would otherwise be eligible to participate. Moreover, Ravinetto et al. state that children in SSA are the most vulnerable patients and, therefore, exclusion from research would be unfair and create a selection bias [15].

2) Inclusion of the child with consent by the minor parent, considered emancipated or a "mature minor". However, guidance concerning these definitions is ambiguous. In general medical treatment, emancipated adolescents may not always be deemed capable of consenting for themselves. At the same time, becoming a parent would, in some legislations, directly allow them to consent for their children [84]. Also, medical treatment does not necessarily translate equally to the sensitive field of clinical research.

3) Inclusion of the child with consent by a legally acceptable representative (LAR) that is not the minor parent. Again, guidance concerning appropriate persons to consent on behalf of

children is ambiguous [81]. Is additional assent or co-consent by the minor parent needed and feasible? How can the culturally rooted decision-making process, which may be different from legislation, be respected?

Recently, various initiatives focusing on facilitating paediatric CT conduct were launched [85, 86]. The StaR Child Health Initiative contributed extensively to an improvement of paediatric CT quality by raising evidence about gaps in paediatric CT methodology and developing recommendations also addressing IC [87, 88]. However, although this initiative also refers to special considerations in resource-limited countries, they do not address the case of consent for children with minor parents.

As infants will continue to be a target population, especially when it comes to the development of vaccines in resource-limited countries, there will also be a probability of such infants to have minor parents. There is insufficient evidence to what extent this population has been considered in the past, as there seems to be a general lack of transparency about their enrolment in clinical research. It is important and in line with the spirit of patient-centeredness to consider minority groups, address them appropriately, and provide them with adequate access to research and its potential benefits. Hence, the goal of Manuscript II (Informed consent approaches for clinical trial participation of infants with minor parents in sub-Saharan Africa: A systematic review) was to review literature to provide evidence and recommendations on IC approaches for such children. In addition, the goal of Manuscript III (Transparent reporting of recruitment and informed consent approaches in clinical trials recruiting children with minor parents in sub-Saharan Africa: A systematic review) was to determine and promote transparency regarding this situation in CT publications in order to adequately protect the rights of this extremely vulnerable population and facilitate their recruitment in the future.

1.7 Objectives

1.7.1 Research aim

The PhD thesis is exploratory, and the overall goal is to contribute to the understanding of how clinical trial (CT) quality is composed from a resource-limited settings (RLS) perspective to allow an effective and efficient CT quality management.

1.7.2 Research questions

1) CT Quality definition
   a) How is CT quality defined by stakeholders involved in the conduct of CTs in RLS (sponsors, investigators, and monitors)?
   b) Are there differences to CT quality definitions in developed settings?
   c) Can developed settings benefit from a RLS perspective on CT quality?
2) Informed consent (IC) for CTs involving children with minor parents
   a) What IC approaches have been reported for children with minor parents in SSA?
   b) What needs to be considered to allow an appropriate IC approach for these children?
   c) How is the transparency on the recruitment and IC approach for these children in CT publications?
   d) How does the IC for children with minor parents relate to the overall CT quality?

1.7.3 Specific objectives

The specific objectives of the thesis were:

1) CT Quality definition
   – To conduct interviews with CT stakeholders (sponsors, investigators, and monitors) from SSA.
   – To provide an overview of how these stakeholders define CT quality.
   – To develop a framework representing these CT quality definitions.
   – To determine the appropriateness of existing frameworks for developed settings.
   – To highlight possible differences from existing frameworks for developed settings.
   – To identify quality perspectives that could be of potential benefit for developed countries (reversed innovation).
2) IC for CTs involving children with minor parents
   – To review literature systematically to identify IC approaches for CTs with children of minor parents.
   – To determine the appropriateness of these IC approaches and highlight gaps.
   – To provide recommendations for the development of an appropriate IC approach for children of minor parents.
   – To provide recommendations for appropriate reporting of the IC approach.
   – To determine the relation of the IC management to the overall CT quality.

1.8 Justification

This thesis aimed to contribute to a common understanding of CT quality by including the perspective of stakeholders involved in the conduct of CTs in resource-limited countries. Initially, an exploratory mixed methods approach was planned. It first included a qualitative part, involving semi-structured interviews to define a conceptual framework of CT quality, and was followed by a quantitative part, involving a survey to confirm and elaborate the concept. However, after defining the methodology, we gained awareness about a similar project conducted by a research group at the Department of Clinical Research at the University Hospital of Basel. The research group was developing a quality framework for clinical research based on a comprehensive literature review, followed-up by a Delphi-survey [46, 47]. The development of the quality framework was already advanced and conducted on a larger scale, leading to a reconsideration of the methods in this thesis. Eventually, an added value was recognised particularly in the qualitative part serving as a triangulation of methodology to challenge the quality framework and potentially complement it with specific aspects arising from resource-limited countries.

Also, the decision to limit the research methodology for the CT quality definition to a solely qualitative approach, was reinforced and justified by the inclusion of a highly relevant, second research topic within the framework of CT quality. During the course of the first year, our Institute's Clinical Operations Unit (formerly: Pharmaceutical Medicines Unit) encountered a specific challenge during a CT conducted in sub-Saharan Africa: The informed consent approach for children with minor parents. An analysis of this problem was found to be a relevant contribution the understanding of CT quality from the perspective of resource-limited countries, hence, it was included in this thesis. As the informed consent part required the conduct of a systematic literature review, it also added a secondary methodological approach to the thesis, which eventually required more capacity than initially expected. However, the timeliness and the lack of information on the subject justified this effort.

1.9 Ethical clearance

The PhD project was reviewed by the Ethikkommission Nordwest- und Zentralschweiz (EKNZ) and did not fall under the remit of the cantonal or federal law (Human Research Act). Hence, it was granted an exemption from ethical approval. However, the ethics committee confirmed that the project "fulfils general ethical and scientific standards for research with humans and poses no health hazards" (Appendix 6.2). As the interviews were conducted either in Basel or remotely from Basel (via phone or Skype), no international ethics clearances were necessary. Before starting the interviews, participants were informed (Appendix 6.3 and 6.4) and asked to provide oral consent, which was repeated for the record at the beginning of the interview. No ethical clearance was needed for the systematic literature review.

1.10 List of manuscripts

Table 1: Resulted manuscripts

Manuscript title	**Journal**	**Status**
Defining clinical trial quality from the perspective of resource-limited settings: A qualitative study based on interviews with investigators, sponsors, and monitors conducting clinical trials in sub-Saharan Africa	PLOS Neglected Tropical Diseases	Published
Informed consent approaches for clinical trial participation of infants with minor parents in sub-Saharan Africa: A systematic review	PLOS One	Published
Transparent reporting of recruitment and informed consent approaches in clinical trials recruiting children with minor parents in sub-Saharan Africa: A systematic review	BMC Public Health	Published

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2 Manuscript I: Defining clinical trial quality from the perspective of resource-limited settings: A qualitative study based on interviews with investigators, sponsors, and monitors conducting clinical trials in sub-Saharan Africa

Angela De Pretto-Lazarova[1,2]*, Claudia Fuchs[1,2], Peter van Eeuwijk[3,4], Christian Burri[1,2]

[1] Department of Medicine, Swiss Tropical and Public Health Institute, Basel, Switzerland

[2] University of Basel, Basel, Switzerland

[3] Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, University of Basel, Basel, Switzerland

[4] Social Anthropology Department, University of Basel, Basel, Switzerland

* Corresponding author

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2.1 Abstract

2.1.1 Introduction

Increasing clinical trial cost and complexity, as well as a high waste of clinical trial investment over the past decades, have changed the way clinical trial quality is managed. Recent evidence has highlighted that the lack of a clear clinical trial quality definition may have contributed to previous inefficiencies. This study aims to support the understanding of what clinical trial quality entails from the perspective of resource-limited settings.

2.1.2 Methods

We conducted 46 semi-structured interviews involving investigators, sponsors, and monitors with experience in conducting clinical trials in 27 countries in sub-Saharan Africa. The questionnaire addressed the overall meaning of clinical trial quality and a conclusive clinical trial quality definition, as well as specific aspects of resource-limited settings across the clinical trial process. We held the interviews either in person, via Skype or by phone. They were recorded and transcribed verbatim, and we performed the analysis using The Framework Method.

2.1.3 Results

The analysis of clinical trial quality definitions resulted in 11 elements, which were summarised into a clinical trial quality concept consisting of two components: 1) clinical trial quality building factors (Scientific factors and Moral factors) and 2) promoting factors (Context adaptation; Infrastructure; Partnership; Operational excellence; Quality system). 12 resource-limited settings specific themes were identified. These themes were all categorised under the promoting factors "Context adaptation", "Infrastructure", and "Partnership".

2.1.4 Conclusions

We found that in order to enable comprehensive clinical trial quality management, clinical trial quality should be defined by a multidimensional concept that includes not only scientific and ethical, but also quality-promoting factors. Such a concept is of general relevance and not limited to clinical trials in resource-limited settings, where it naturally carries particular weight. In addition, from the perspective of sub-Saharan Africa, we identified specific categories that appear to be critical for the conduct of clinical trials in resource-limited settings, and we propose respective changes to a particular existing clinical trial quality framework (i.e., INQUIRE).

2.2 Author summary

In recent decades, the quality management of clinical trials has been criticised for being inefficient and ineffective. This has led to a waste of clinical trial investment and has made it particularly difficult to conduct clinical trials in settings with limited resources. The lack of a universally accepted comprehensive definition of clinical trial quality was suggested as one of the possible causes of inadequate quality management. However, resource-limited countries were not considered in the attempt to create such a definition. In our study, we developed a quality concept based on qualitative interviews from the perspective of investigators, sponsors, and monitors with experience in conducting clinical trials in sub-Saharan Africa. The analysis of these stakeholders' definitions of clinical trial quality has produced a Clinical Trial Quality Concept that includes quality-promoting factors (i.e., Context adaptation; Infrastructure; Partnership; Operational excellence; Quality system) in addition to conventional scientific and ethical factors. The results thus support the need for a multidimensional quality concept to reflect clinical trial quality more comprehensively. We recommend the term "Comprehensive Quality Management (CQM)" for this concept. CQM has the potential to serve as a basis for the current revision of quality management principles in international clinical trial guidelines. Furthermore, the sub-Saharan African perspective has highlighted additional considerations compared to the existing comprehensive INQUIRE clinical trial quality framework. Therefore, we propose including the following three points relevant to resource-limited settings in the frame- work: 1) Communicating potential infrastructural disadvantages to funders, sponsors, and auditors. 2) Preventing potential exploitation of research populations and workforce in low- and middle-income countries by following existing ethical frameworks. 3) Including "Context adaptation" as an additional framework category (i.e., promoting factor).

2.3 Introduction

The conduct of clinical trials (CTs) in low- and middle-income countries (LMICs) is essential, as it contributes to combatting the burden of poverty-related diseases. Irrespective of the research setting, CTs must meet international standards to assure the public of the participants' safety and data integrity [1]. Today's most widely recognised CT guideline is the Good Clinical Practice guideline by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH-GCP) [2].

The guideline is defined as "ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects" [3]. However, it is unclear to what extent it is actually linked to the quality of CTs, as its development was

criticised for not being evidence-based [4, 5]. Moreover, it was developed mainly based on a pharmaceutical industry and regulatory authority perspective from the Global North, which leads to challenges when the guidance is applied to other settings, e.g., non-commercial, academic CTs, or CTs conducted in LMICs [4, 6, 7].

Also, an overly restrictive interpretation of the ICH-GCP guideline has been associated with decreasing efficiency in CT conduct in the past. Particularly, there was increasing evidence that the practice of assuring CT quality by implementing extensive monitoring was ineffective [1, 4, 8]. This "reactive" quality management approach had contributed to CT protocols becoming increasingly complex, in turn fuelling the demand for restrictive quality control measures and driving CT costs [9, 10]. Consequently, the concept of quality management in CTs was reconsidered in CT guidance, promoting a risk-based approach, which was integrated into a first amendment of the ICH-GCP guideline in 2016 [3]. The ICH guideline is currently being completely revised, with one of the goals being to promote a proactive consideration of quality when designing CT protocols and processes by identifying "Critical to Quality Factors" [11-13].

It has further been demonstrated that as much as 85% of investment in global CT implementation has been wasted [14]. The main reasons were deficiencies in research question selection; study design, conduct, and analysis; CT regulation and management; publication and accessibility of results; and completeness and usability of reporting [15]. These findings highlight that the conduct of CTs has essential quality attributes that go beyond compliance with the current ICH-GCP guideline.

A recent systematic literature survey found that there is no generally accepted consensus on a definition of CT quality [16]. A possible difference in understanding by the various stakeholders involved in CTs about what constitutes quality in CTs can inherently lead to both, undervalued and wasteful activities. Consequently, the authors of that study developed a quality framework called INcreasing QUality In patient-oriented academic clinical REsearch (INQUIRE) to summa- rise the quality criteria for CTs and achieve broad consensus [17]. The framework also provides an overview of existing standard tools to assure the quality of different parts of a CT (e.g., systematic reviews to define research questions, the SPIRIT statement for protocol development, the CONSORT statement for study publications, following GCP during the CT conduct, monitoring, and auditing). However, for the development of the INQUIRE framework, a LMICs' perspective was not considered, nor was an openly formulated CT quality definition sought.

Our study aims to provide a complementary viewpoint on the definition of CT quality from the perspective of CTs conducted in sub-Saharan Africa. On the one hand, this perspective allows

the identification of challenges of CT conduct in LMICs. On the other hand, the analysis of CT quality in the context of resource-constraint situations may give insight into critical factors contributing to quality and efficiency in the conduct of CTs anywhere in the world.

2.4 Methods

This explorative research follows both an inductive (based on raw data) and deductive (based on concept) theoretical approach. Such an interpretive model represents and involves the interplay of evidence and ideas. By this, collected data are reviewed in terms of theories and concepts and critically reflect on meaningful and reasonable causal relationships, contrasts and similarities, and homogeneity and heterogeneity in view of received meanings, perceptions and notions. The identified significant patterns of meaning are of scientific, practice, or policy relevance. Consequently, the analytical procedure of this study is grounded on The Framework Method according to Gale et al. and its seven steps of data analysis [18].

2.4.1 Ethics statement

The study was reviewed by the ethics committee Ethikkommission Nordwest- und Zentralschweiz (EKNZ). It was granted an exemption from ethical approval, as it did not fall under the Human Research Act's remit. The ethics committee confirmed that the project "fulfils general ethical and scientific standards for research with humans and poses no health hazards".

The stakeholders were contacted by email and received an information sheet addressing the study aim, privacy information, and the interviewers' contact details and credentials. The privacy information included that the interview was voluntary, that withdrawal from the study was possible at any time, and that all identifying information are kept confidential. If they agreed to participate, an appointment was made for the interview. At the beginning of each interview, participants gave verbal consent to participate and their statements to be audio-recorded. We followed the consolidated criteria for reporting qualitative research (COREQ, Appendix 6.5, Table S1) [19] and verified the trustworthiness of our methods based on criteria described by Anney [20].

2.4.2 Study design and setting

The study followed a qualitative research approach based on interviews with stakeholders having CT experience in at least one country in sub-Saharan Africa (SSA). The stakeholders could originate from in or outside SSA. Due to the large number of targeted countries, no travelling was intended. The interviewers were based in Switzerland and most interviews were

conducted remotely, either by phone or via Skype. Some interviews were conducted face-to-face in Switzerland, with visiting stakeholders.

We focused on three stakeholder groups composed of sponsor representatives (referred to as 'sponsors'), investigators, and monitors with experience in conducting CTs in SSA. These stakeholder groups were selected as they are involved in CT planning, conduct, and quality control and were expected to provide comprehensive knowledge about the entire CT scope.

A semi-structured interview guide using open-ended questions was chosen. It offered the possibility to define the interview's core components but still allowed the interview participants to address further topics intuitively.

The interviews were conducted by the lead and the second author. Both are pharmacists, female, and acquired interview experience in training and pilot rounds prior to the study. The application of the methods and interpretation of the findings was supervised and reviewed by an experienced social scientist.

2.4.3 Sampling and recruitment

First, purposive sampling was applied: a list of interventional studies conducted in SSA (excluding South Africa) between 2013 and 2017 was extracted from the WHO International Clinical Trials Registry Platform (ICTRP) [21]. The ICTRP was chosen as it accesses CT data from multiple providers, including ClinicalTrials.gov [22] and the Pan African Clinical Trial Registry (PACTR) [23]. The study period was chosen in order to access stakeholders conducting CTs according to latest ethical guidelines (i.e., the latest update of the Declaration of Helsinki in 2013) and having most current contact details. Also, in earlier study periods, less countries in SSA were involved in the conduct of CTs. South Africa was excluded from the sample to achieve greater diversity of SSA countries, as South Africa accounts for a disproportionately high number of CTs compared to other countries in SSA.

All investigators and sponsor and monitor organisations available in the ICTRP extract were systematically contacted.

Second, as sponsors and monitors in particular were difficult to access through information provided in CT registries, we additionally applied a strategy of snowball sampling: a) We drew on an independent network that we established at international conferences prior to the study. Thereby, we distributed flyers and approached CT stakeholders asking them about their interest in participating in the interview and requesting their contact details. In addition, we screened for contacts based on the conference participant lists. b) We reached out to the Swiss Tropical and Public Health Institute's (Swiss TPH) professional network.

Interested members of these networks were asked to participate in the interview, as well as to provide us with further contacts until we reached sufficient participants in each stakeholder group. The sample size was defined according to the principle of saturation: Once the interviewers had the impression that no or only a few new content-related elements were mentioned per stakeholder group, the sample size was considered sufficient. Thereby, the focus was set on defining key elements of CT quality.

While investigators were reached through both sampling strategies (purposive and snowball), sponsors and monitors were mainly reached through snowball sampling (Box 1).

Box 1: Interview participant recruitment and response rates

77 potential investigators were contacted based on the ICTRP and previous personal contact:
→ 17 persons accepted, 11 refused, the rest didn't reply to our interview invitation
103 potential sponsors and sponsor's organisations were contacted based on the ICTRP:
→ 1 person accepted, 4 refused, the rest didn't reply to our interview invitation
43 potential (known and unknown) monitors and CRO's were contacted based on the ICTRP:
→ 3 persons accepted, 8 refused, the rest didn't reply to our interview invitation
71 potential participants (sponsors, investigators, and monitors) were personal contacts from international conferences and recommendations:
→ 25 persons accepted, 21 refused, the rest didn't reply to our interview invitation
48 interviews were conducted
→ 2 interviews were excluded as the participant only had experience in observational research and not in clinical trials
46 interviews were finally included

ICTRP: International Clinical Trials Registry Platform; CRO: Contract Research Organisation

2.4.4 Data collection

The semi-structured interview guide (Appendix 6.6, Table S2) was based on an extensive preliminary literature review to cover the entire CT scope. Nine pilot testing interviews involving staff from the home institution with experience in CTs were conducted to gain information, limit the topic, identify a clear focus of the research scope, and improve the interview guide's clarity. The participant information sheet and interview guide were written in English and translated into French to extend the range of possible participants. The translation was checked for correct terminology by French- and English-speaking persons.

The following key topics were covered in the interview guide with reference to CTs conducted in SSA: personal and professional background; interpretation of CT quality in general; experience in CT planning, design, initiation, conduct, and termination; collaboration of CT stakeholders; reflection on CT quality; and conclusion based on a one-sentence CT definition.

The interviews were conducted between March and August 2018 and lasted 35–75 minutes. They were recorded using a digital voice recorder (Olympus Digital Voice Recorder VN-733PC), transcribed verbatim, and coded using MAXQDA 2018 VERBI software. During the interviews, the interviewer took notes to reflect and apply minor clarifications to the interview

guide for the subsequent interviews. Each audio file was re-listened by a second person, and the interview transcript was double-checked. The data output was anonymised to prevent the identification of interview participants or organisations. Only the lead author has access to the key for data anonymisation.

2.4.5 Data analysis

The interviews were coded and analysed according to The Framework Method [18]. First, we developed framework matrices for the one-sentence and general CT quality definitions provided by the respondents. The one-sentence CT quality definition matrix served as the basis for defining main categories that form the components of a CT quality concept. The general CT quality definition matrix was used to confirm and complement these categories.

Second, the complete interview transcripts were screened collecting additionally resource-limited settings (RLS) specific themes. These themes were assigned to the CT quality concept categories. The RLS-specific themes were identified by reflecting on which aspects mentioned by respondents across all interview topics dare likely to be influenced by the research setting.

Two authors coded and analysed the one-sentence CT quality definition. The remaining text was coded and analysed by one author and reviewed by a second author. All interviews were re-coded once by the same or a second author. During the coding process, memos on the content were created to support reflections. The codes as well as initial and final categories were reviewed and discussed with the co-authors.

2.5 Results

2.5.1 Participants

We conducted 46 interviews, including 21 investigators, 13 sponsors, and 12 monitors. Saturation of information was reached after 10–12 interviews. For the investigators' group, saturation was reached after almost double that number, as a large proportion (n=8/21) of investigators only had experience in investigator-initiated trials (IITs). Interview participants had experience in 27 countries in SSA and the workplace of more than half of all participants (n=25/46) was in SSA.

The participant characteristics show some notable differences between groups (e.g., workplace, place of CT conduct, years of experience, research environment). However, the characteristics of the total number of interview participants were relatively balanced (Table 2).

Table 2: Interview participant characteristics

Stakeholder		Gender		Workplace		Place of CT conduct		Av. CT exp.	Research environment		
Type	**Number**	**Female**	**Male**	**SSA**	**Non-SSA**	**Only SSA**	**SSA, Non-SSA**	**Years**	**IIT**	**Ind.**	**Mix**
Investigators	21	10	11	10	11	11*	7*	9.9	20	9	7
Sponsors	13	5	8	4	9	2	11	13.0	3	10	13
Monitors	12	5	7	11	1	9	3	13.5	7	9	6
Total	**46**	**20**	**26**	**25**	**21**	**22**	**21**	**11.8**	**30**	**28**	**26**

* No response from 3 interview participants; SSA: Sub-Saharan Africa; CT: Clinical trial; IIT: Investigator-initiated trial; Ind.: Industry-sponsored; Mix: Product-development partnership (PDP), Public-private partnership (PPP), or other partnerships.

The average CT experience of the interview participants was 11.8 years. Most participants were involved in phase II and III CTs and focused on drugs (Table 3). About half of the participants experienced more than one CT phase (n=24/46) and more than one intervention type (n=23/46).

Table 3: Interview participant experience distribution

Characteristic		Investigators (n=21)	Sponsors (n=13)	Monitors (n=12)
Clinical trial experience	<4 years	4	3	1
	4 – 9 years	7	2	1
	10 – 19 years	7	4	9
	20 – 30 years	2	4	1
	ND	1	0	0
Clinical trial phase	I	8	9	7
	II	14	10	12
	III	15	11	11
	IV	6	8	9
Intervention	Drug	16	12	12
	Vaccine	11	5	10

Many participants (n=30/46) had CT experience in more than one country in SSA. When considering the registered number of CTs conducted in SSA [20], the countries of conduct were broadly reflected in this study (Table 4). While some countries were slightly underrepresented (Malawi, Nigeria, Rwanda, Cameroon, Zambia), only two (Zimbabwe and Botswana) were clearly underrepresented [20]. As expected, sponsors (5.4) and monitors (4.8) had on average worked in more countries in SSA than investigators (1.7).

Table 4: Countries of clinical trial experience

Countries (n=27)	Number of participants, n
Tanzania	19
Kenya	18
Uganda	13
Burkina Faso	12
Mali	11
Gabon	10
Ghana	10
Mozambique	8
Côte d'Ivoire	7
The Gambia	6
Ethiopia	5
Guinea	5
Malawi	5
Nigeria	5
Senegal	4
Sudan	4
Democratic Republic of Congo	3
South Africa	3
Cameroon	2
Rwanda	2
Sierra Leone	2
Zambia	2
Guinea-Bissau	1
Various countries in SSA	7

SSA: Sub-Saharan Africa

2.5.2 Quality definition

Participants were first asked about their initial thoughts on the meaning of quality in a CT context. Then, the various stages of a CT were run through to create a general overview of the CT process, and in the end, the participants were requested to define the term "clinical trial quality" in one sentence. The outcome of this task perfectly summarised the challenge of narrowing this topic down, as many participants (n=15/46) expressed that this request was challenging or even impossible, and the responses diverged widely and mostly contained multiple aspects:

"[Laughs] I don't know, one sentence is really difficult because it's so much, it's so many aspects I would say you cannot really define it in one sentence [...]."

– Investigator, female, 8 years of CT experience, based outside SSA

The original responses can be found in (Appendix 6.7, Table S4). We coded the aspects mentioned by the participants when defining CT quality and grouped them into the following main elements according to descending frequency (Table 5): Data integrity; Adherence; Soundness of research; Participant safety and rights; Quality system; Operational excellence; Partnership; Infrastructure; Relevance and patient-centeredness; Documentation; and Context adaptation.

Table 5: Categorisation of the clinical trial quality codes into elements

Element	**Codes**
Data integrity	Clinical trial data reflect the clinical trial quality; ensuring that the data are reproducible, verifiable, reliable, solid, credible, authentic, consistent, accurate, good, conclusive, close to reality, trustworthy, excellent, clear, and complete; entering data systematically; safeguarding the data integrity; successful achievement of a correct conclusion from a study
Adherence	Strict/disciplined/rigorous/mandatory adherence to general requirements, such as good clinical practice (GCP), good clinical laboratory practice (GCLP), good manufacturing practice (GMP), and ethical standards, adherence to specific requirements, such as the protocol, standard operating procedures (SOPs), study manuals, and national regulations
Soundness of research	Doing the right; good science; sound scientific premise; no waste; excellent research question; robust study design; clear and simple protocol; looking for the right kind of data; minimisation of bias; sound research methodology; sample management; ability to get valid/meaningful/valuable results/correct conclusions/representative figure; meeting the objectives; clear data collection tools
Participant safety & rights	Quality equals safety; protecting/ensuring safety, wellbeing, rights, confidentiality; integrity of volunteers; subjects not put at risk; good participant experience; think about participant safety first; applying all necessary safety measures; having a good safety awareness; no harm
Quality system	A number of aspects should be fulfilled; interaction of multiple factors; totality of data, material and staff; quality is everything/a continuous process/the whole package/a sum of overall implementation; looking at all aspects; a set of factors enabling the collection of data; having robust quality management; steps to ensure quality/consistency; having SOPs at each level; having manuals; ensuring maintenance of instruments; having a risk-management plan; implementing on-site supervision; doing clinical trial administration; keeping control/oversight; having quality control procedures (e.g., implementing monitoring/audits); checking in real-time; picking up errors in time; immediate checks; automatic checks
Operational excellence	Doing it right; doing the best; clever approaches; proper implementation; sophisticated; making an effort; setting the right priorities; smooth/sound clinical trial execution; flexibility; reasonability
Partnership	Desired by site investigator; maintain relationships; networking/exchanging; motivation; communication; meeting the expectations by all parties involved (e.g., sponsors, investigators, local investigators, CRO); alignment of expectations; sharing values, beliefs, and principles; mutual acceptance; taking the community into account; consider the study type; capacity building
Infrastructure	Having a good team; qualified personnel; trained personnel; experience; expertise; dedication; competence; accountability to participants, funders, communities; quality awareness; basic clinical trial understanding (e.g., GCP, GCLP); specific research project understanding; knowing what to do, sticking to the timelines; continuous staff training; mentoring; systems knowledge; variable regulations; adequate facility/equipment/resources
Relevance & Patient centeredness	Generating meaningful results for the population (e.g., life improvement of a vulnerable population); having an important research question; utility of the results; putting more focus on the safety than on the publication; having outcomes that people can see; understanding the participants' needs; addressing the populations' needs; benefits are rather early than late
Documentation	Trace the research; having a trial master file; having a research protocol; having documented what you have formulated in your case report forms; transparency; having logs
Context adaptation	Adapted to the context (e.g., study environment, population, disease); variable norms (e.g., meaning of blood samples in a cultural context, involvement of the community); consider regional aspects (e.g., weather, politics, etc.); adapted to local guidelines and regulations

The major consensus we identified, when comparing the CT quality definitions, is that "clinical trial quality" involves multiple layers (n=10/46).

> *"Let's say, it's a full quality assurance management system that looks at all the aspects and tries to set up systems for all these aspects, not too heavy, but that can cover many aspects and not only one [...]. I mean not just SOP's [standard operating procedures], it goes beyond SOP's, it goes...it's also just [...]. Yes, how to cleverly recruit people, how to cleverly follow the data, so, it has several aspects."*
>
> – Investigator, female, 20 years of CT experience, based outside SSA

While data integrity as well as participant safety and rights, generally ranked among the elements most frequently associated with CT quality, several participants (n=6/46) referred uniquely to those two broad elements. Half of these participants were sponsors, and half were investigators who had experience in sponsored CTs (commercial or non-commercial).

> *"Clinical trial quality is about [...] providing assurance that the data you collect is credible and accurate and at the same time making sure that, you know, all the safety, the wellbeing, the rights, integrity of the volunteers are taken into account or are protected."*
>
> – Investigator, male, over 10 years of CT experience, based in SSA

The elements of data integrity as well as participant safety and rights, were overall most frequently addressed by sponsors, while adherence was most frequently mentioned by monitors, and investigators referred most frequently to the soundness of the research.

When considering additionally the request to describe the meaning of quality in an unrestricted way, the same elements defining CT quality were found. Interestingly, although the overall ranking of elements was slightly variable between the unlimited and the one-sentence CT quality definition, the stakeholder groups mentioning the elements most frequently remained the same, as described above.

Overall, the 11 CT quality elements could be organised into two components: 1) CT quality building factors covering the entire CT process (i.e., concept, plan, conduct, analysis, and reporting) and 2) CT quality-promoting factors. The building factors were further subdivided into i) Moral factors, including the elements "Participant safety and rights"; and "Adherence" to general requirements, and ii) Scientific factors, including the elements "Relevance and patient-centeredness"; "Scientific soundness"; "Adherence" to study specific requirements; "Documentation"; and "Data integrity". The promoting factors include the elements "Context adaptation", "Infrastructure", "Partnership", "Quality system", and "Operational excellence" (Figure 2).

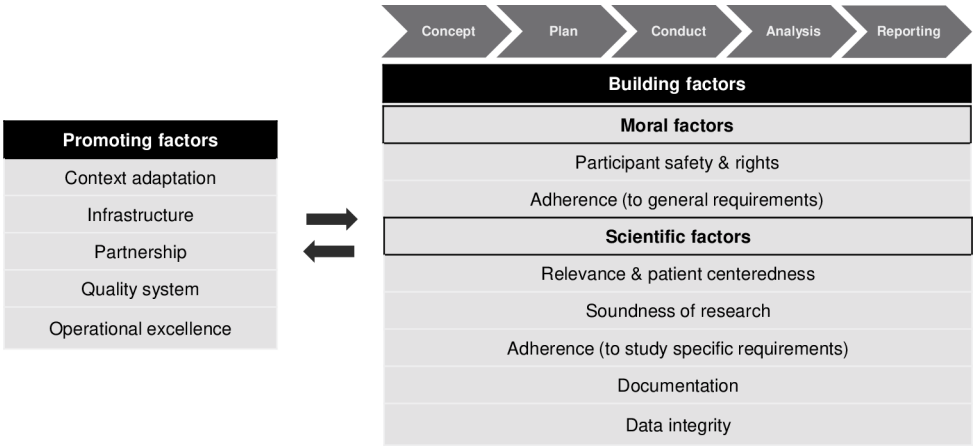

Figure 2: Clinical trial quality concept

2.5.3 Resource-limited setting specific themes

When asking about the influence of conducting CTs in resource-limited settings (RLS) on the overall perception of CT quality, some participants first stressed that the quality standard for CTs should be the same, no matter where the CT is conducted.

Nevertheless, participants also indicated that RLS show several characteristics that need to be taken into account to allow the implementation of the same standards. These characteristics could be mainly associated with the CT quality-promoting factors "Context adaptation", "Infrastructure", and "Partnership" (Coding tree, Appendix 6.8, Table S5).

2.5.3.1 Context adaptation

Several interviewees mentioned the need to adapt CT processes to the context relating to the population's overall health conditions (n=15/46), accessibility (n=11/46), and education levels (n=25/46), as well as to consider cultural (n=10/46) and regional (n=7/46) specificities as subthemes.

Health condition. Some interviewees highlighted the researchers' responsibility to consider the generally limited access to healthcare and to manage it ethically (e.g., motivation for CT participation, post-trial treatment access, and appropriate compensation). Also, there is a higher probability of serious co-morbidities and unregistered concomitant medication (e.g., using traditional medicine), which should be addressed, as they could affect patient management and study outcomes. Further, the eligibility criteria should be based on population-specific laboratory norm values, and the development of simultaneous research activities or health intervention programs in the area should be observed.

"But also it could be, and this is an example [...] where [...] the local circumstances were such that one of the communities had been heavily researched. It was actually over-researched, and then people are actually tired. So, if you go into that particular area to do a trial again, you may end up with low rates of recruitment [...]."

– Investigator, male, over 10 years of CT experience, based in SSA

Accessibility. Some interviewees mentioned that potential study participants might be difficult to access, particularly in rural areas. They may live far away from health and research facilities, have limited or no mobile phone access, as well as unregistered households. Moreover, neglected diseases may be rare and spread over large areas, requiring adapted recruitment and follow-up approaches (e.g., active recruitment with mobile laboratories).

Education levels. Due to limited access to health education, research populations in RLS may have lower awareness about the meaning of research. Some interviewees emphasised that such awareness should be raised before any CT activity is started to prevent rumours and misconceptions (e.g., the meaning of blood, signatures, stigma), as they may seriously impede the recruitment of CT participants. Especially when developing the informed consent process, high illiteracy rates, and the fact that the national language may not be spoken and some local languages may not exist in writing should be considered (e.g., availability of literate impartial witnesses and translators, audio-visual consent tools).

"Good informed consent is [...] the one that can be managed best between being short in text and also complying with all the points that have to appear in an informed consent as of ICH-GCP. [...] we more and more go towards audio, audio informed consents. The reality is that in sub-Saharan Africa, in most of the West African countries and East African countries, languages are not written. [...] Even if a very literate person speaks well his native language, he can never read it."

– Monitor, female, 14 years of CT experience, based in SSA

Overall, many interviewees (n=15/46) stressed that the informed consent form should be kept short or simple. Some also recommended assessing the participants' understanding depending on their background knowledge and the research complexity before including them in the study.

Culture. Many interviewees (n=23/46) stressed the importance of engaging community representatives when developing the informed consent process (see also the subtheme Collaboration), as certain aspects may vary according to the cultural context, such as the age of consent, the definition of appropriate representatives to consent on behalf of children, the need of an initial consent by community leaders before addressing individuals, or the appropriateness of group sessions.

"Usually, for the informed consent, you take the initials of the subject. But in Africa, you can find some people with six to seven names, and the legal representative is also not necessarily he father and mother; an aunt or an uncle could act as a legal representative or elderly people from the same village [...]. So, I think an understanding of the culture while you are conducting a clinical trial is also important."

– Sponsor, female, over 3 years of CT experience, based outside SSA

Region. Some interviewees mentioned that the seasonal disease variability, climatic conditions, political stability, and public holidays might further impede the participant recruitment (e.g., participant reachability) or interfere with internet and mobile phone network connectivity, shipment and transport schedules, as well as storage conditions.

2.5.3.2 Infrastructure

A key topic emerging from many interviews (n=13/46) when asking about aspects in RLS that affect CT quality were the long timelines that must be considered because of infrastructural shortcomings. Such shortcomings were mainly associated with the subthemes of health authority approval, availability of guidelines, staff qualification, and facility level.

Health authority approval. Responses by interviewees clarified that the experience and responsibilities of health authorities may vary widely across SSA. For example, ethics committees may have different requirements (e.g., serious adverse event reporting timelines, inspections, periodic reports, personal or electronic protocol submission). Their approval time may range from two weeks to over one year. Twelve interviewees, who combined had experience in 20 countries in SSA, stressed that national ethics committees' approval time was often long and unpredictable. Internal bureaucracy and high workload with limited capacity were blamed for the delays. The ethics committees' diversity was perceived as a particular challenge when conducting multinational trials, and a joint review was recommended. A few interviewees also mentioned that in some countries, the ethics committees' capacity had improved significantly over the past years and rather considered the regulatory authorities' capacity one of the most limiting factors. Overall, interviewees recommended anticipating long approval processes in RLS, prioritising, and planning more flexibly.

Availability of guidelines. A monitor with experience in about half of all reported countries in SSA (n=13/27) highlighted that some countries might have established CT guidelines at a national or institutional level, while others may have none. Another interviewee further noted that some countries might be in the process of establishing a research infrastructure; therefore, country-specific requirements may change frequently, and researchers have to adapt to them for every new CT.

All interview participants mentioned that they followed the ICH-GCP guideline. Established guidelines were reportedly mainly based on the ICH-GCP guideline, including additional, country-specific operationalisations.

> *"So, some of the recommendations of the ICH-GCP are contextualised in the local guidelines, so, they are really brought to the context of the countries. But they are largely the same, so, we don't see many divergences from these in critical things."*
>
> – Sponsor, male, over 3 years of CT experience, based in SSA

Examples of such setting-specific requirements included: reporting frequency to ethics committees; participant compensation; initial community permission; community engagement; blood draws; sample and drug im-/exportation; disease-specific guidance; staff licences (e.g., qualifications for principal investigators/monitors); insurance cover and indemnity; participant type specific guidance (e.g., paediatrics); and informed consent (e.g., age of assent/ consent).

Staff qualification. When considering staff qualification, interviewees (n=11/46), who together had CT experience in over two-thirds of the reported countries in SSA (n=19/27), called out some disadvantages in the education system: The principles of scientific work and GCP were not sufficiently represented during medical training; therefore, in some regions, the graduates were less familiar with, e.g., the concepts of documentation, validation, and deviation. This situation could have consequences for CT quality, as one respondent explained:

> *"Medical doctors, investigators, are not trained to use a computer in their routine practice. If you ask them to report [...], you face a bottleneck. If you want to go around this and say, ok, we will hire data entry clerks; those data entry clerks can't read the medical handwritings. They can't, because these people aren't trained for research to write them clearly! So, if you want to go around this, too, you will now design very nice source documents, you know, you see where we are going now. We are going to a very tricky, and I call it a poisonous way of doing, but it is now invading clinical research in Africa. You will now design some sort of source document, which is actually a printout of the CRF. Just a data capture tool. The medics and the investigator will just complete that data capture tool and will no more do their medics. They will not do routine practice!"*
>
> – Monitor, female, 14 years of CT experience, based in SSA

Interviewees also emphasised that inexperienced researchers need time to grow accustomed to these concepts before taking on responsibilities in a CT. One sponsor pointed out the need to start working with an inexperienced site at least one year before implementing the CT. Overall, pilot runs, being initially accompanied by or following experienced researchers from other institutions, and close supervision were considered essential for CT quality when working with less experienced staff.

Facility level. Facilities described by interviewees could be very variable and ranged from field labs over primary to tertiary health care facilities to specialised CT units within hospitals or institutional research centres. Urban and rural settings were both common. Most stakeholders had experience using existing facilities, which were frequently upgraded in terms of CT equipment and space. Some (n=8/46) had also experienced establishing facilities from the ground up.

When working in remote, rural facilities, the coordination of material supply, as well as limited power and internet connectivity, were the main concerns for CT quality due to possible delays. According to interviewees, shipments could involve a lot of bureaucracy in some regions, while the limited internet may require the use of paper Case Report Forms (CRFs), losing the benefits of electronic CRFs, which were summarised by an interviewee as follows:

> *"Before, you would have to go through all these papers, and after a few hours, you also get slightly dizzy. But now they have these electronic CRFs that alert you already if there is something out of range [...] probably an error that was entered. So, this combination of this electronic CRF, also the way that we now electronically download, e.g., biochemistry and haematology data and upload it into the database prevents a lot of unnecessary query resolution."*
>
> – Investigator, female, 10 years of CT experience, based outside SSA

Some interviewees (n=9/46) highlighted the importance of a site assessment visit or questionnaire for an appropriate site selection and study planning. However, a sponsor also warned that formal site assessments were not always desired due to the possibility of harming a centre's reputation.

2.5.3.3 Partnership

Under the element of "Partnership", CT quality was mainly associated with the subthemes of collaboration, communication, and sustainability.

Collaboration. Since various organisations and stakeholders are always involved in the conduct of CTs, interviewees mentioned the importance of good collaboration. Thereby, half of all interviewees (n=23/46) stressed the importance of community engagement when planning a CT (e.g., involving a community advisory board or community representatives).

> *"So, this is the group of volunteers of the community, who sort of act as a communication channel between the clinical trial team and the community. So, those also look at whatever you are planning to do, and they give feedback."*
>
> – Investigator, male, 7 years of CT experience, based in SSA

Funders may explicitly require community engagement, and in some cases, the ethics committee may be responsible for organising it. Community engagement could also involve research activities to assess the community's perspective on CTs.

Many interviewees (n=30/46) emphasised the need to involve site investigators and their team early in the CT development in order to adapt to the site's working capacity (assessing the need for assistance or extra staff for, e.g., budgeting, accounting, or quality management) and the staff's routines and schedules (e.g., consider weekends and holidays) as well as to assure protocol and CRF suitability, and particularly to share responsibility.

> *"We always involve people in the very early stages of an idea. Because you can have a very nice idea, but if it's impossible, people are not motivated to do so, it's not going to work out. So, involving people from sub-Saharan Africa at a very early stage is very important to make sure that they are also owner of the idea and owner of the program. So, ownership is crucial!"*
>
> – Investigator, male, over 15 years of CT experience, based outside SSA

Communication. Good communication was associated with CT quality by many interviewees (n=36/46). Thereby, interviewees referred to having a communication system between all parties involved in the CT and good communication tools. Some emphasised the notification of important stakeholders about the planning of a CT, reporting to, e.g., ethics committees during the CT, and informing the community about the CT outcomes. For external sponsors and principal investigators, regular and open communication was recommended (e.g., clear definition of roles, communication of expectations, exchange experiences). Moreover, cultural sensitivity was mentioned for the way of communication between the site staff and research participants, as well as between monitors and the site staff. It was also considered crucial for external sponsors to visit research sites to gain a good understanding of the study environment.

Sustainability. In some interviews (n=17/46), it became clear that funding mechanisms, which could also depend on the CT model (i.e., IIT, industry, mixed partnerships), could be very variable and indirectly affect CT quality by influencing capacity building and sustainability. According to interviewees, some funders had clear expectations for CTs (e.g., following ICH-GCP, implementing capacity building, electronic data capturing tools, or community engagement), while others predominantly cared for the CT to deliver results. One interviewee emphasised that applying for competitive grants could particularly result in very limited funding, with only a little flexibility for adjustment. However, flexibility in the budget was necessary for many interviewees (n=25/46) who had to adjust the funding mainly because, e.g., the CT had taken longer than expected or due to protocol amendments.

Five interviewees raised particular concerns about the importance of adequate core funding and long-term partnership to provide workplace security and sustain research expertise inbetween studies.

> *"The core funding, and the core support for clinical trial teams is often very limited, and that means also that after one trial that even if it's only half a year or a one-year break in-between, you might have to start again from scratch because the team could not be paid throughout and they, of course, go somewhere else […]."*
>
> – Investigator, male, 8 years of CT experience, based outside SSA

Moreover, the establishment of local education programs (e.g., involving students in the CT conduct) and creating more research opportunities by increasing the visibility of research sites, investing in blood-/biobanks, or expanding laboratory capacity were proposed to increase the capacity and sustainability of CT conduct. However, three interviewees stressed that this could only be achieved if governments were more committed. For example, in some countries in SSA, research was considered a "luxury" and therefore as a lower priority.

2.6 Discussion

To the best of our knowledge, this study provides a first overview of the definition of the term "clinical trial quality" by researchers with experience in conducting CTs in RLS. Moreover, it offers an insight into how the research context may contribute to this understanding. The interviewees who represented typical CT models (i.e., IIT, industry, mixed partnerships) in RLS had vast and diverse experience, sometimes in multiple CT models and countries, and could provide comparisons.

Overall, the complexity and multi-layered nature of CT quality, as well as the difficulty of expressing it, led to great variability in its definition (Appendix 6.7, Table S4). A conceptual interpretation of the definitions was therefore considered the best way to capture the different layers. The resulting quality elements were compiled into a composition of CT quality building (i.e., scientific and moral factors) and -promoting factors (Figure 2). In comparison, these components correspond surprisingly well to the building blocks of the existing INQUIRE framework [17]. On a conceptual level, our results support the defined quality dimensions and the way they span across the different study stages, as presented in the INQUIRE framework. However, variation was found when comparing the CT quality promoters in both quality concepts. In the INQUIRE framework, the CT quality promoters were limited to "Infrastructure" and "Sus-

tainability/Education", while next to "Infrastructure", our concept additionally identified "Context adaptation", "Partnership", "Operational excellence", and "Quality system" as quality promoters. The theme "Sustainability/Education" was thereby classified under "Partnership" in our concept, whereas "Quality system", "Operational excellence", and parts of "Partnership" could be allocated to "Infrastructure" in the INQUIRE framework. Uniquely, "Context adaptation" is a completely new concept that is not reflected in the INQUIRE framework. However, this gap can be explained since the authors of the INQUIRE framework explicitly stated that they did not consider societal aspects and beliefs [16], which are central in our element of "Context adaptation".

When considering the frequency of CT quality elements mentioned per stakeholder group in the one-sentence CT quality definitions, the proportions of monitors mentioning adherence, and sponsors mentioning data integrity as well as participant safety and rights were highest. Investigators mostly mentioned scientific soundness. However, the proportions per element addressed by investigators were distributed more evenly. Overall, the different stakeholder groups tended to focus on the quality aspects most important for their own role. In the case of sponsors, their particular focus on data integrity as well as participant safety and rights might also well be rooted in a perception of CT quality which is influenced by existing guidelines that use exactly these two broad (!) terms to describe what should be aimed for in CTs [3, 12]. Awareness about the divergence between the stakeholder groups may promote effective cooperation.

Focusing on RLS-specific factors with potential influence on CT quality, the resulting themes were considered CT quality promoters and could be categorised under "Context adaptation", "Infrastructure", and "Partnership". These themes reflect aspects frequently discussed in the literature. However, existing literature addressed these aspects mainly from the perspective of ethics [24, 25], ICH-GCP applicability [2, 26, 27], or lessons learned when implementing specific studies in specific regions in SSA [28-30]. In contrast, our study was transnational and strictly oriented towards associations with CT quality, which could but did not necessarily have to overlap with these perspectives. We are aware of one other study focusing on quality indicators for CTs in RLS [31]. However, the quality indicator list was restricted to CT implementation rather than the entire CT scope.

When assessing a potential complementary introduction of RLS-specific themes into the INQUIRE framework, there were significant overlaps, indicating that the INQUIRE framework is a very comprehensive tool, even for RLS. Overlaps mainly concerned "Infrastructure" and "Partnership", since "Context adaptation" was not addressed. Still, two aspects should be

highlighted that need to be considered in addition to the framework in order to be more inclusive towards RLS: 1) Under "Infrastructure": Emphasis on clearly communicating potential infrastructural disadvantages and their impact on timelines and, ultimately, the quality of CTs to funders, sponsors, and auditors. 2) Under "Sustainability/Education": Prevention of potential exploitation of research populations and workforce in LMICs by following specific ethical frameworks (e.g., *The benchmarks of ethical research in developing countries* [25]*, and Good collaborative practice: reforming capacity building governance of international health research partnerships* [32]). As final amendment, we recommend adding 3) "Context adaptation" as an additional CT quality promoter to the INQUIRE framework.

An aspect worth exploring in more detail for an appropriate representation in CT concepts was the distinction or similarity of community engagement versus the engagement of patient representatives. A recent study has shown that there are overlaps but also clear distinctions between both notions [33]. However, in the interviews, it was not clear to what extent these concepts were distinguished or combined under one of the respective terms. Furthermore, it was suggested that the term "patient representative" could be discriminative or exclusive towards research involving healthy populations (e.g., vaccine research).

2.6.1 Strengths and limitations

This study has some limitations: We focused on the region of SSA, however, the results may not be transferable to all of SSA or RLS outside SSA. Also, we focused only on investigators, sponsors, and monitors without including other CT stakeholders' perspectives, such as participants, ethics committees, funders, and regulatory authorities. Therefore, further research, including different stakeholder groups and regions, may offer new insights.

Moreover, with our initial sampling strategy using the ICTRP we intended to reach stakeholders independently from each other to maintain confidentiality. However, based on CT registers, mainly investigators and fewer sponsors and monitors could be identified and contacted directly. The overall participation rate remained low, and the following reasons may have contributed to this: Compared to surveys, interviews take much longer, which may have influenced the interest in participation; interviews also require a smaller number of participants, which may have reduced the pressure to participate. In addition, the contacts in the database could be outdated. Therefore, we decided to recruit more participants additionally via the snowball method, whereby a particular selection bias (i.e., personal relationship among interviewees) could hardly be avoided. However, in order to remain as independent as possible, we did not only approach known contacts, but also generated new contacts at conferences.

Further, we intended to increase generalisability by targeting many countries in SSA. which limited us in conducting interviews in person, possibly carrying over this distance into the interview atmosphere. However, since the interviewees were often participating in international research, they were used to the idea of communicating virtually. Also, the topics addressed were not personal, increasing the acceptability of this method. Talking about quality may have also been perceived as a "testing" situation by some participants. We tried to prevent this sentiment by addressing it upfront in the information sheet.

Due to the limited time and budget, we were not able to seek feedback from the interview participants on the interview transcripts and the results. Also, given that many interviews were conducted remotely, we were not able to verify if other persons may have been present in the background during interviews, which may have influenced the responses.

The methodology was qualitative; hence, numerical descriptions should be considered with caution. We also acknowledge that the interviewees' perspectives may be personal and not generalisable. However, our aim was to look for overarching CT quality aspects and we managed to involve stakeholders with extensive experience, often in several CTs and countries in SSA. Therefore, we believe that the methodology was suitable to produce a usable initial CT quality concept incorporating the perspective from RLS. Nevertheless, the concept could benefit from further research aimed at broader agreement, including transferability to other RLS, transferability to high-income countries, and the inclusion of participant and external feedback.

Finally, our specific methodological approach maintains data trustworthiness by securing the following quality label: this research measures what it should measure (validity); it reproduces reliable results if it will be repeated (reliability); it is objective in the sense that no unwanted influences are exerted by involved persons (objectivity).

2.7 Conclusions

A clear overview of quality components emerged from interviews with investigators, sponsors, and monitors with CT experience in SSA. These components form a CT Quality Concept that, in contrast to the conventional two-dimensional quality standard of the ICH-GCP (R1 & R2), which focuses primarily on scientific and ethical requirements, additionally emphasises "CT quality-promoting factors" as a CT quality component.

Our results suggest that considering CT quality-promoting factors in the definition of CT quality can lead to a more adequate balance of quality management activities and thus a more efficient and successful CT conduct. This finding is in line with the existing INQUIRE framework,

which also represents a multidimensional quality concept and includes the component of quality promoters [17].

Consequently, our results underline that future CT guidelines should not only be founded on two-dimensional but on multidimensional quality concepts, including scientific, ethical, and quality-promoting aspects. We recommend this approach to be understood as "Comprehensive Quality Management (CQM)". CQM could be considered in the ongoing revision (R3) of the ICH-GCP E6 guideline and/or the current draft of the ICH-E8 (R1) guideline and discussed as a basis for the identification of "Critical to Quality Factors" [11–13], enabling a true risk-based approach to CT planning, implementation and oversight.

Insights from the SSA perspective suggested that important considerations in RLS are primarily categorised under the CT quality-promoting factors. Hence, when using a traditional two-dimensional quality standard as a basis to manage and assess CT quality, these considerations are neglected, potentially affecting the CT quality and efficiency.

Furthermore, RLS-specific aspects resulted in an additional promoter, Context adaptation, as well as additions to the existing promoters in the INQUIRE framework. Therefore, we open the discussion to include the following points in the INQUIRE Framework to be inclusive towards critical reflections in CTs conducted in LMICs: 1) Addressing potential infrastructural disadvantages and their impact on timelines and, ultimately, the quality of CTs to funders, sponsors, and auditors. 2) Preventing potential exploitation of research populations and workforce in LMICs by following specific ethical frameworks (e.g., *The benchmarks of ethical research in developing countries, Good collaborative practice: reforming capacity building governance of international health research partnerships*). 3) Adding "Context adaptation" as an additional CT quality promoter category, including reflections on the populations' socio-economic, as well as cultural and regional aspects.

However, these suggestions are based on exploratory qualitative research. Therefore, they should not be considered exhaustive and need to be validated in further studies.

2.8 Acknowledgement

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3 Manuscript II: Informed consent approaches for clinical trial participation of infants with minor parents in sub-Saharan Africa: A systematic review

Angela De Pretto-Lazarova[1,2]*, Domnita Oana Brancati-Badarau[1,2,3], Christian Burri[1,2]

[1] Department of Medicine, Swiss Tropical and Public Health Institute, Basel, Switzerland

[2] University of Basel, Basel, Switzerland

[3] Life and Health Sciences and Aston Brain Centre, Aston University, Birmingham, United Kingdom

* Corresponding author

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3.1 Abstract

3.1.1 Background

Regulations are vague regarding the appropriate decision-maker and authority to consent for children of minor parents participating in clinical trials. In countries with high rates of underage mothers, such as in sub-Saharan Africa, this lack of guidance may affect the rights of potential paediatric participants already bearing increased vulnerability. It can also influence the recruitment and generalisability of the research. We provide evidence and discuss informed consent management in such cases to inform best practice.

3.1.2 Materials and Methods

We searched PubMed/MEDLINE, Embase, CINAHL, and Google Scholar for articles published up to March 2019. In total, 4382 articles were screened, of which 16 met our inclusion criteria. Studies addressing informed consent in clinical trials involving children with minor parents in sub-Saharan Africa were included. We performed descriptive and qualitative framework analyses. The review was registered in PROSPERO: CRD42018074220.

3.1.3 Results

Various informed consent approaches were reported. Articles supporting individual consent by minor parents based on emancipation or "mature minor" status lacked evidence in the context of research. National laws on medical care guided consent instead. When no laws or guidance existed an interpretation of the local decision-making culture, including community engagement and collaboration with local ethics committees, defined the informed consent approach.

3.1.4 Conclusions

The review emphasises that the implementation of informed consent for children with minor parents may be variable and hampered by absent or ambiguous clinical trial regulations, as well as divergent local realities. It may further be influenced by the research area and study-specific risks. Clear guidance is required to help address these challenges proactively in clinical trial planning. We provided a set of questions to be considered in the development of an ethically acceptable informed consent approach and proposed information that should be integrated into international clinical trial guidelines.

3.2 Introduction

Enrolment of children into clinical trials (CTs) is mandatory to enable the development of new medicines for this population [1]. Infectious diseases and malnutrition remain essential factors affecting childhood mortality, with around 50% of all cases occurring in Africa [2-4]. Compared to Europe or the USA, a higher proportion of CTs conducted in sub-Saharan Africa (SSA) involve children [5, 6]. Adolescent birth rates in SSA countries are also among the highest worldwide [7], increasing the likelihood that research staff might have to deal with the ethical challenge of obtaining valid informed consent (IC) for infant participation from minor parents.

International guidelines on the conduct of CTs state that by being recognised as "emancipated" or "mature minors" through marriage, parenthood, etc. [8, 9], adolescents may be allowed to consent autonomously. However, it remains unclear whether autonomous consent refers only to adolescent's own research participation or whether such minors may consent independently for their child as well.

Further specifications regarding the "emancipated" or "mature minors" status are subject to national provisions [8-10]. In the UK and the USA, professional guidelines recognise that minor parents can be responsible for medical decision-making for their children if they are considered competent. Nevertheless, these guidelines lack strict criteria or principles defining such competence in relation to minor parents and its applicability to clinical trials [11, 12].

In some SSA countries, such as Kenya, guidelines may be in place (e.g., a national CT regulation or institutional guidance for the conduct of CTs) determining whether minor parents may consent for their children [10, 13]. However, such guidance may be missing, unclear, or difficult to source in other SSA countries. Even when concepts for "emancipated" or "mature minors" exist in general national legislations or research specific guidelines, their transferability to the context of CTs and the consent for children of minors often remain unspecified [14]. In addition, social and cultural norms may differ from country to country posing challenges for researchers in the development and implementation of IC procedures [10, 15].

Considerable efforts in the past decades sought to improve quality standards in global paediatric research, including strengthening recommendations on IC practices [16-18]. However, formal international guidance on implementing an ethically acceptable approach to the IC process for children with minor parents in various CT contexts is still lacking. There is a paramount need for best practices on IC, which ensure adequate protection while maintaining the option to enrol children under such circumstances.

The objective of this study was to address this gap by mapping the reported approaches to IC in paediatric CTs involving minor parents in SSA as identified through a systematic literature review.

3.3 Materials and methods

This review followed the PRISMA 2009 statement (Appendix 6.9, Table S6) [19] and was registered in the PROSPERO database (CRD42018074220) [20].

3.3.1 Eligibility criteria and screening

We exported all search results to a reference management software (Endnote X7). After removing duplicates, we created an MS Excel table capturing selected information from the extracted literature (Author, Year, Journal/Publisher, Title, Abstract, Keywords, ISBN/ISSN, DOI, and URL). Two independent reviewers (ADP and DOB) received a copy of the excel sheet and first screened articles based on title and abstract according to predefined eligibility criteria (Box 2).

Box 2: Eligibility criteria

Inclusion criteria

Including any type of study, if relating to all of the following four key elements:

- Informed consent procedure (proxy decision-maker, autonomous consent, assent, preterm consent)
- Clinical trials (drug trials, vaccine trials, diagnostic trials, medical device trials, surgical trials, emergency research trials, nutritional supplementation trials)
- Children as
  a. Participants (neonates, infants, toddlers, small children) with the age of 0.0-4.9 years
  b. Minor parents (adolescents, teenagers, mature minors, emancipated minors) with the age of 12.0-17.9 years
- Sub-Saharan Africa (or global or international relevance, including sub-Saharan Africa)

Exclusion criteria

Excluding any type of study, if relating to:

- Adults
- Children with the age of 5.0-11.9 years
- Vulnerable participants in the broader sense (individuals with disabilities, geriatric subjects, ethnic minorities, migrants, etc.)
- Developed countries only
- Informed consent procedure in other than clinical trials:
  - Observational studies (with and without blood samples), quality of life studies, preventive interventions (health care/health behaviour/immunisation)
  - Reproductive health care (HIV testing, abortion, fertilisation, contraception, adoption, pregnancy, circumcision/sterilisation, etc.)
  - Biobanking, organ donation, blood transfusion
  - Genetic testing, new-born screening
  - Diverse treatments
  - Euthanasia/end-of-life decision-making
  - Surgery (as treatment)
  - Emergency treatment/treatment of serious illnesses
  - Nutritional studies, if only addressing natural behaviour, such as breastfeeding
  - If it is a study report using blood samples from a primary clinical trial
- Other informed consent topics, such as addressing exclusively:

- Informed consent understanding
- Informed consent return rates
- Informed consent confidentiality issues

– Other language than English and French

When eligibility was unclear based on title and abstract, available full-texts were screened. The interrater reliability was moderate (Cohen's Kappa κ = 0.47) for the initial screening and substantial (Cohen's Kappa κ = 0.71) for the update search screening [21]. Disagreements between reviewers were mostly systematic and were all resolved in several rounds of discussion. One reviewer (ADP) performed the full-text assessment and a second reviewer (DOB) verified a random sample of 10 %. Included papers' full-text was screened systematically looking for minor parents using pre-defined search terms (Box 3).

Box 3: Screening strategy

Full-text screening 1
In case of missing key information after the title and abstract screening:

– Screen/Read pre-defined text sections (abstract, consent section, method section, and conclusion) and check if the *key elements* are addressed.
– Search for information about the *key elements* using the following pre-defined search terms:
  - "consent" OR "assent" OR "permi*"
  - "trial" OR "research"
  - "child*" OR "ped*" OR "paed*" OR "minor" OR "infant" OR "adolescent" OR "teen" OR "matur*" OR "parent" OR "mother" OR "father" OR "guardian" OR "repr*"
  - "inter*" OR "global" OR "countr" OR "develop*" OR "income" OR "resource"

Full-text screening 2
For all included papers after the title, abstract and full-text screening 1:

– Screen/Read pre-defined text sections (abstract, consent section, method section, and conclusions) and check if the topic of *minor parents of paediatric clinical trial participants* is addressed.
– Search for information about *minor parents of paediatric clinical trial participants* using the following pre-defined search terms:
  - "prox*" OR "surr*"
  - "consent" OR "assent"
  - "child" OR "adol*" OR "minor" OR "teen" OR "age"
  - "major" OR "eman*" OR "marr*"
  - "parent" OR "mother" OR "father"
  - "capa*" OR "compe*"

3.3.2 Search strategy

We conducted a systematic literature review and searched PubMed/MEDLINE, Embase, CINAHL, and Google Scholar to collect information on IC practices for children with minor parents included in CTs conducted in SSA. We used search terms related to the elements of IC, decision-making, CTs, minors, and SSA (Box 4). Reference lists of included articles were also screened. We performed the initial search in July 2017 (Appendix 6.10, Table S7) and updated it in March 2019 based on a reviewed search strategy by a medical librarian. The changes applied to the search strategy included: improving the combination structure of registered and

free-text terms, removing language filters, removing animal studies, instead of limiting to humans, removing redundancies (term combinations were removed as single terms already covered them), complementing child MeSH and free text terms, as well as adding the terms "research", "placebo", and all sub-Saharan African countries. Information on search strategies for all other databases can be found in the Supporting information (Appendix 6.10, Table S7). No protocol was published for this review.

Box 4: Search strategy (updated search)

Key elements
Informed consent **AND** minors **AND** decision-making **AND** clinical trials **AND** sub-Saharan Africa

PubMed
("Informed Consent"[Mesh] OR "Parental Notification"[Mesh] OR "Presumed Consent"[Mesh] OR "patient information"[tiab] OR consent[tiab] OR consented[tiab] OR consenting[tiab] OR assent*[tiab] OR parental permission*[tiab])
AND
("Minors"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh] OR "Child, Orphaned"[Mesh] OR "Pediatrics"[Mesh] OR "Pregnancy in Adolescence"[Mesh] OR "Maternal Age"[Mesh] OR "Vulnerable Populations"[Mesh] OR "Child Health Services"[mh] OR "Hospitals, Pediatric"[mh] OR "Intensive Care Units, Pediatric"[Mesh] OR minor*[tiab] OR pediatr*[tiab] OR paediatr*[tiab] OR child[tiab] OR children[tiab] OR childhood[tiab] OR infant*[tiab] OR newborn*[tiab] OR new born*[tiab] OR baby[tiab] OR babies[tiab] OR neonat*[tiab] OR perinat*[tiab] OR postnat*[tiab] OR kid[tiab] OR kids[tiab] OR boy*[tiab] OR girl*[tiab] OR preschool*[tiab] OR kindergar*[tiab] OR prepuberty*[tiab] OR prepubescen*[tiab] OR juvenil*[tiab] OR youth*[tiab] OR puber*[tiab] OR pubescen*[tiab] OR schoolchild*[tiab] OR highschool*[tiab] OR underaged*[tiab] OR underage[tiab] OR teen*[tiab] OR adolescen*[tiab])
AND
("Parents"[Mesh] OR "Legal Guardians"[Mesh] OR "Caregivers"[Mesh] OR "Decision Making"[Mesh] OR "Judicial Role"[Mesh] OR "Mental Competency"[Mesh] OR "Comprehension"[Mesh] OR "Liability, Legal"[Mesh] OR "Personal Autonomy"[Mesh] OR "Child Welfare"[Mesh] OR "Infant Welfare"[Mesh] OR parent*[tiab] OR proxy[tiab] OR representative*[tiab] OR guardian*[tiab] OR caregiver*[tiab] OR care giver*[tiab] OR surrogate*[tiab] OR decision making*[tiab] OR capacity[tiab] OR capab*[tiab] OR competen*[tiab] OR legal-competen*[tiab] OR legally-competen*[tiab] OR matur*[tiab] OR emancipat*[tiab] OR waiv*[tiab] OR exempt*[tiab] OR autonomy[tiab])
AND
("Biomedical Research"[Mesh] OR "Clinical Trials as Topic"[Mesh] OR "Research Subjects"[Mesh] OR trial[tiab] OR trials[tiab] OR random*[tiab] OR RCT[tiab] OR placebo[tiab] OR research*[tiab])
AND
("Developing Countries"[Mesh] OR "Poverty"[Mesh] OR "Neglected Diseases"[Mesh] OR "Culture"[Mesh] OR "Culturally Appropriate Technology"[Mesh] OR "Global Health"[Mesh] OR "Health Resources"[Mesh] OR "Global Burden of Disease"[Mesh] OR low income*[tiab] OR low-resource*[tiab] OR resource*[tiab] OR resource-limited[tiab] OR resource-poor*[tiab] OR resource-restricted[tiab] OR developing countr*[tiab] OR global*[tiab] OR international*[tiab] OR developing world*[tiab] OR less-developed[tiab] OR less-advanced[tiab] OR poverty-related*[tiab] OR LMIC*[tiab] OR low-and-middle-income[tiab] OR angola[tiab] OR angolan[tiab] OR benin[tiab] OR botswana[tiab] OR "burkina faso"[tiab] OR "upper volta"[tiab] OR burundi[tiab] OR "côte d'ivoire"[tiab] OR "cote d'ivoire"[tiab] OR "ivory coast"[tiab] OR cameroon[tiab] OR camerun[tiab] OR kamerun[tiab] OR "central african republic"[tiab] OR chad[tiab] OR congo[tiab] OR zaire[tiab] OR djibouti[tiab] OR "equatorial guinea"[tiab] OR eritrea[tiab] OR ethiopia[tiab] OR gabon[tiab] OR gambia[tiab] OR guinea[tiab] OR "guinea bissau"[tiab] OR kenya[tiab] OR lesotho[tiab] OR liberia[tiab] OR malawi[tiab] OR mali[tiab] OR mauritania[tiab] OR mozambique[tiab] OR namibia[tiab] OR niger[tiab] OR nigeria[tiab] OR nigerian[tiab] OR rwanda[tiab] OR senegal[tiab] OR "sierra leone"[tiab] OR somalia[tiab] OR south africa[tiab] OR "south sudan"[tiab] OR sudan[tiab] OR swaziland[tiab] OR tanzania[tiab] OR togo[tiab] OR uganda[tiab] OR zambia[tiab] OR sambia[tiab] OR zimbabwe[tiab] OR rhodesia[tiab] OR "Africa South of the Sahara"[mesh]) NOT (animals[mh] NOT humans[mh])

We requested inaccessible articles from different libraries but did not contact authors. Articles and conference abstracts potentially relating to our topic, but for which a determination of eligibility was impossible without full-text access, were listed in the Supporting information (Appendix 6.11, Table S8). Books were rarely accessible and, therefore, completely excluded

from the analysis. When available information on a book (accessible or inaccessible) suggested that it might relate to our search, the book was also listed in the Supporting information (Appendix 6.11, Table S8). We did not limit our review to a particular study type and searched for any publication containing information about IC by minor parents in paediatric CTs conducted in SSA.

3.3.3 Data extraction and analysis

For the included articles, we extracted characteristic information on study type and procedures, country, health conditions, and the medical interventions addressed. We performed a descriptive and qualitative framework analysis using MAXQDA (VERBI GmbH) and MS Excel [22].

3.3.4 Critical appraisal of studies

Due to the information and study types identified in this review, no conventional assessment of bias risk or quality appraisal was applicable. We addressed the quality of the information descriptively in the results by reviewing the source and comprehensiveness of the implemented and recommended IC approaches, and did not exclude articles based on type or quality.

3.4 Results

We initially identified 3346 articles from the literature search (Figure 3). After removing duplicates (n=414), we screened the titles and abstracts of 2932 articles, and when eligibility remained unclear, we screened the full-text. 2501 articles were excluded, and the full-text of 431 was assessed, resulting in 9 articles included in the analysis. Our search update found 1450 additional articles from which seven were eligible, amounting to a total of 16 articles. The reasons for exclusion were: out of scope, emancipated/mature minors consenting for themselves, not their children, duplicates, languages other than English and French, master theses, PowerPoint presentations, books, and non-accessible full-texts of conference abstracts and papers.

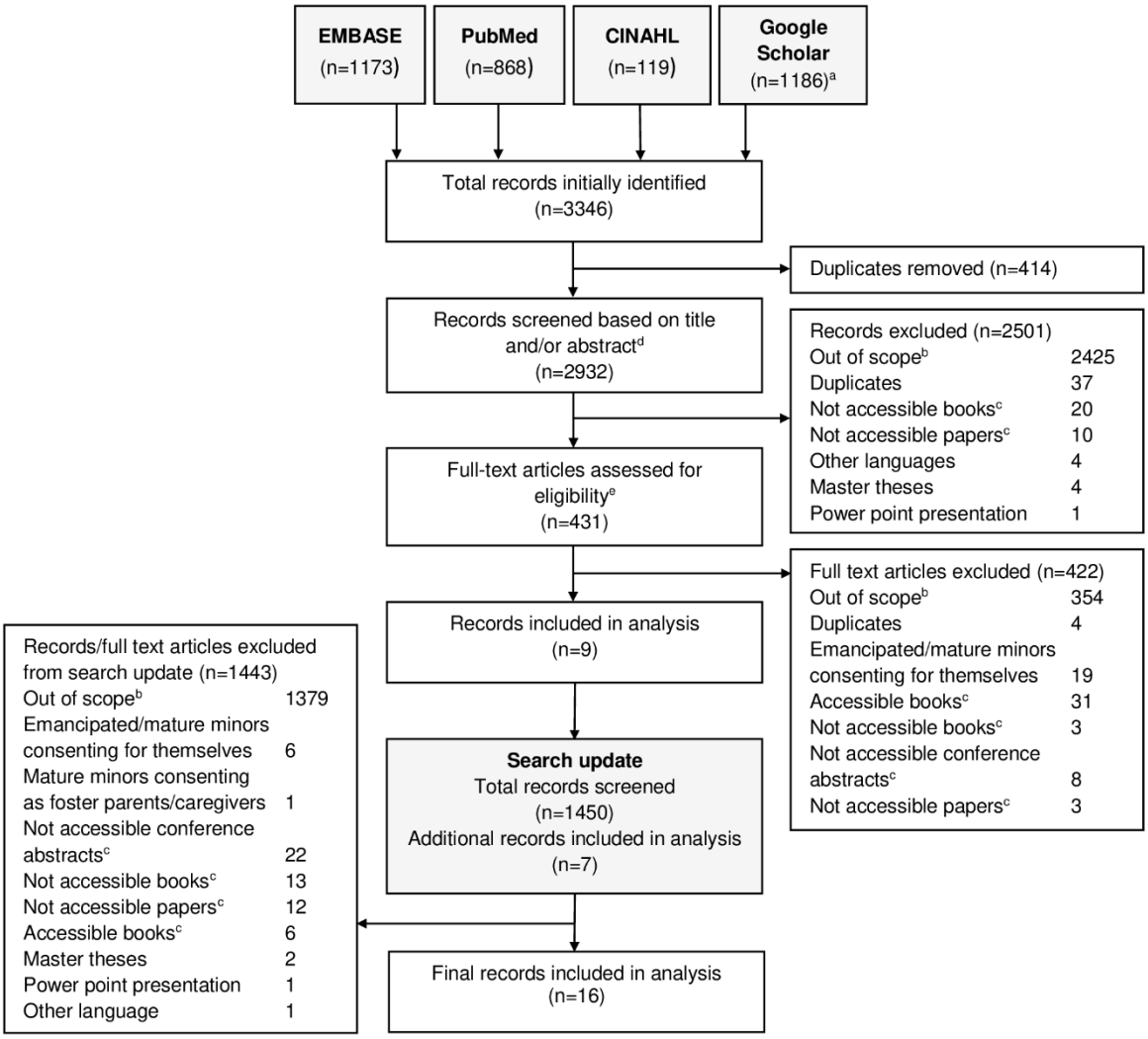

Figure 3: Study-selection flow diagram

[a]The total number comes from three combined Google Scholar searches. [b]Out of scope: not addressing informed consent, not addressing SSA, not addressing children < 5, not addressing clinical trials, not addressing minor parents, not clear if addressing minor parents. [c]A list of these books/papers/conference abstracts can be found in the Supporting information (Appendix 6.11, Table S8). [d]If information about the key elements of the search lacked in the abstract or title, articles' full text was also screened using keywords (Box 3). [e]Full-text assessment was done based on a secondary screening using keywords relating specifically to minor parents (Box 3).

The 16 identified articles included various study types (Table 6) categorised into: case studies (n=4) [23-26], one of which included a review [25], reviews of national legislations and ethical discussions (n=4) [27-30], reviews of IC challenges (n=3) [31-33], meeting/workshop reports (n=3) [34-36], and mixed-methods research (n=2) [37, 38]. Nine studies addressed six particular SSA countries (Senegal, Côte d'Ivoire, Kenya, Botswana, South Africa, and Uganda), while the others related to SSA, low- and middle-income countries, or global CTs in general. Infectious diseases were the most prevalent health conditions, and vaccines were the most frequently discussed medical intervention. Five articles were secondary publications of CT experiences [23-26, 37] and described the IC approach for children with minor parents applied in specific CTs [39-43]. Five further articles discussed the national legislation concerning IC

requirements, including in the case of minor parents [27-30, 38]. The remaining articles mentioned IC by minor parents among several ethical challenges faced in clinical research conducted in resource-limited countries [31-36].

Table 6: Study Characteristics

#	Study	Study type	Country	Health condition	Medical intervention	Content
1	Diallo et al. (2003) [23]	Case study	Senegal	Alternative nutrition/Malnutrition	Nutritional supplement	Practical informed consent experience in a specific CT [42]
2	N'Goran et al. (2019) [24]	Case study	Ivory Coast	Schistosomiasis	Drug	Practical informed consent experience in a specific CT [39]
3	Ott et al. (2019) [25]	Case study and review of national legislation, Ethical discussion and consensus by an international panel	Global (CT example in Latin America, but including African view)	Unspecified (CT example of Clinical Otitis Media and Pneumonia)	Unspecified (CT example about a vaccine)	Practical informed consent experience in a specific CT [43] and IC recommendations
4	Preziosi et al. (1997) [26]	Case study	Senegal	Pertussis	Vaccine	Practical informed consent experience in a specific CT [41]
5	Slack and Strode (2016) [27]	Review of national legislation, Ethical discussion	South Africa	Unspecified (example of HPV vaccine trial with adolescents)	Unspecified (example of HPV vaccine trial with adolescents)	Proxy consent recommendations for CTs
6	Strode et al. (2014) [28]	Review of national legislation, Ethical discussion	South Africa	HIV	Drugs and vaccines	Recruitment challenges with adolescents in CTs
7	Strode and Slack (2011) [29]	Review of national legislation, Ethical discussion	South Africa	Unspecified (Research with more than a minor increase over minimal risk)	Unspecified (Research with more than a minor increase over minimal risk)	Parental informed consent responsibilities in CTs
8	van Wyk (2003) [30]	Review of national legislation, Ethical discussion	South Africa	HIV	Vaccines	Informed consent rights for minors in CTs
9	Colom and Rohloff (2018) [31]	Scoping review	Low- and middle-income countries	Unspecified	Unspecified	Cultural informed consent challenges in CTs
10	Idoko et al. (2016) [32]	Review and experience report	Sub Saharan Africa	Infectious diseases	Vaccines	Informed consent challenges in CTs
11	Lema et al. (2009) [33]	Review and experience report	Sub Saharan Africa	HIV/AIDS, cancer, diabetes, hypertension and congenital anomalies/congenital disabilities	Drugs and vaccines	Informed consent challenges in CTs
12	Mamotte et al. (2010) [34]	Meeting report	Sub-Saharan Africa	HIV/AIDS, tuberculosis, and malaria	Vaccines	Ethical challenges in CTs

13	Ravinetto et al. (2010) [35]	Workshop and meeting report	Sub-Saharan Africa (example of Uganda)	Tropical diseases	Unspecified	Ethical challenges in CTs
14	van Hoog (2013) [36]	Report	Global	Infectious diseases	Vaccines	Recruitment challenges with young people in CTs
15	Angwenyi et al. (2014) [37]	Mixed methods (IDI, FGD, survey, observations, document reviews)	Kenya	Malaria	Vaccine	Practical informed consent experience in a specific CT [40]
16	Kasule (2013) [38]	Mixed methods study (PhD thesis: cross-sectional exploratory study)	Botswana	HIV	Drugs and vaccines	Practical informed consent experiences in CTs

CT, Clinical trial; FGD, Focus Group Discussion; IDI, In-Depth Interview.

One article [31] was a review, which included another of the included articles [25]. We considered it for analysis only when it provided additional information.

We systematically extracted information on minor parents according to six themes: The frequency and age of these parents, the IC approach and the related references, IC challenges, and recommendations affecting the IC approach (Table 7).

Table 7: Framework of themes concerning minor parents

#	Study	Frequency of minor parents	Age of minor parents (years)	IC approach with minor parents	References linked to the IC approach with minor parents	Challenges addressed concerning IC with minor parents	Recommendations with potential influence on the IC approach with minor parents
1	Diallo et al. (2003) [23]	2 (1.4%) of CT participants had a minor mother	15 and 16	IC provided by minor mothers. However, the father or paternal grandparents were included in the information process and contributed to decision-making. Only with the mother's authorisation was the child included. The primary CT report states "oral informed consent was obtained from all mothers of the study infants" [42].	No source referenced.	The child's father and grandparents did not consider the minor mothers as mature enough to decide on the research participation of children. The practicability of this IC approach is, therefore, questionable. The study was conducted without an ethical approval: A local EC/IRB did not exist, and an EC in the Sponsor's country was not consulted as no EC had experience with research in resource-limited countries; the local Ministry of Health approved the protocol.	No recommendation provided.
2	N'Goran et al. (2019) [24]	Unspecified	< 21	IC not provided by minor mothers. Although married minors are considered emancipated under local law, they could not provide consent for their children, as decided by the national ethics committee. However, it remains unclear to what extent the minor parent participated in decision-making (e.g., assent). No CT report published yet.	The reference provided for the Ivory Coast minority law (1970) [44] addresses emancipation of minors through marriage, however, it does not explicitly refer to emancipated minor's right to consent for their child's participation in CTs.	No clear interpretation of the rights afforded by the "emancipated" status for minors versus the legal age of majority was provided in the local law. The EC decided that emancipated minors could not consent.	Involving fieldworkers with knowledge of the local population could facilitate the study recruitment. Revision of the ICH-GCP guidelines to reflect the flexibility and allow for adaptation to local settings.
3	Ott et al. (2019) [25]	211 (3%) of CT participants had a minor parent	< 18	IC was first provided by minor parents alone. During the CT, the IC procedure changed, and an additional consent was required by either the other parent (if an adult), or by the grandparents. Re-consent by the minor parent alone was sought once the age of majority was reached.	No source referenced.	No clear local laws or guidance on the IC process in the case of minor parents existed. The study was reviewed and approved by national public health authorities and a local EC, but after a routine review, the EC changed its requirements for the IC approach.	The EC took a decision based on the local cultural norm. The authors conducted a review of relevant literature and provided detailed recommendations: Involve local institutions, ethics committees, and community stakeholders proactively in the definition of the IC process, respect the minor parents and involve them in decision-making, include another decision-

				The primary CT report (conducted in Latin America) addresses minor parents [43].			making party depending on cultural context and the minor's capacity, implement a careful, adapted consent process, mitigate additional vulnerabilities of children of minor parents, and community engagement for a better understanding of the local context.
4	Preziosi et al. (1997) [26]	85 (4.1%) of CT participants had a minor mother	< 18	IC provided by minor mothers. The IC is explicitly considered valid. The primary CT report states "…and those whose parents agreed were vaccinated" [41].	No source referenced.	No challenges mentioned. As local EC/IRB did not exist, the protocol was reviewed and approved only abroad by an EC affiliated with the collaborative study and the Human Subjects IRB of the CDC.	Clinical trials in resource-limited countries should be reviewed by a sponsor's EC (if external) and a local one. Subsequent studies had, therefore, involved locally established "ad hoc" committees.
5	Slack and Strode (2016) [27]	Unspecified	< 18	IC should not be provided by minor mothers. When the mother is under the age of 18, her mother (the child's grandmother) will be the child's guardian. There is no information on whether the marital status of minor mothers makes a difference to this approach and how to handle IC when minor mothers have lost the support of their parents (as mentioned in earlier articles by the same authors, *see Strode & Slack 2011, 2014*).	The sources refer to South African CT regulations (2013) [45] and a position paper about guidelines for the involvement of adolescents in research [46]. Neither source confirms the IC approach explicitly. The South African CT regulations generally state that "any IC given to the research must be in line with public policy" and non-therapeutic research with minors needs additional ministerial consent. The position paper for research with adolescents states that mature or emancipated minors (married or in military service) can consent for themselves. It also states that "other minors authorised to consent may include those who are parents". But it does not explicitly address IC for the CT participation of their children.	There are no specific challenges mentioned.	The authors provide recommendations aimed at researchers who want to implement parental/guardian consent, which is distinguished from caregiver consent. Its implication on IC by minor parents is not addressed.
6	Strode et al. (2014) [28]	Unspecified	< 18	The legal competency of a married or unmarried, underage mother to consent is not evident (Strode and	The source referenced [47] does not explicitly address minor parents consenting to CT participation of	A law reform (Section 71 of the National Health Act) limits proxy consent to parents or legal guardians,	The authors criticise the new restrictive legislation to be reducing adolescents' access to research

				Slack 2011 provide more information). It is vaguely suggested that IC can be provided by minor mothers if they are married. The consent right in the case of unmarried minor mothers who have lost the support of their parents appears uncertain. Apparently, unmarried minor mothers used to consent as caregivers (especially when they had lost the support of their parents). As such caregiver consent is not accepted anymore according to a reform of the National Health Act; children of such mothers might be excluded from future research.	their children. The IC approach seems to be based on a conclusion by the authors that the restriction of the law around adolescent participation in research will affect children of minor mothers who lost the support of their parents and subsequently lose their right to consent as caregivers.	excluding IC by caregivers. The authors highlight that "this principle will also apply to mothers under the age of 18 who have lost parental support..."	participation while promoting an IC approach that is adapted to the research setting.
7	Strode and Slack (2011) [29]	Unspecified	< 18	IC provided by minor mothers if they are married. IC provided by maternal grandmothers if the minor mothers are unmarried and the father of the child has no parental responsibilities and rights.	The South African Children's Act (2005) [48] is clear about the minor mothers' guardian being also the guardian of the minor mother's child when she is unmarried (and in case the father has not guardianship rights). According to a legal review of the South African law [49], minor mothers are recognised as their child's guardians once they are married. This source was inaccessible, and the statement could not be confirmed. Strode and Slack also state that as guardians, married minor mothers can then consent to "all forms of research" on behalf of their child. This is the authors' interpretation, as no source is referenced. The South African Children's Act (2005), does not explicitly state that this IC regulation also relates to research participation.	Local laws (Children's Act and the National Health Act) and ethical guidance are inconsistent concerning children's capacity to consent to research as well as adults' authority to provide proxy consent.	Based on a review of South African legislation, the authors conclude that "a biological mother, as the child's legal guardian, has the authority to consent to all forms of health research on behalf of the child as long as she is 18 years or older, or under the age of 18 and married."

8	van Wyk (2003) [30]	Unspecified	< 21 (at time of study, currently: < 18)	Minor parents above 14 may provide consent for therapeutic research. Minors over 18 may also consent for non-therapeutic research (preventive HIV vaccine trials are considered non-therapeutic research). Proxy consent in non-therapeutic research is, however, limited by requiring consent by a legally authorised representative, assent by the participant and no more than negligible research risk (preventive HIV vaccine trials are considered more than negligible risk).	The South African Child Care Act [50] confirms that: 1) Minors over 14 may consent for themselves and their children for "any medical treatment". The authors interpret medical treatment as interventions that benefit the individual patients and, therefore, extend the definition to "medical research of therapeutic nature". 2) Minors over 18 may consent for "any type of operation. " The Authors extend this to cover also non-therapeutic research. However, consent for their children is not explicitly mentioned. (The referenced law is outdated and was replaced by the South African Children's Act No 38 of 2005 in 2007 [48])	Under South African legislation, there is no consistent approach regarding the minor persons' capacity to consent to research. There are inconsistent definitions of minors in law: e.g., the age of majority is reached at 21, but children are defined as minors under the age of 18. Restrictions for proxy consent for non-therapeutic research bearing a more than negligible risk result in a prohibition to include infants in such research.	The authors advise that research enrolment in non-therapeutic trials bearing more than negligible risk should be restricted to participants above the age of 21.
9	Colom and Rohloff (2018) [31]	Unspecified	Unspecified	The study addressing minor parents in this review refers to an included paper (*see Ott et al. 2018*).	*See Ott et al. 2018*	*See Ott et al. 2018*	Local ethics committees are expected to play a substantial role in defining adaptive processes for IC. The community should be involved, and the local sociocultural context should be considered.
10	Idoko et al. (2016) [32]	Unspecified	< 18	IC provided by minor mothers. This approach is commonly allowed in most settings in Africa when the minor mothers are considered as mature or emancipated minors. However, some sponsors don't agree with this definition.	There is no source referenced for the specific settings in Africa defining IC by mature or emancipated minors.	The authors state that there is "considerable debate" about the possibility of minor mothers to consent for themselves and their children in vaccine trials. It seems the issue is that some sponsors resist going along with local customs around this aspect. The issues perceived by sponsors concerning *minor mothers being allowed to consent for research participation of their children in most settings in Africa when considered as mature or emancipated minors*,	Sponsors should give more consideration and leeway to the local culture while ensuring that the children's rights are safeguarded. Regulatory authorities should be informed of the IC practice agreed upon by the sponsors and local researchers.

						are due to "legal reasons and may thus result in discrimination of this segment of the population."	
11	Lema et al. (2009) [33]	Unspecified	Unspecified	Not defining if IC by minor parents is acceptable for research. Only acknowledging the possibility of consent by minor mothers. However, researchers faced the scenario when consent from mothers (not specified if adult) with legal guardianship was later withdrawn by fathers, challenging the mother's authority and the research team's decision not to consult fathers. Also, elders in the family may generally "have to be consulted to give their nod before one can consent."	No source referenced.	Cultural norms (i.e., patri- or matrilineal hierarchies) or a lack of legal clarification (e.g., individual parental rights, marital status, variations in research and medical care) may complicate the IC requirements for women in general and impede them from being able to consent autonomously. The authors highlight the paradox that minor mothers may not be considered able to consent autonomously for their own research participation, while at the same time being considered the legal guardians of their children enabled to consent to medical care.	Researchers should respect local social and cultural norms and values to prevent conflicts with the local communities. The IC process should be evaluated individually for every CT to potentially detect specific issues. This process should be budgeted for.
12	Mamotte et al. (2010) [34]	Unspecified	Unspecified	Not defining if IC by minor parents is acceptable. Only acknowledging that the case of minor parents is possible when obtaining proxy consent.	No source referenced.	Proxy consent in the case of minor parents may pose challenges.	Proxy consent in the case of minor parents requires special consideration.
13	Ravinetto et al. (2010) [35]	Unspecified	Unspecified	IC provided by minor mothers is accepted. The authors base this approach on the Guidelines of the Uganda National Council for Sciences and Technology, evaluating "adulthood" beyond age-dependence.	The Ugandan research guideline [51] does not confirm this approach. It states that emancipated minors (including minor parents) can consent for themselves, but it does not explicitly address IC for the CT participation of their children.	The authors consider the issue of minor parents as "more specific challenges" in relation to IC validity.	The decision whether minor parents are allowed to consent needs to balance social, cultural and legal factors. The definition of "adulthood" should be based on more than just a person's age. The authors recommend involving social scientists and anthropologist in the development of effective, relevant, and ethical research and IC tools.

14	van Hoog (2013) [36]	Unspecified	< 18 (mostly, but global range 14–21)	IC provided by minor mothers for their children is recorded as accepted by most countries as these mothers are considered legally mature minors.	The source referenced [52] for this approach is not clear. It states that minor parents can be considered mature minors and consent for their own CT participation. It is not explicitly addressing CT participation of their children. Also, the approach is based on a personal communication concerning research in the USA.	The authors highlight that parental consent could be a barrier to research participation of young people.	Legal barriers need to be overcome, and youth organisations should be involved. Research advisory boards should also reflect and represent the specific target population. The IC process should be adapted to the needs of the participants or parents.
15	Angwenyi et al. (2014) [37]	Unspecified	16–17	No explicit statement on who gave informed consent in the case of minor parents. The primary CT report states "Written informed consent was obtained from the children's parents or guardians" [40].	No source referenced.	No challenges mentioned.	No recommendation provided.
16	Kasule (2013) [38]	Unspecified	< 21 (at time of study, currently: < 18)	IC might theoretically be provided by minor parents if considered as mature minors. However, due to a lack of clear guidance, the IC was not provided by minor parents. A parent below the age of majority needed to be accompanied by an adult. It remains unclear to what extent the minor parent was enrolled in decision-making (e.g., assent).	The reference provided for mature minors did not address minor parents [53]. The Botswana Children's Act (2009) [54] does not explicitly relate to emancipated/mature minors or IC for CT participation of their children.	Botswana does not have a national law on research with children, or a law on the concept of 'mature' or 'emancipated minors'. Also, various legal acts in Botswana contain different concepts of 'child', 'parent', and 'guardianship' and different laws state different ages for childhood. (the Children's Act now states clearly that whenever there is a conflict between the Children's Act and other legislation/regulation, then the Children's Act has to be considered unless it would harm the child). Due to a lack of clear guidance, IC was sought from representatives of the minor parents.	Clear research guidance for the legal and cultural context of Botswana is needed.

CT, Clinical trial; IC, Informed consent; IRB, Institutional Review Board; EC, Ethics Committee; CDC, Centers for Disease Control and Prevention; ICH, International Council of Harmonization for Technical Requirements for Pharmaceuticals for Human Use; GCP, Good Clinical Practice.

Three of the articles relating to specific CTs mentioned explicitly the number of children with minor parents ranging from 1.4 to 4.1% [23, 25, 26]. The legal age of majority was 18 in most countries, except for Côte d'Ivoire where it was 21 (Botswana and South Africa had recently changed from 21 to 18) [45, 55]. One article highlighted that the legal age of majority might range from 14 to 21 globally [36].

In five articles, minor parents were allowed to consent for research participation of their children [23, 26, 32, 35, 36]. In four articles, consent by minor parents was denied [24, 25, 27, 38]. One of these articles reported that researchers first allowed minor parents to consent for the CT, but later reconsidered their procedure, as the ethics committee changed its policy during the course of the CT [25]. Three other articles proposed conditional approaches to consent by minor parents, e.g., depending on the research risk or the marital status of the mothers [28-30], and two more articles simply acknowledged that the case of minor parents is possible and may pose challenges [33, 34]. One article involved a CT including children of minor parents, however, it did not report any details on the IC approach [37].

A majority (n=11) of articles addressed challenges in designing an appropriate IC approach for CTs involving children with minor parents [23-25, 29, 30, 32-36, 38]. Most of these articles highlighted a lack of or inconsistency in local laws and guidance on the rights of minors in relation to clinical research [24, 25, 29, 30, 32, 33, 38]. A further challenge addressed in two older articles was a lack of local ethical review, as no local ethics committee existed at that time [23, 26]. Hence, one study was only reviewed by a foreign ethics committee and IRB [26], while the other was additionally submitted to the local ministry of health [23]. In the latter study, researchers experienced challenges when asking minor mothers to provide formal consent, as families viewed these mothers as immature; this resulted in involving the grandparents or fathers in the decision-making [23]. Two further articles addressed another challenge posed by a South African law reform restricting consent for children to adult parents and legal guardians, excluding other caregivers [27, 28]. This reform resulted in a specific barrier to recruiting children whose parents were minors and had lost the support of their parents [28].

Several articles provided specific references to IC approaches proposed for children with minor parents, such as four national laws on children's rights [44, 48, 50, 54], one national research regulation [45], one national research guideline [51], and four position papers on children's rights in research [46, 47, 52, 53]. One source referred to a legal review inaccessible for our study [49]. Based on these references, none of the applied or proposed IC approaches reported in the initial articles could be confirmed as mandatory or an established standard of practice. Some references mentioned conditions for adolescents' autonomous consent for their own research participation without explicitly invoking their children [44, 46, 51, 52]. The

only reference directly referring to consent approaches for children of minor parents was the South African Children's Act (and its predecessor, the South African Child Care Act) [48, 50]. However, none of the national laws on children's rights (including the South African ones) addressed clinical research [44, 48, 50, 54].

Overall, only two articles provided comprehensive recommendations on IC for CT participation of children with minor parents [25, 29], as presented in detail in Table 3. One of these articles based the IC approach on a review and discussion of national legislation of children's rights [29]. The other one addressed ethical considerations for the development of an IC approach for children of minor parents based on a review of relevant literature and guidelines, including consensus by an international expert panel [25].

Other articles offered general recommendations concerning IC implementation in SSA [24, 26-28, 31-33, 35, 36, 38]. These involved a consideration for the local context and norms [24, 28, 32, 33, 35], the capacity of local ethics committees and regulatory authorities [31, 32], the availability of context-adapted research guidelines and laws [27, 38], and the representation of target populations in research advisory boards [36].

Finally, we provide an overview of additional challenges for IC in research in SSA (Table 8) mentioned across the 16 articles. These are general considerations, which may benefit the development of an appropriate IC approach for CTs involving children with minor parents in resource-limited settings (RLS).

Table 8: Additional considerations for informed consent in sub-Saharan African research

Theme	Issue
Additional vulnerabilities of children with minor parents	– Increased poverty (including less access to health care, less educated parents) – Interpersonal complications through possible child marriage – Greater power differential between the minor parent and the researcher – Less decision-making experience – Impact of stressful conditions (child suffering from a chronic disease) on decision-making capacity
Research risk	– Consent requirements may vary according to the research risk – Research with minimal risk/a minor increase over minimal risk may allow for consent from caregivers – Increased risk research requires consent by one or both parents or legal guardians
Legal aspects	– Many resource-limited countries experience a cultural transition – Variable laws across and within countries (e.g., Common Law and Customary Law) – The population may lack legal records, such as birth certificates and identification documents
IRB/EC Approval	– ECs need to know relevant international and national regulations – The review by the ECs varies from country to country – Local laws and guidelines have to be considered – When there is no law or guidance, relying on the decision by the ECs according to their ethical norms – Studies sponsored from abroad should undergo dual review by local ECs and ECs abroad
Community stakeholder	– Community engagement and pre-trial design efforts may be needed to set-up research activities – Initial consent from local community stakeholders, leaders, or other key decision-makers may be needed

Decision-making culture	– Communal, family and/or individual consent may be the norm – Consultation with spouses or close family members may be needed – Variable norms across and within countries (e.g., rural and urban areas)
Gender dynamics	– Mothers and fathers may have different decision-making authority – Determinations of decision-making authority may depend on the social structure (i.e., patri- or matrilineal) – Mothers may have to consult their husbands, parents, or other family members (e.g., maternal uncles) – Silent refusals by delaying research procedures are possible – Biological fathers may not automatically also be the legal guardians of their children – The marital status for both men and women may be criteria for the assignment of parental authority
Assent	– The ability to assent depends on a child's maturity and is recognised at different ages in various countries – This concept of shared decision-making may not be consistent with local norms
Autonomous consent by adolescents	– The balance of adolescents' privacy needs and the demand for parental consent poses difficulties – Parental consent may represent an obstacle to adolescent research participation (e.g., in sexual health research due to stigmatisation) – Minors may be allowed to consent for themselves when they are considered mature or emancipated
Caregivers vs legal guardians	– Unclear if consent by a caregiver is acceptable in some countries and under what circumstances – The effort required to distinguish between parents, legal guardians, and caregivers is unclear – Due to a lack of legal records, special precautions may be required, such as village chiefs confirming the identity of people
Orphans	– Orphans are increasingly recognised as a special research population in resource-limited countries in terms of HIV risk and transmission – There is an ambiguity in defining the right decision-maker in the case of orphans and their children (e.g., consent by a High Court) – Ambiguity may lead to the exclusion of orphans and their children from research for convenience reasons

IRB, Institutional Review Board; EC, Ethics Committee.

3.5 Discussion

This systematic literature review presents evidence on CT recruitment and IC practice for children with minor parents in SSA. Overall, our results show that researchers experienced the need to find a solution concerning IC when enrolling children with minor parents and were challenged by the lack of a specific regulation or guidance.

A similar number of articles accepted or denied minor parents providing independent IC for their children and both approaches involved specific uncertainties. Becoming an emancipated or "mature minor" was the key argument promoting independent consent by minor parents [32, 35, 36]. When considering the referenced literature, however, we found this approach to lack legislative clarity and generalisability [44, 46, 51, 52]. First, the emancipation or "mature minor" status did not explicitly relate to clinical trials with children of minors. Instead, it related either to autonomous consent by adolescents for their own research participation or to medical care rather than research. Further, the conditions to reach emancipated or "mature minor" status, through marriage, parenthood, etc., vary across countries, as do the rights ensuing

from the respective status. In N'Goran et al., minor parents could be considered emancipated when married; however, they could not provide consent for their children's research participation [24]. Lema et al. mention that minor parents may have the authority to consent for their children's medical care while not being considered mature enough to consent to their own research participation autonomously [33]. A recent position paper by the American Academy of Pediatrics confirms this ambiguity: All (US) states accept medical decision-making by minor parents for their children, without necessarily acknowledging minor parents as emancipated or mature to authorise their own medical care [12]. Another perspective is yet added by the Guidelines for Conduct of Clinical Trials in Kenya, which consider minor parents directly as "emancipated minors" able to consent for themselves and being explicitly allowed to consent to CT participation of their children [13]. These examples indicate that the legal status alone does not always equate to an adolescent's capacity for decision-making and emphasise the need for clear conditions establishing minor parents' competence to consent for themselves and their children.

In studies where minor parents were not considered emancipated or competent to consent independently for their children, consent was provided by an adult proxy [24, 25, 38], which included the other parent (if an adult), grandparents, or legally authorised representatives or guardians. This approach raises the problem of identifying appropriate decision-makers, a known issue for paediatric research in the SSA context [31]. It involves the additional consideration of gender dynamics, hierarchical family structures (e.g., matrilineal, or patrilineal), or shared versus individual decision-making within the family or community [31, 33, 35, 36, 38]. Also, formal identification of individuals accompanying children may pose problems, as people in RLS may lack birth certificates or identity documents [24, 27]. In one study, the village chief was therefore asked to confirm identities [24]. Ignoring local norms may affect the IC validity and, hence, the protection of CT participants and could result in a recruitment failure or subsequent consent withdrawal [33]. Therefore, community involvement in the development and approval of the IC approach before CT implementation is essential to address specific scenarios upfront and find practical and acceptable solutions.

CT participation risks may further influence the IC approach. Risks play a role in deciding whether one or both parents have to provide consent and at what age a person is capable of consenting. Earlier interpretations of South African laws restricted non-therapeutic trials bearing more than a negligible risk to participants above the age of 21 [30]. The research area may also have an influence, and in certain fields, such as HIV transmission prevention, additional consent by grandparents may pose a barrier to research participation of minor parents and their children, due to privacy reasons and fear of stigmatisation [36]. Hence, individual consent

by minor parents alone might be encouraged to improve access to such research. Independent consent by minor mothers might also be encouraged in cases when children are typically accompanied by their mothers and health facilities are difficult to access [10, 23]. Requiring these mothers, when competent, to always consult their husbands or families before being able to consent, may be disruptive to the recruitment of these children. At the time when communities are informed about the CT, however, willingness to participate in the CT can also be discussed in advance, particularly in families where such a situation is expected.

In the case of consent by adult proxies, included studies lacked information on the extent of minor parents' involvement in the IC process. Only one article mentioned explicitly how minor parents were consulted in parallel with the consent of an adult. It proposed that minor parents could first provide a co-consent and then re-consent independently when reaching majority during the CT [25]. This approach is supported by acknowledgements across literature in the past decade that minors should be involved in decision-making according to their developmental capacity [56, 57].

We further detected limited transparency for reported IC procedures for children of minor parents in primary CT publications. This is emphasised by the fact that we did not identify any primary CT publication addressing minor parents in our results. Five included articles, which were secondary studies on CT experiences, however, referenced primary CT publications. We reviewed these publications, and in three of them, we could not find any indication of the parents' ages, and the IC statement was limited as well [40-42]. Minor parents' involvement was only evident in the secondary studies' publications [23, 26, 37]. One of the three primary CT publications stated that "oral IC was obtained from all mothers of the study infants", and more information on minor mothers', parents' and husbands' participation in decision-making was reported as significant only in the secondary study [42]. The second primary CT publication stated "those whose parents agreed were vaccinated" without mentioning that some of the consenting parents were minors [41]. The third primary CT publication provided the following statement: "written IC was obtained from the children's parents or guardians" [40]. It is debatable how much more information beyond such blanket statements should researchers report in primary CT publications to effectively describe the IC procedures applied, considering typical word limitations in publishing and the relevance of the topic in relation to other information provided in CT publications.

3.5.1 Strengths and limitations

This review has some limitations. Information about minor parents was scarce and typically included as a tangential thought only. Hence, we additionally developed a full-text screening strategy to increase our screening efficiency (Box 3). This strategy may have led to overlooking some relevant terms and articles limited to these terms. We identified many articles, representing secondary studies based on primary CT publications, which sometimes included minor mothers. Most of these primary CT reports, however, did not figure in our search results independently, probably due to lacking specific links to standardised keywords. As many of those primary CT publications also lacked a reference, we systematically excluded them, except when including the secondary studies, then we also considered the information provided in the primary CT publications, if accessible.

Further, we used Google Scholar to access also grey literature, such as dissertations, organisation reports, government publications, etc. The translated search, however, yielded more articles than Google Scholar was able to display, as it is limited to a maximum of 1000 articles [58]. We decided to include all accessible articles and ran two additional, very limited searches on Google Scholar to maximise the output of relevant publications under the given circumstances. This also explains why the number of articles detected on Google Scholar, as presented in the flow chart is larger than 1000. Also, we did not systematically search the supplementary files of articles, which may have contained information on minor parents.

Moreover, the review clarifies that information about minor parents is typically published in secondary studies and in qualitative reports on CT experiences, and not in primary CT publications. This suggested that IC information required in CT publications might be too brief to allow an adequate picture of ethical issues faced during the CT conduct and IC issues may be preferably addressed elsewhere (e.g., protocol, ethics committee review, supplementary files, or secondary article on CT challenges). Hence, future research could focus on identifying more details from screening CT protocols involving infants in SSA published in CT registries, as these may better reflect ethical considerations. However, technicalities on the identification of decision-makers may not be addressed in protocols either and may only become evident based on CT management manuals, standard operating procedures, or IC trackers, which are inaccessible to the public, if not specifically self-reported or requested.

Despite available information on the subject being rare and the related challenges to detect such information, we consider this review valuable in supporting future CT conduct. With the help of an elaborate search strategy and the unlimited consideration of various study types,

we present a first overview of IC approaches applied for CT involving children with minor parents in SSA. We thereby raise evidence on the challenges faced in these situations and point to evidence-based solutions.

3.6 Conclusions

This review highlights that there is no one-size-fits-all approach in handling IC in CTs with children of minor parents in SSA. The status of guidance is variable across countries and, frequently, clear conditions establishing minor parents' competence to consent for themselves and their children are missing. Nevertheless, challenges can be mitigated through increasing awareness about the IC approach and appropriate planning before CT implementation. Thereby, the following should be considered: 1) Is a local law available regarding emancipation, or the "mature minor" status? 2) Does the law define whether and under what conditions minors are considered competent to consent on behalf of their children in a CT? Local laws often lack in the context of research, but when regulations on medical care exist, their provisions could also apply to research (see example by Strode and Slack (2011)), 3) Is there an existing official approach (e.g., in a national CT guideline or regulation, institutional guidance)? Did important stakeholders, including the ethics committee and the community approve the approach? Are the ministry of health, regulatory authorities, and local leaders aware of it? 4) Is the approach applicable under the individual circumstances of the CT, considering the local social and cultural context and study related risks? 5) When developing a new approach, have specific ethical considerations and practical challenges been addressed (see example provided by Ott et.al 2018 and Table 8 of this article)? 6) Was the approach described or referred to in the study protocol and were possible practical challenges mitigated? 7) Was the possibility of minor parents addressed in the CT publication? We argue that special IC situations should be described in publications and, if this is not possible due to restrictions of word count, in an appendix to the publication.

We further conclude that international CT guidelines, such as the ICH Clinical Investigation of Medicinal Products in the Pediatric Population E11 (R1), should be amended to include a general statement on the variability of IC for children of minor parents, e.g., "National guidance on the IC for children must be adhered to; where they are missing or local conventions deviate from such guidance, the process must be described in the study protocol and be mentioned in scientific publications".

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4 Manuscript III: Transparent reporting of recruitment and informed consent approaches in clinical trials recruiting children with minor parents in sub-Saharan Africa: A systematic review

Angela De Pretto-Lazarova[1,2]*, Domnita Oana Brancati-Badarau[1,2,3,4], Christian Burri[1,2]

1 Swiss Tropical and Public Health Institute, Basel, Switzerland

2 University of Basel, Basel, Switzerland

3 Centre for Primary Health Care (uniham-bb), Liestal, Switzerland

4 Aston University, Birmingham, United Kingdom

* Corresponding author

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4.1 Abstract

4.1.1 Background

Standardised checklists of items to be addressed in clinical study protocols and publications are promoting transparency in research. However, particular specifications for exceptional cases, such as research in resource-limited countries, on rare diseases or patients unable to personally consent to participation are missing. This study aimed to examine the level of transparency regarding recruitment and informed consent approaches in publications of clinical trials recruiting children with minor parents in sub-Saharan Africa. We thereby focused particularly on the transparency about consenting persons (i.e., proxy decision-makers) and assessed the need to expand reporting guidelines for such exceptional cases.

4.1.2 Methods

We conducted a secondary analysis of a systematic review, searching multiple scientific databases up to March 2019. Clinical trial publications addressing consent and potentially recruiting children with minor parents in sub-Saharan Africa were included. 44 of the in total 4,382 screened articles met our inclusion criteria. A descriptive analysis was performed.

4.1.3 Results

None of the included articles provided full evidence on whether any recruited children had minor parents and how consent was obtained for them. Four proxy decision-maker types were identified (parents; parents or guardians; guardians; or caregivers), with further descriptions provided rarely and mostly in referenced clinical trial registrations or protocols. Also, terminology describing proxy decision-makers was often used inconsistently.

4.1.4 Conclusions

Reporting the minimum maternal age alongside maternal data provided in baseline demographics can increase transparency on the recruitment of children with minor mothers. The CONSORT checklist should require clinical trial publications to state or reference exceptional informed consent procedures applied for special population groups. A standardised definition of proxy decision-maker types in international clinical trial guidelines would facilitate correct and transparent informed consent for children and children with minor parents.

4.1.5 Study registration

CRD42018074220.

4.1.6 Keywords

Clinical trials; Informed consent; Children; Minor parents; Reporting; Sub-Saharan Africa.

4.2 Background

Children under five years in sub-Saharan Africa (SSA) are disproportionately affected by malnutrition and infectious diseases [1, 2], which contributes to a higher percentage of paediatric clinical trials (CTs) performed in SSA compared to Europe or the US [3, 4]. As teenage pregnancy rates in SSA are among the highest worldwide [5], researchers will likely encounter children with minor parents when conducting CTs in this region [6-8].

Previous evidence from CTs in resource-limited countries indicates that researchers face particular challenges when implementing IC for children with minor parents. The appropriate consenting person (i.e., proxy decision-maker[4]) in this case may vary, depend on local legal and cultural conditions, and *ad hoc* solutions tailored to local customs might be implemented [7, 9]. However, despite the need for careful ethical considerations for this research group [10], evidence on practices is scarce and described typically in secondary studies, which suggests low transparency in primary CT publications [11].

Ethical guidance in research requires not only that consent is provided, but that it is documented and reported transparently [12], which promotes public confidence in research [13]. As insufficient transparency was found to be a significant source of waste in the conduct of research [14], CT registration and publication of CT protocols, results, and participant-level datasets have been widely promoted to increase the usefulness and value of CT documentation [15]. For a more consistent and complete availability of CT information, standardised checklists of critical items to be addressed in CT protocols and publications were implemented [16, 17]. The Consolidated Standards of Reporting Trials (CONSORT) statement guides the CT publications' content. It also includes requirements for details on CT registration and access to study protocols. The Standard Protocol Items: Recommendations for Interventional-Trials (SPIRIT) statement guides protocol contents. The endorsement of reporting guidelines contributed to an improved reporting quality of CTs over time [18].

[4] Please refer to Footnotes 4.8.8

Paediatric CTs require special considerations and researchers have argued for a specific checklist with additional reporting items for children. An informal CONSORT adaptation for children was published in 2010 [19]. Different, evidence-based extensions of the CONSORT and the SPIRIT checklists for children are currently being developed [20]. However, in the published development steps, neither of these checklists addresses unique circumstances encountered in resource-limited countries, such as children with minor parents.

Based on a systematic literature review, we gained evidence on how IC is provided for children with minor parents in SSA. In a primary analysis, published elsewhere [11], we included any type of publication providing information on the CT recruitment and consent process for such children. Thereby, no CT publication providing such evidence was found. We therefore conducted a secondary analysis of the identified CT publications, aiming to determine the level of transparency relating to CT participation of children with minor parents and consent by proxy decision-makers. We discuss the need to expand reporting guidelines for such exceptional cases to increase transparency in CT publications.

4.3 Methods

We carried out a systematic literature review registered in the PROSPERO database (CRD42018074220) [21] and followed the PRISMA 2009 statement (Appendix 6.12, Table S9) [22]. All the criteria and terms guiding this review were pre-defined, but no protocol was published.

This secondary analysis was based on the same search strategy and screening steps as the primary analysis [11], but we used different eligibility criteria and performed separate full-text assessments.

4.3.1 Search strategy

We searched PubMed/MEDLINE, Embase, CINAHL, and Google Scholar without any time limitation. The search strategy included the elements of IC, decision-making, CTs, minors, and SSA. We performed the first search in July 2017 and updated it in March 2019 based on a revised and improved search strategy [11]. The references of included articles were not systematically searched. However, for publications that explicitly stated that some methodology details were published in other articles, we considered secondary sources for the analysis. We did not list the secondary articles separately in the results, but included them as supplementary data accompanying primary CT publications.

4.3.2 Eligibility criteria

Articles were included if they were publications of CTs involving children in SSA whose parents were potentially minors. Minor parents were broadly defined as adolescents between the age of 12 and the respective age of majority in each country, who are the biological parents of a CT child participant. If information on the parental age was not given, we considered studies in which child participants were < 5 years, because for this age group the probability of minor parents is higher [23]. We referred to CTs as prospective health-related interventions in persons [24]. Health-related interventions included drug, vaccine, diagnostic, medical device, surgical, emergency research, and dietary supplements trials. CTs had to have taken place in at least one sub-Saharan African country. We only included publications in English or French.

4.3.3 Data extraction and analysis

The search results were imported into the reference management software Endnote X7. After removing duplicates, we extracted information (Author, Year, Journal/Publisher, Title, Abstract, Keywords, ISBN/ISSN, DOI, and URL) into an MS Excel table for screening. The identified articles were screened in two steps: First, two independent reviewers (ADP and DOB) screened titles and abstracts for potentially eligible articles. Second, if information about an inclusion criterion was missing, one reviewer (ADP) screened additionally full-texts. The reviewers reached a moderate and substantial agreement for the title and abstract screening of the initial and updated search, respectively [25]. Disagreements were mostly systematic, mainly concerning the distinction of study types, and were all resolved through discussion. One researcher (ADP) then assessed the full-texts of potentially included articles for final eligibility and extracted data. The second reviewer (DOB) crosschecked 10% of the full-text articles for eligibility and the extracted information.

Extracted data of resulting full-text articles included CT characteristics and the following elements for analysis: Study location, health condition, medical intervention, population size and type, CT design, ethics committee (EC)/institutional review board (IRB) approval, information sections addressing eligibility criteria, IC approach, and proxy decision-makers. Whenever applicable, we accessed the referenced regulatory and ethical guidance, CT registration details, supplementary files, and referenced protocols. We considered specific sections of the CONSORT statement [17], and its adaptation for children [19] to identify information concerning the recruitment and IC approach for children with minor parents. The considered CONSORT sections included the eligibility criteria, participant flow diagram (exclusions), baseline data, ethical considerations, and access to protocol and registry information. We performed a descriptive analysis using MAXQDA (VERBI GmbH) and MS Excel.

In order to assess transparency on reported proxy decision-makers, we defined three levels of transparency according to the level of detail of their description: A basic level of transparency was assigned when neither the type nor the number of proxy decision-makers was specified. A first level of extended transparency was defined when the type or number of proxy decision-makers was specified. A second level of extended transparency was attributed when also the proxy decision-makers' age or competence was taken into account.

4.4 Results

The literature search initially identified 3,346 articles (Figure 4). After removing duplicates (n=414), 2,932 articles were screened, of which 2,872 articles were excluded. The full-text was assessed for 60 articles, resulting in 33 included publications. A search update identified 1,450 additional articles, from which 11 were eligible. In total, 44 articles were included in the analysis.

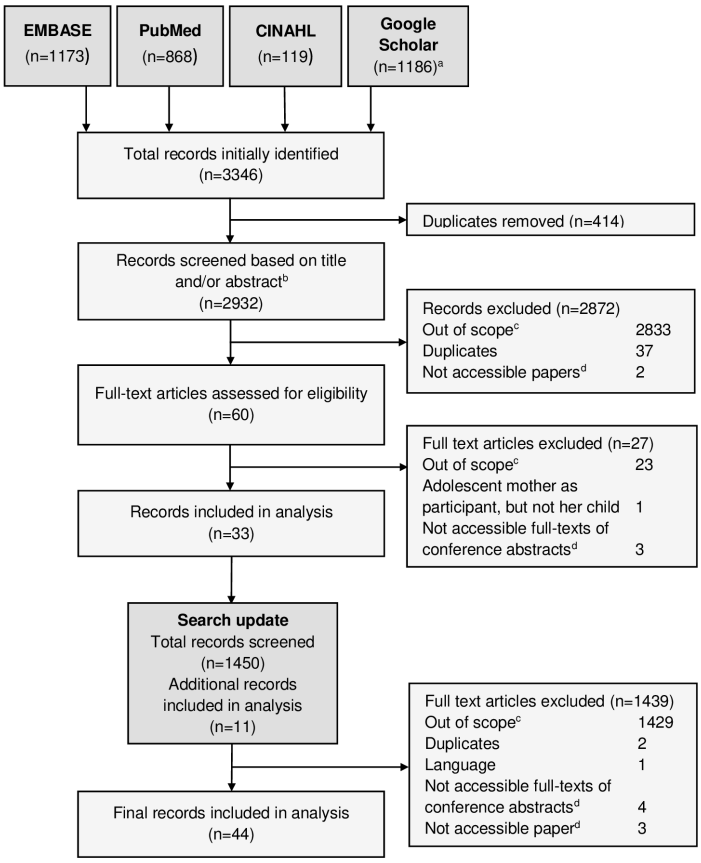

Figure 4: Study-selection flow diagram

[a] Total number results from three combined Google Scholar searches. [b] If the title or abstract lacked information on key elements of the search, the full text of the articles was also screened. [c] Out of scope: not addressing SSA, not addressing children < 5, clearly addressing adult parents, and not being a clinical trial publication. [d] List can be found in the additional material (Appendix 6.13, Table S10).

The included articles' publication dates ranged from 1990 to 2017. More than half of them (n=25/44, 56.8%) were published from 2011 onward (Table 9). Two of the included articles were conference abstracts [26, 27]. The CTs were conducted in 17 different countries in SSA, with Malawi mentioned most frequently, followed by Ghana and South Africa. Malaria followed by undernutrition, and rotavirus gastroenteritis were the most frequently addressed health conditions, while antimalarials, followed by dietary supplements and vaccines were the most reported interventions. Included study participants were mostly infants, only (n=17/44, birth to <2years), or infants and children combined (n=17/44, birth to <12 years). Five studies also enrolled adolescents (12 to <18 years), four also included adults (18 years and over), and one addressed only children (n=1/44, 2 to <12 years). 31 of the 44 publications provided the possibility of stratification according to the participants' age and included a total of 75,063 children under five years.

Table 9: Study Characteristics

#	Author	Country	Health condition	Intervention	Study Population size	Study population age range
1	Achonduh et al. (2012) [26]	Cameroon	Malaria	Dietary supplements (vitamin A, zinc)	100	6–24 months
2	Adegbehingbe et al. (2010) [28]	Nigeria	Clubfoot	Surgical methods (Ponseti method and extensive soft tissue surgery)	105	0–adult
3	Afolabi et al. (2013) [29]	The Gambia	HIV	Vaccine	48	0–9 months
4	Aluka et al. (2013) [30]	Nigeria	Fever	Coldwater sponging, oral paracetamol	88	12–120 months
5	Amadi et al. (2002) [31]	Zambia	Diarrhoea and malnutrition (cryptosporidiosis)	Antiparasitic (nitazoxanide)	96	1–7 years
6	Arimond et al. (2017) [32]	Ghana, Malawi, Burkina Faso	Undernutrition	Dietary supplements (lipid-based)	2622, 1318, 1093, 625	0–18 months
7	Armah et al. (2010) [33]	Ghana, Kenya, Mali	Gastroenteritis (Rotavirus)	Vaccine	5468	4–12 weeks
8	Armah et al. (2013) [34]	Ghana	Gastroenteritis (Rotavirus)	Vaccine	998	0–29 days
9	Christofides et al. (2006) [35]	Ghana	Anaemia (Iron deficiency)	Dietary supplement (iron)	133	6–18 months
10	Corbett et al. (2010) [36]	Malawi	HIV	Antiretrovirals (lamivudine, stavudine, nevirapine)	18	1–13 years
11	Egere et al. (2012) [37]	The Gambia	Pneumonia (Streptococcus pneumoniae)	Vaccine	328	2–30 months
12	Gilliams et al. (2014) [38]	Malawi	Malaria	Antimalarials (chloroquine-azithromycin)	320	20–46 months
13	Goodhew et al. (2014) [39]	Tanzania	Trachoma	Mass drug administration (azithromycin)	264	1–6 years
14	Hassall et al. (2015) [40]	Kenya	Malaria	Umbilical cord red blood cell transfusion	55	0–6 years

15	Hess et al. (2015) [41]	Burkina Faso	Undernutrition (Growth stunting)	Dietary supplements (lipid-based)	3220	9 months
16	Hesseling et al. (2005) [42]	Malawi	Burkitt Lymphoma	Chemotherapy (vincristine, methotrexate, leucovorin, cyclophosphamide, prednisone)	60	3–16 years
17	Hussey et al. (1990) [43]	South Africa	Measles	Dietary supplement (vitamin A)	189	0–13 years
18	Isanaka (2017) [44]	Niger	Gastroenteritis (Rotavirus)	Vaccine	3508	6–14 weeks
19	Kone et al. (2010) [45]	Mali	Malaria (Glucose-6-phosphate dehydrogenase deficiency)	Antimalarials (artemether-lumefantrine, artesunate-mefloquine)	315	>1 year
20	Koram et al. (2005) [46]	Ghana	Malaria	Antimalarials (amodiaquine-artesunate, artemether-lumefantrine, sulfadoxine-pyrimethamine, chloroquine)	168	6–59 months
21	Madhi et al. (2011) [47]	South Africa	Childhood diseases (Hepatitis B, diphtheria, tetanus, pertussis, polio, Haemophilus influaenzae)	Vaccines	715	0–3 days
22	Madhi et al. (2012) [48]	South Africa, Malawi	Gastroenteritis (Rotavirus)	Vaccine	3168	6–16 weeks
23	Maka et al. (2015) [49]	Cameroon	Malaria	Antimalarials (artesunate, quinine)	238	3 months–15 years
24	Mangani et al. (2015) [50]	Malawi	Undernutrition (Growth stunting)	Dietary supplements (lipid-based, corn-soy blend)	840	5.5–6.5 months
25	Meremikwu et al. (2006) [51]	Nigeria	Malaria	Antimalarials (artemether-lumefantrine, artesunate-amodiaquine)	119	6–59 months
26	Meremikwu et al. (2016) [27]	Nigeria	Malaria	Antimalarials (artesunate-amodiaquine, dihydroartemisinin-piperaquine, artemether-lumefantrine.	493	6–59 months
27	Michael et al. (2010) [52]	Nigeria	Malaria	Antimalarials (artemether-lumefantrine, artesunate-amodiaquine)	193	12–132 months
28	Ngasala et al. (2011) [53]	Tanzania	Malaria	Antimalarials (artemether-lumefantrine)	300	3–59 months
29	Nji et al. (2015) [54]	Cameroon	Malaria	Antimalarials (dihydroartemisin-piperaquine, artesunate-amodiaquine vs artemether-lumefantrine)	720	6 months–10 years
30	Nwanyanwu et al. (1996) [55]	Malawi	Malaria	Antimalarials (sulphadoxine-pyrimethamine)	159	0–5 years
31	Phuka et al. (2008) [56]	Malawi	Undernutrition (Growth stunting)	Dietary supplements (fortified spread, micronutrient-fortified maize-soy flour)	182	6–18 months
32	Rahimy et al. (1999) [57]	Benin	Fever (in Sickle Cell Disease)	Antibiotics (outpatient management)	61	0–12 years
33	Robertson et al. (2011) [58]	Uganda	Perinatal asphyxial encephalopathy	Therapeutic hypothermia	36	3 hours
34	Roca et al. (2011) [59]	The Gambia	Pneumococcal disease	Vaccine	5441	0–adult
35	Sazawal et al. (2007) [60]	Zanzibar	Undernutrition (Mortality)	Dietary supplement (zinc)	42546	1–36 months

36	Schellenberg et al. (2001) [61]	Tanzania	Malaria and anaemia	Antimalarials (sulphadoxine-pyrimethamine) alongside routine vaccinations	701	0–1 year
37	Singana et al. (2016) [62]	Republic of Congo	Malaria	Antimalarials (artesunate-amodiaquine, artemether-lumefantrine)	198	<12 years
38	Sissoko et al. (2016) [63]	Guinea	Ebola	Antiviral (favipiravir)	111	>1 year
39	Sow et al. (2012) [64]	Mali	Gastroenteritis (Rotavirus)	Vaccine	1960	48 days (median age)
40	Te Water Naude et al. (2000) [65]	South Africa	Tuberculosis	Chemotherapy (isoniazid, rifampin, pyrazinamide)	206	0–14 years
41	The Zinc Against Plasmodium Study Group (2002) [66]	Ecuador, Ghana, Tanzania, Uganda, Zambia	Malaria	Antimalarial and dietary supplement (chloroquine and zinc)	1087	6–60 months
42	Urban et al. (2008) [67]	South Africa	Nutrition (Infant growth)	Dietary supplements (biologically acidified milk, probiotics)	85	0-1 week
43	Waggie et al. (2011) [68]	South Africa	Polio	Vaccine	800	0–30 days
44	Yohannan et al. (2013) [69]	Tanzania	Trachoma	Mass drug administration (azithromycin, tetracycline)	2261	0–5 years

4.4.1 General reporting characteristics

Table 10 summarises general reporting characteristics relating to the research design, EC/IRB approval, implementation of regulatory or ethical guidance, CT registration, availability of supplementary material, and the section addressing informed consent (IC).

Table 10: General Reporting Characteristics

Characteristics	**n (Total n=44)**	**(%)**
CT design		
Randomised, controlled (including cluster- and community-randomised)	37	(84.1)
Placebo-controlled	12	(32.4)
Treatment-controlled	24	(64.9)
No treatment-controlled	1	(2.7)
Blinded (including double-, single-, and partially-blinded)	21	(56.8)
Open-label	10	(27.0)
Unclear	6	(16.2)
Phase I	1	(2.7)
Phase III	3	(8.1)
Unclear	33	(89.2)
Non-randomised, single-arm	6	(13.6)
NDA	1	(2.3)

EC/ IRB approval		
By multiple national and external ECs/IRBs (local regulatory authorities, local IRBs, national ECs, international ECs, external national ECs, and external IRBs)	24	(54.5)
By multiple local (local regulatory authorities, local IRBs, national ECs)	1	(2.3)
Only by local EC/IRB	13	(29.5)
Only by national EC	1	(2.3)
NDA	5	(11.4)
Regulatory/ethical guidance[a]		
Good Clinical Practice	13	(29.5)
Declaration of Helsinki	9	(20.5)
National/local regulatory requirements	7	(15.9)
Good Laboratory Practice	1	(2.3)
n/a (Conference abstract)	2	(4.5)
NDA	27	(61.4)
Supplementary material[a]		
CT registration[b]	21	(47.7)
CT publications including supplementary files	9	(20.5)
Protocol as supplementary file[c]	6	(13.6)
CT publication sections and files addressing IC[a]		
Abstract	18	(40.9)
Methods	41	(93.2)
Eligibility	27	(65.9)
Ethics	34	(82.9)
Results	15	(34.1)
Discussion	1	(2.3)

CT, Clinical trial; EC, Ethics committee; IRB, Institutional review board; NDA, No data available; IC, Informed consent. [a] Numbers do not add up, since several features may apply and some publications were inconclusive in the description. [b] 60% of publications since CT registration became a requirement by the ICMJE in 2005 [70]. [c] 24% of publications since protocol publication became a requirement by the CONSORT statement in 2010 [17].

4.4.2 Transparency of CT recruitment of children with minor parents

43 of the 44 included publications provided information about CT eligibility. While in most CTs, children were directly recruited, in four CTs, recruitment was first based on the eligibility of pregnant women [32, 34, 67, 68]. One of these four publications [32] referred to a CT mentioning minor mothers in the eligibility criteria. This CT took place in Malawi, recruited mothers and children explicitly as a dyad, and considered minor mothers 15 years and older eligible [71]. Further insight was provided in the study flow diagrams included in the Results section. The Malawian trial excluded "underage" mothers (and their children), but without making it clear if the exclusion was due to mothers not meeting the legal age of majority or being under 15 [71]. Additionally, maternal age was listed in the Results among the baseline data, but only the mean age, including standard deviation, was provided without explicitly stating the minimal

age of included mothers. Two more CT publications mentioned maternal age in the same way [41, 67] and no other CT report provided details about parental age in the Results section.

4.4.3 Transparency on proxy decision-makers for children's CT participation

Proxy decision-makers providing IC for children's CT participation were mentioned 77 times across the CT publications or supplementary materials (i.e., CT registration, protocol, or referenced articles further detailing the methodology) (Table 11). We found the terminology used to describe proxy decision-makers to be variable and identified four main types: "parents" (39.0%); "parents or guardians" (36.4%); "caregivers" (13.0%); and "guardians" (11.7%). Further details were provided in some CT publications or supplementary materials specifying a subtype and number of proxy decision-makers. Subtypes were specified in a third (32.5%), and the number was specified in about half (50.6%) of all cases. In 40.3% of all cases, neither the subtype nor the number was specified.

Table 11: Proxy decision-maker types, subtypes, and numbers mentioned across CT publications and supplementary files

Proxy decision-maker description	**n**	**(%)**
Total	77	(100.0)
Parents	**30**	**(39.0)**
Unspecified parents	23	(29.9)
Unspecified number	15	(19.5)
One[a]	8	(10.3)
Mother	4	(5.2)
Mother involving fathers/partners/husbands involved in the decision-making	1	(1.3)
Mother able to understand study procedures and give consent/of a specific age	2	(2.6)
Parents or guardians	**28**	**(36.4)**
Unspecified parents or guardians	21	(27.3)
Unspecified number	13	(16.9)
One[a]	6	(7.8)
At least one	1	(1.3)
Each	1	(1.3)
Parents or legal guardians/legally acceptable representatives	4	(5.2)
Unspecified number	2	(2.6)
One[a]	1	(1.3)
Each	1	(1.3)
Parents or guardians of legal age/adult/with the ability to give informed consent	3	(3.9)
Unspecified number	2	(2.6)
One[a]	1	(1.3)
	10	**(13.0)**

Caregivers (incl. caretaker, carer)		
Unspecified caregivers	5	(6.5)
Unspecified number	3	(3.9)
One[a]	1	(1.3)
At least one	1	(1.3)
Family	3	(3.9)
Unspecified number	3	(3.9)
Primary caregiver (Mother/Father/Legal guardian)	2	(2.6)
One[a]	2	(2.6)
Guardians	**9**	**(11.7)**
Unspecified guardians	3	(3.9)
One[a]	2	(2.6)
At least one	1	(1.3)
Authorised/identifiable/legal guardian	5	(6.5)
One[a]	3	(3.9)
At least one	2	(2.6)
Guardian capable of providing consent	1	(1.3)
One[a]	1	(1.3)

[a] Single proxy decision-makers were counted whenever the singular was employed to refer to consent by a parent/guardian. When consent was provided by mothers with no other specification, only one decision-maker was counted. Otherwise, terms in their plural form, as well as the designation of "parental" were recorded as "unspecified number", unless other indications regarding multiple consenters were provided.

The terms used to describe proxy decision-makers were sometimes inconsistent within publications (n=20/44, 45.5%), as well as between publications and registrations (n=16/21, 76.2%) or protocols (n=6/6, 100%). Most inconsistencies within CT publications included a reduction from "parents or guardians" to "parental" consent, or from "legal" or "authorised" guardians to "guardians" only (n=12/20, 60%). However, some CT publications (n=8/20, 40%) also applied the terms interchangeably by, e.g., first using "caretaker" then "guardian", or by switching between "parents" and "primary caregivers" or "mothers" (Appendix 6.14, Table S11). Inconsistencies between publications and registrations or protocols mostly included more or less specification of proxy decision-maker types and some included an interchangeable use of terms.

Table 12 shows the transparency levels of reported proxy decision-makers in publications and supplementary files. When considering only the CT publications, without supplementary material, and focusing on the most detailed description of proxy decision-makers within each publication, in half of all CT publications (50.0%) neither the type nor the number of proxy decision-makers was specified. In less than half CT publications (45.5%) transparency on the type of proxy decision-makers was extended, and only one publication provided a second level of extended transparency [32].

Table 12: Transparency levels of reported proxy decision-makers in CT publications and suppl. files

Transparency level	Proxy decision-maker description	All proxy decision-makers in all document types		Most specific proxy decision-makers in CT publications	
		n	(%)	n	(%)
Basic	Informed consent from an undefined representative (e.g., parents, parents or guardians, caregivers, guardians, etc.)	31	(40.3)	22	(50.0)
Extended 1	Representative specified by number (e.g., at least one, each, one) or type (e.g., mothers, family, legal/authorised/identifiable guardian, etc.)	40	(51.9)	20	(45.5)
Extended 2	Representatives defined by age or competence (e.g., adult/of legal age, ability/capability to understand and give consent, a person with power of attorney)	6	(7.8)	1	(2.3)
Total		**77**	**(100.0)**	**43** [a]	**(97.8)**

[a] For one CT, the proxy decision-maker was only mentioned in the CT registration [62].

4.5 Discussion

While some CT publications identified in our analysis indicated that children with minor parents might have been considered, none of the CT publications met a sufficient level of transparency to confirm whether such children were truly enrolled in the CTs and who consented on their behalf. Considering previously reported rates of children with minor parents recruited in individual CTs in resource-limited countries, which ranged from 1.4-4.1% [6-8], 1,051 to 3,078 of the children in our review may have had minor parents unless they were excluded at screening based on parental age.

4.5.1 Transparency on the recruitment of children with minor mothers

Publications of CTs recruiting children and their mothers as dyad may list maternal age among the eligibility criteria and the effective reasons for exclusion [32]. In other CT publications, however, maternal eligibility requirements were uncommon, perhaps because research focused on children independently from their mothers. Several CT publications included maternal data among the baseline data. These data contained maternal age (mean and standard deviation), years of education, or literacy levels [32, 41, 50, 60, 66-69]. The reporting of these aspects might aim at acknowledging some confounding factors pertinent for the study results. Two of the included CT publications also discussed possible relations between maternal data and study cooperation or the generalisability of study results [41, 68], which emphasises the importance of including information on special population groups in CT publications. Hence, standard reporting of maternal age when including small children as CT participants and the additional provision of the maternal age thresholds (i.e., minimum and maximum age) is a

straightforward way for researchers to increase transparency on the inclusion of children with minor mothers who are also the primary caregiver.

4.5.2 Transparency on proxy decision-makers

In half of all CT publications, only a blanket statement was provided in the Methods section that IC was granted by four main proxy decision-maker types: "parents", "parents or guardians", "guardians", or "caregivers". The other half of the CT publications additionally specified subtypes of proxy decision-makers (e.g., mother, legal guardian, and primary caregiver) and their number (at least one, each, and one). In 11% of the CT publications (n=5/44), CT registrations (n=5/21, 23.8%) and corresponding protocols (n=2/6, 33.3%) providing more transparency about the possible involvement of children with underage parents and the requirements for proxy decision-makers were referenced. Therein, consent was required from parents or guardians who were adults (or of legal age) or able (or capable) to understand study procedures and give consent [33, 34, 44, 63, 69]. However, since the corresponding CT publications contained only blanket statements that the consent was given by "parents or guardians", the final procedure remained unclear.

Overall, the information on proxy decision-makers in CT publications was very brief and overlooked any difficulties or exceptions. This is surprising since previous literature shows that, for example, identifying suitable proxy decision-makers in resource-limited countries can be challenging [72]. Moreover, depending on the policy, context or law applied, the meaning of the main types of proxy decision-makers may vary and leave room for interpretation (Appendix 6.14, Table S11). This requires special attention in developing and reporting on the IC process. In the included CT publications, it remains uncertain whether these aspects were considered. It may well be that researchers are unfamiliar with the ethico-legal terminology on consent and consequentially interpret certain terms as synonymous and employ them as such in practice. Confusion may also arise from the possible variability of the terms across countries. This may explain the high frequency of inconsistencies within and between publications and their registrations or protocols, as found in this analysis. We, therefore, believe it is useful to establish standard operational definitions of possible proxy decision-maker types (e.g., guardians, legal guardians, legally acceptable representatives, caregivers) in international CT guidelines to facilitate a correct and coherent use of terminology.

Some of the publications referred to national CT guidelines they followed. However, again we could not find any particular statement on the case of children with minor parents. The general absence of information on children with minor parents in CT publications may suggest, first, that this case did not occur in these CTs, and, second, that researchers are not sensitised to

the possibility of children having minor parents. In contrast, for example, several CT publications included additional details on other exceptional factors related to IC in resource-limited countries, such as high illiteracy rates and providing oral consent with thumbprints, or the need for prior community consent. One publication also discussed the impact of the social and cultural background of the population on consent [57]. Third, authors of CT publications may focus more on reporting *that* IC was granted, regardless of *how* this was achieved.

Previous research showed that a detailed description of the consent process is uncommon in CT publications [73]. Consequently, the need to provide more details was debated [74]. Some critics question the practicality of adding succinct IC process descriptions, implying that it can be assumed that the adequacy of IC was evaluated and established by a competent ethics committee that has approved the CT [75]. While we agree that extensive IC descriptions in CT publications are not practical, given journals' limited word count, it can also not be ignored that consent processes carry not only ethical but also scientific implications. IC procedures must be appropriate and tailored to the risks involved in each trial and may contribute to selection bias [76]. A description of how the IC procedure is handled for specific groups may, therefore, be useful for the overall picture of the CT.

For ethics committees to approve the appropriateness of IC procedures, these must be described in the CT protocol or reference must be made to applicable guidelines. Only publications can confirm what processes were actually applied. Publishing specific IC processes would not only help ensure the consent's validity, but would also provide guidance for future researchers, prevent protocol deviations, and possibly highlight areas that need new guidance. Also, it can incentivise researchers to consider possible practical challenges early on, mitigating recruitment delays and consent withdrawals, and to strengthen reflections on risk-benefit analyses. We, therefore, recommend the general presentation of IC processes in CT publications and argue for the inclusion of evidence on exceptional IC cases. At a minimum, this should be described in an appendix to the publication in case of space limitations.

Ethical considerations, including consent, are currently not part of the CONSORT checklist [17]. Although the explanation and elaboration of CONSORT refers to IC and mentions that obtaining consent should be reported, it defers to journal instructions for specific ethical requirements [77]. The CONSORT adaptations for children, however, deem IC in paediatrics more complicated than for adults and propose consent related considerations to the checklist, such as reporting if assent was provided [19, 20]. This view reinforces our recommendations, as similar to paediatric CTs, consent procedures in CTs conducted in resource-limited countries may require specific considerations meriting additional clarification in publications. In case a new CONSORT extension for paediatric CTs is developed, it should address ethical

requirements and ask for an explicit description of exceptional IC situations for special population groups and of the solutions implemented.

The SPIRIT protocol development checklist already contains a requirement to specify how the IC should be obtained from participants [16]. Our review found that CT protocols that were likely developed after the implementation of SPIRIT provided increased transparency about the proxy decision-maker, emphasising the possible benefit of including consent requirements also in checklists for CT publications.

Furthermore, our study found that only a small number of publications provided information on the CT phase. However, a clear indication of the phase is useful to ascertain IC validity, as it is an indicator of research borne risks. It potentially has an impact on the operationalisation of the IC, including the selection and number of proxy decision-makers. The CONSORT explanation and elaboration paper also recognises that specifying the phase may be relevant in drug trials [77].

4.5.3 Strengths and limitations

To our knowledge, this is the first systematic review specifically analysing the recruitment and consent of children with minor parents in CT publications. The search strategy was designed to identify articles that relate to consent and proxy decision-makers in the abstract. If articles did not include such information in the abstract and were not otherwise linked to our topics of interest, they were not detected in some of the databases. Moreover, we included only CT publications that provide information on consent. Previous studies have shown that a small percentage of CT publications do not report the provision of consent [78, 79]. Additionally, by focusing on children with minor parents in SSA, our review addressed a vulnerable research population in resource-limited countries. Researchers on these trials may manifest an increased cautiousness to individual challenges, which can lead to significant reporting of IC information [78]. Hence, the extent of IC information provided in our selection of CT publications may not be generalizable. However, these limitations also suggest that we identified CT publications that provide above-average information on consent. Therefore, it is likely that, overall, the management of children with minor parents in research might be even less transparent than shown in our analysis, which underlines the importance of increasing standards in reporting.

Also, due to the nature of our search that excluded individual protocol publications, articles including IC information only in the corresponding CT protocol may have been missed. Further, CT publications that referred to other literature for more details on the research methodology, but did not specifically refer to "consent" or "permission" within their text, may have

been missed. Our search strategy may have also overlooked some specific terms. For example, we searched for "adolescent pregnancy" but did not explicitly include the term "pregnant women", which may inadvertently excluded studies in which children of underage parents could be the focus of CTs with pregnant women. Further strengths and limitations were previously published [11].

4.6 Conclusions

Despite the increased probability to encounter minor parents when recruiting children under five years of age in CTs in SSA countries, no CT publication in our analysis allowed us to ascertain whether such children were indeed included and who provided consent on their behalf. Transparency on the recruitment of children with minor parents could be increased when reporting additionally the minimum maternal age alongside maternal data provided in baseline data. Furthermore, CT publications should include or reference exceptional IC procedures applied for special population groups and these ethical considerations should be required by the CONSORT checklist. A standardised terminology on proxy decision-maker types in international CT guidelines would also facilitate correct and transparent consent processes for children in general and, more importantly, for children with minor parents.

4.7 List of abbreviations

SSA: Sub-Saharan Africa; CT: Clinical trial; CONSORT: Consolidated standards of reporting trials; SPIRIT: Standard protocol items: Recommendations for interventional trials; EC: Ethics committee; IRB: Institutional review board; IC: Informed consent; EDCTP: European and developing countries clinical trial partnership.

4.8 Declarations

4.8.1 Ethics approval and consent to participate

Not applicable.

4.8.2 Consent for publication

Not applicable.

4.8.3 Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

4.8.4 Competing interests

The authors declare that they have no competing interests.

4.8.5 Funding

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4.8.6 Authors' contributions

ADP and CB conceived of the study, ADP developed the methods and search strategy, and DOB reviewed the search strategy. DOB and CB participated in the design. ADP and DOB performed the literature search, applied inclusion criteria, and data extraction. ADP wrote the first draft of the manuscript, DOB, and CB contributed to interpretation of the data and drafting of the manuscript. All authors revised it critically for intellectual content and approved the final version of the final manuscript.

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4.8.8 Footnotes

Proxy decision-maker is used throughout the manuscript in its colloquial form as employed by researchers and not in the legal sense. As such, it can refer to parents as (legal) surrogate decision-makers or formal and informal proxies, such as grandparents, other caregivers or court appointed guardians.

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5 Discussion

5.1 Clinical trial quality definition

Despite continuous debate about CT quality in recent years, no evidence-based definition of CT quality was yet available, which still represented a potential source of wasteful as well as undervalued CT activities. In response to the REWARD campaign, an academic quality framework called INcreasing QUality In patient-oriented academic clinical REsearch (INQUIRE) was developed to provide an understanding of different aspects influencing CT quality [1, 2]. However, when developing the framework, the authors did not particularly consider the perspective of RLS. A recent report on the ongoing complete revision of the ICH-GCP guideline has increased focus on the need to redefine the meaning of "high-quality" trials and opened a discussion on how best to incorporate RLS-specific factors in CT guidelines [3]. This thesis aimed to contribute to the definition of CT quality by including the perspective of researchers with experience conducting CTs in such settings.

5.1.1 How was clinical trial quality defined?

We approached the definition of CT quality by performing semi-structured qualitative interviews and analysing them using the framework method. We involved three CT stakeholder types (investigators, sponsors, monitors) experienced in conducting CTs of various models (i.e., IIT, industry, and mixed partnerships) across multiple countries in SSA. To get a holistic picture of what interviewees perceive as CT quality, we asked them first to define it in their own words in an unlimited way and second to try to phrase it in one sentence. We first analysed the one-sentence definition to define an initial framework of elements that build up CT quality. Then, we used the unlimited definition to confirm and elaborate on the CT quality elements.

CT quality definitions resulted in 11 elements. These elements formed a quality concept, which we organised into two components: (i) CT quality-building factors and (ii) CT quality-promoting factors. CT quality-building factors consisted of a) Scientific factors (Relevance and patient-centeredness; Scientific soundness; Adherence to study-specific requirements; Documentation; Data integrity) and b) Moral factors (Participant safety and rights; Adherence to general requirements). CT quality-promoting factors included Context adaptation; Infrastructure; Partnership; Quality system; and Operational excellence (Figure 2, p.32).

5.1.2 How did the resource-limited settings perspective contribute to the clinical trial quality concept?

Searching the interviews for RLS-specific aspects resulted in 12 themes: Health conditions; Accessibility; Education levels; Culture; Regional specificities; Health authority approval; Availability of guidelines; Staff qualification; Facility level; Collaboration; Communication; and Sustainability. The RLS-specific themes were all assigned to the CT quality-promoting factors "Context adaptation", "Infrastructure", and "Partnership".

Many of these RLS-specific themes have been previously reported in the literature; however, they are not from a perspective strictly oriented towards associations with CT quality. For example, existing literature addressed RLS-settings-specific aspects mainly from the perspective of ethics [4, 5], ICH-GCP applicability [6-8], or challenges and lessons learned when implementing specific studies in specific regions in SSA [9-11]. One other study focused explicitly on quality indicators for CTs in RLS [12]; however, it was restricted to CT implementation rather than the entire CT scope. Hence, this study offers the first comprehensive CT quality concept, which includes the perspective from RLS.

5.1.3 How does our clinical trial quality concept relate to the INQUIRE framework?

Our approach to defining CT quality contributed to the understanding of CT quality in multiple ways: First, we used the opportunity to complement the existing INQUIRE framework through methodological triangulation. By applying qualitative interviews, we could collect independent perspectives, while the INQUIRE framework was principally based on a review of existing concepts [2].

Second, the building elements of our CT quality concept were comparable to the INQUIRE framework. Given the complexity of quality, it was remarkable that the results, which emerged inductively from our interview analysis, had many parallels to the INQUIRE framework. Our approach to methodological triangulation supports thus how quality in clinical research was conceptualised in the INQUIRE framework [1]. Thereby, an essential similarity was the idea of a multidimensional CT quality concept. In particular, considering "CT quality-promoting factors" as a separate CT quality dimension resulted in being a shared conceptual complement to the conventional two-dimensional quality standard of the ICH-GCP guideline, which primarily focuses on scientific and ethical requirements [13]. Also, the fact that all RLS-specific themes were categorised as CT quality-promoting factors underlines the need to consider such factors when managing CTs in RLS.

Third, our concept also confirmed variability between the main interests of stakeholder groups, as reported by the authors of the INQUIRE framework. For example, the authors of the INQUIRE framework found that Academic research and Clinical Trial Units focused mainly on the following themes: Absence of bias, and Relevance and transparency, whereas the Pharmaceutical industry and Contract Research Organisations focused mainly on high-quality data [2]. In our concept, investigators mainly associated CT quality with scientific soundness, while sponsors emphasised participant safety and rights and data integrity, and monitors focused primarily on adherence (i.e., to guidelines, regulations, protocol, and SOPs). This variability, especially between sponsors and investigators, may be explained by the fact that sponsors are less involved in implementing the CT. Therefore, they may relate quality more to CT goals, such as safe participants and data integrity, which are also defined as critical CT aspects by current guidance on CT quality management (i.e., ICH-GCP, CTTI perceptions) [13, 14]. In contrast, investigators may have a more ongoing focus on scientific work during the CT implementation process.

Fourth, our findings also brought some additions to the INQUIRE framework: In our CT quality concept, the "CT quality-promoting factors resulted in being more diverse including Context adaptation, Infrastructure, Partnership, Quality system, and Operational excellence. In comparison, the INQUIRE framework includes only two promoters: Infrastructure and Sustainability and Education. While most of the promoters listed in our concept were categorised differently in the INQUIRE framework, some topics were entirely absent. For example, we could not identify the themes under Context adaptation in the INQUIRE framework; however, the authors addressed this gap partially in their limitations (i.e., not considering societal aspects and beliefs). Hence, the following points that emerged from our interviews could complement the INQUIRE framework: 1) Clear communication of infrastructural disadvantages and their potentially significant impact on timelines and, ultimately, the quality of CTs to funders, sponsors, and auditors, 2) Prevention of exploitation of research populations and workforce in resource-limited countries by following specific available ethical frameworks, and 3) Context adaptation, including the consideration of the participants' health conditions, participant accessibility, education levels, cultural, as well as regional aspects.

5.1.4 Can developed settings benefit from a resource-limited settings perspective on clinical trial quality?

Our findings from the RLS perspective emphasised the need for a multidimensional CT quality concept to contribute to comprehensive quality management (CQM). Such a comprehensive perception offers the opportunity to use resources in a more targeted and economical manner.

From the RLS perspective, context adaptation, infrastructure, partnership, operational excellence, and quality system emerged as supplementary quality-promoting factors that influence CT quality in addition to the traditional focus on scientific and ethical aspects. A quality concept that encompasses these factors offers the possibility to systematically consider them in the CT process.

The RLS-specific aspects were broadly categorised as context adaptation, infrastructure, and partnership, and therefore these categories can be considered as key variables when working in different CT environments.

The three CT quality-promoting factors (i.e., context adaptation, communication of infrastructural disadvantages to CT stakeholders, and prevention of exploitation of workforce and study populations) we suggested to complement the INQUIRE framework may also be useful for developed settings, as these are also present in settings in the Global North, although to a lower degree or more difficult to detect.

Further, some themes emerged from the interviews based on RLS that need further research to understand their potential impact on CTs conducted in developed settings. One such theme was the different funding mechanisms in RLS and their role in CT quality. For example, depending on the funding mechanisms, CT quality expectations of the funders could be very variable. In this context, some of our interviewees stated that external governmental funders often just cared for the CTs to deliver results, while international funding mechanisms provided clear CT expectations (e.g., to follow GCP, implement capacity building, electronic data capturing tools, community engagement, etc.) based on the respective study context.

Another concept mentioned repetitively in the context of CT planning in RLS was community engagement, which supports adapting a CT to local circumstances. However, it is not clear how far it overlaps with the concept of the engagement of patient representatives, which is also common in developed research settings. A recent study has shown that these concepts overlap and need further clarification [15]. Also, our interviews did not reveal the extent to which the interviewees distinguished between these concepts. Moreover, one interviewee suggested that the term "patient representative" could be stigmatising or exclusive towards research with healthy populations (e.g., vaccines, preventive treatments). Hence, clear definitions of these concepts may help determine their role in CT quality and their potential impact in diverse settings.

5.2 Informed consent by minor parents

In SSA, there is a higher probability of children involved in CTs to have minor parents. However, clear international guidance on the appropriate person to consent on behalf of such children is missing. In some countries, the legal age of majority and conditions for emancipation or "mature minor" status may not be defined by law [16]. Even if such legislation exists, it may not correspond to local customs [17]. Due to these uncertainties, we performed two analyses based on a systematic literature review. The first one addressed reported IC approaches for the CT recruitment of children with minor parents in various studies, and the second one focused on the level of transparency about the CT recruitment of children with minor parents, specifically in CT publications.

Our first study showed that informed consent in this situation is implemented in various ways: While in Kenya, a minor mother would be directly allowed to consent [18], in Côte d'Ivoire, she would not, despite becoming legally emancipated when being married [19]. When no guidance existed, the decision of whether minor mothers were able to consent for their child could be drawn from concepts of medical care [20] or depended on the local decision-making culture [21]. In the latter case, the process had to be established in collaboration with the local stakeholders (e.g., community and ethics committees). In order to facilitate the development of an appropriate IC approach that considers these various realities, we provided seven recommendations (3.6 Conclusions, p.68). We also recommended including specific reporting requirements in international guidelines to promote transparency about such exceptional cases (3.6 Conclusions, p.68).

We further analysed the level of transparency in CT publications about recruiting children with minor parents. This analysis revealed that none of the included articles provided robust evidence on whether any recruited children had minor parents and how consent was obtained for them. Specific descriptions of decision-maker types were provided rarely and mainly in referenced CT registrations or protocols. Also, terminology describing proxy decision-makers was often used inconsistently. We provided several recommendations on how to improve reporting quality (4.6 Conclusions, p.90).

The informed consent for children with minor parents represents a showcase of how contextual aspects can impact CT quality if not addressed appropriately. Considering the challenges are on a very specific level, involving children of minor parents, which represent an "exception of an exception", researchers may be placing less emphasis on the detail of information needed to truly assure transparency. Hence, the essence of IC is often not sufficiently represented in as many details in study publications as "scientific" aspects [22]. Despite being only a small aspect in the process compared to the overall context of a CT, IC carries both ethical

but also scientific implications [23]. On the one hand, IC ensures the rights of patients. On the other hand, IC also influences the recruitment of study participants, which ultimately affects the study outcomes. Moreover, IC is a sensitive issue that determines the relationship between participants and researchers, which, in a more distant sense, can also affect the participants' safety or future study recruitment successes.

In the existing CT guidelines, patient rights and safety already play a central role [13, 14]. However, this example shows that the management of exceptional cases lacks transparency and thus fails to correlate with its importance. A CT quality framework could integrate tools for handling such cases and promote appropriate consideration at each stage of a CT (i.e., planning, execution, and documentation).

5.3 Methodological challenges and limitations

This thesis was primarily based on qualitative research methodology, considered suitable for answering each research question.

5.3.1 Clinical trial quality concept

We considered conducting qualitative interviews since the research focused on an interpretation of quality based on CT stakeholders' personal experiences. Thereby, we chose a semi-structured design of the interview guide with open-ended questions, as it offered the possibility to define the core components of the interview but still allowed the interview participants to address further topics intuitively. The framework method is commonly used for the analysis of semi-structured interviews and benefited our research through the possibility of combining inductive and deductive data analysis approaches [24].

To minimise bias, we attempted to systematically select participants by filtering CT registries for CTs performed in SSA in the past five years. However, this method required extensive data cleaning before we could contact individuals because the indexing of CTs in the database did not accurately distinguish between CTs and observational studies. After contacting and re-contacting the first group of stakeholders, the response rate was low compared to the effort invested in collecting their contact details. The idea of contacting additionally observational researchers in the hope that they would also have CT experience risked an even lower response rate and was abandoned. However, we still consider CT registries valuable sources for such contacts, but rather when aiming for short surveys instead of one-hour interviews. Hence, we obtained more than half of the sample size through snowball sampling. In addition,

we considered the attendance at conferences combined with the screening of conference participants a helpful method of collecting contacts, which was more systematic than relying solely on known personal contacts.

During the interviews, the answers and follow-up questions could have been influenced by the personal interests of the interviewees as well as by a possible leading by the interviewers. However, a semi-structured interview guide allowed for a common basic interview structure [25].

We conducted the interviews primarily using Skype or a phone, which may have influenced the interview atmosphere or prevented trustworthiness. However, the topics addressed were not personal. Also, as the interviewees often previously participated in international research, they were used to the idea of communicating about quality remotely. Still, in a few cases, there was some reluctance on the part of the interviewees to answer questions due to disruptions of the internet connection. Also, in some cases, interviewees may have felt tested based on the nature of the topic "quality". We tried to prevent this perception by addressing this possibility upfront in the information sheet. Overall, we considered remote interviews appropriate, given the nature of the research topic.

When considering the external validity of this research approach, the main limitation was the small sample size. However, many interviewees had extensive experience from various countries and studies conducted in SSA. Also, we reflected on the potential variability of the countries' infrastructures and tried to generalise only subject levels applicable to most participants.

Another limitation was that we included only three stakeholder groups. We chose these groups as they are closely involved in the conduct of CTs and likely oversee the entire process, and this kind of oversight was considered key to the development of the CT quality concept. Nevertheless, the concept only represents an initial attempt to set a basic framework for CT quality. Hence, the CT concept could benefit from future input, including different stakeholder groups (e.g., ethics committees, study participants, regulatory authorities, etc.). However, adding these perspectives would have exceeded the scope of this project. Also, it seems more suitable to address these stakeholder groups at the local level through the involvement of local researchers.

5.3.2 Systematic literature review

The main challenge of the systematic review was that we searched for a scarce situation (i.e., informed consent by minor parents) among a vast topic (i.e., consent issues in paediatric research in sub-Saharan Africa). Keywords to detect relevant information were very insensitive,

as they were based on qualitative content and blended in with the rest of the literature. Relevant information was rarely addressed as a primary topic and could sometimes be found only in tangential thoughts. The risk of missing this information was high and required a rigorous screening process. Also, distinguishing CTs from other research posed challenges since study characteristics were not always clearly reported in titles and abstracts. Therefore, we had to implement an additional full-text screening strategy to increase screening efficiency.

Some challenges could also be attributed to the reviewers' minimal experience conducting systematic literature reviews. The search strategy and data extraction of such literature reviews are often developed by experienced medical librarians. However, for our studies, we first involved a librarian only at the beginning of the review to comment on the search strategy. We then involved another librarian at a later stage to update the search. However, the lead author performed the main steps in developing the search and screening strategy. Some additional technical challenges can be found in the respective publications (3 Manuscript II, p.46 and 4 Manuscript III, p.74).

5.4 Future implications

Over the past decades, an increasing amount of literature has been published reporting specific challenges in the conduct of CTs in RLS [9-11]. However, little empiric research has been done to translate such learning into helpful guidance [26]. This work attempted to contribute to filling this gap by integrating a RLS perspective in the definition of CT quality.

However, the findings are conceptual and need to be translated into practice. Additionally, further research, including different stakeholder groups, would be beneficial to challenge the concept. A possible approach could involve a presentation of the concept to researchers in RLS involving an international panel. Moreover, researchers involved in developing the INQUIRE framework could be approached to discuss the value of the findings and a potential amendment, integrating the RLS-specific aspects.

The findings could also be considered a validation of the INQUIRE framework since they confirmed the conceptual building blocks and showed its transferability to RLS. Furthermore, this conceptual validation could also inform the current discussion with respect to the renovation of the ICH-GCP guideline about redefining "high quality" in CTs [3]. In doing so, the CT quality concept could help in discussing whether and how to integrate the concept of Comprehensive Quality Management, CT quality-promoting factors and RLS-specific guidance into general guidance.

The second part of this PhD resulted in specific recommendations on how to approach and raise transparency about the informed consent for children with minor parents. These recommendations could have a potential influence on international CT guidance [27] as well as reporting practice [28]. Moreover, it could encourage national and local ethics committees and researchers to take leadership in increasing community engagement to provide local guidance for sensitive subjects.

5.5 Conclusions

Through the involvement of stakeholders with experience in conducting CTs in RLS, we were able to define a CT quality concept combining scientific and ethical aspects, as well as CT quality-promoting factors. This finding is in line with the existing INQUIRE framework, which also represents a multidimensional quality concept and includes the component of quality promoters. Compared to the conventional two-dimensional quality standard of the ICH-GCP (R1 & R2), which focuses primarily on scientific and ethical requirements, a multidimensional CT quality provides oversight and puts critical CT dimensions into context with each other. Such a perception offers the opportunity to use resources in a more targeted and economic manner independently of whether CTs are conducted in the Global North or South. Hence, we propose considering such a multidimensional quality concept as a basis for “Comprehensive Quality Management” (CQM), which may be considered in future global CT quality management guidance.

In our work, RLS-specific CT aspects were mostly related to CT quality-promoting factors. Therefore, considering CT quality-promoting factors in future CT quality models will help manage CT quality more effectively. Also, RLS-specific CT aspects resulted in potential additions to the promoters defined in the INQUIRE framework (i.e., context adaptation, communication of infrastructural disadvantages to CT stakeholders, and prevention of exploitation of workforce and study populations). These additional CT quality-promoting factors are also essential to CT management in the Global North, where they are less visible and, therefore, at risk of being neglected.

A specific topic we addressed in our work was the quality of the IC method for children with minor parents in SSA. This issue emerged during the execution of CTs in RLS. While IC concerns the participants' rights, which is a critical objective in existing quality standards, transparency about the actual methodology used was low. We developed guidance on establishing and reporting the IC methodology in such exceptional cases. Such guidance should find entrance into CT quality concepts, e.g., the INQUIRE framework.

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6 Appendix

6.1 Timeline of major incidents vs release of major guidelines

		WW II	Nazi experiments Unethical experiments on prisoners by Nazi investigators
		1961	Thalidomide tragedy The use of thalidomide (Contergan) led to foetal abnormalities. Regulation of drug-related research had to be tightened.
Declaration of Helsinki	1964		
		1972	Tuskegee Syphilis study Traced the natural history of syphilis in poor African Americans. No protocol existed, and the participants were misled about the study purpose.
WHO/CIOMS Guideline	1982		
ICH-GCP Guideline	1996		
		2000	Release about Trovan study US pharmaceutical company conducted a clinical trial involving children without informed consent in Nigeria in 1996
National Bioethics Advisory Commission Recommendations for developing countries	2001		
Nuffield Council on Bioethics Recommendations for developing countries	2002		
Ethical Principles for Clinical Research in Developing Countries by Emanuel et al.	2004		

Figure S1: Timeline of major incidents in clinical trial conduct vs release of major clinical trial guidelines [1, 2]

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6.2 Ethics review response

EKNZ

Ethikkommission
Nordwest- und
Zentralschweiz

Präsident
Prof. Christoph Beglinger
Vizepräsidenten
Dr. Angela Frotzler
Dr. Marco Schärer

A. Lazarova
Swiss TPH
Socinstrasse 57
4051 Basel

Basel, March, 5th 2018 / CB

EKNZ BASEC Req-2018-00159: Quality in clinical trials - A low-resource settings perspective

Dear Ms. Lazarova

With reference to the documents submitted Feburary, 27th 2018, the Ethics Committee of Northwest and Central Switzerland (EKNZ) acknowledges the received documents for the above mentioned research project and concludes the following:

The research project doesn't fall under the remit of the cantonal or federal law (Human Research Act) and therefore doesn't need an approval by an ethics committee, because your project is not defined as a research project as per HRA Art. 2. Because of this, the EKNZ cannot officially approve your project.

As requested, we have reviewed the submitted documents and can confirm that the research project fulfils the general ethical and scientific standards for research with humans and poses no health hazards (see Art. 51 Abs. 2 HRA).

With the Committee's best wishes for the success of this project.

Yours sincerely,

i.V. mgjane.

Prof. Ch. Beglinger
President of the Ethics Committee
Northwest and Central Switzerland / EKNZ

Documents reviewed:
- 00 TemplateZustaend...2.2018, signed.pdf
- 01 EKNZ, cover lett...rected, signed.pdf
- 02 PhD proposal, V0...2.2018, signed.pdf
- 03a CV Angela Lazar...6.02.2018, ALA.pdf
- 03b CV Med Christia...3.10.2017, CHB.pdf
- 04 Information all ...01, 26.02.2018.pdf
- 05a Interview guide....2018, CF, ALA.pdf
- 05b Interview guide...01, 26.02.2018.pdf
- 05c Interview guide...03, 26.02.2018.pdf

Geschäftsführerin Irene Oberli | Hebelstrasse 53 | 4056 Basel | Tel 061 268 13 50 | Fax 061 268 13 51 | eknz@bs.ch | www.eknz.ch

6.3 Participant information sheet in English

Swiss TPH
Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut
Institut Tropical et de Santé Publique Suisse

Associated Institute of the University of Basel

Department of Medicine
Angela Lazarova
PhD Student

Information for interview participants

Quality in Clinical Trials - A Resource-Limited Settings Perspective

The interview is part of a research project focusing on the concept of quality in clinical trials from a resource-limited settings perspective. The purpose of this interview is to explore the opinion of different stakeholders (sponsors, investigators, and monitors) involved in the conduct of clinical trials in sub-Saharan Africa about the meaning and conception of the term *quality* within the framework of clinical trials. Your opinion can help us to develop a better understanding of what factors are deemed relevant to clinical trial quality. By outlining the multifaceted layers of clinical trial quality we aim to facilitate appropriate clinical trial quality management in resource-limited settings. This interview is not meant to test or evaluate you.

Privacy information:
Your participation in this interview is voluntary. You will not be paid for your participation. The interview will last approximately 45 minutes. There are no known or anticipated risks or direct benefits.

If you agree, the interview will be electronically recorded. The recording will be transcribed and used as a basis for qualitative analysis. Before transcription, the filenames of the recordings will be anonymised by assigning a unique code. Any identifying data collected for communication purposes will be handled confidentially and stored in a separate file with restricted access. Only the interviewers will have access to these files. If you do not agree to be electronically recorded, your answers will be captured in hand-writing by the interviewer. Some of your statements may be quoted in a scientific publication, but will not contain your name, the name of your organization or any information that could lead back to you. You may skip any question at your discretion and you may withdraw from the study at any time (before, during, and after data collection) without giving any reason. If you decide to withdraw after the interview please inform us by an e-mail to the address indicated at the end of this letter. If at the time of withdrawal any data were collected but not yet submitted for publication, they will not be included in the publication. Your acceptance, refusal, or withdrawal from this study will also be kept confidential. In case you have any questions, please contact us via the e-mail address provided below.

By agreeing to participate in this interview, you confirm that you understand the information provided to you in this document. Do you agree to participate in this interview? Do you agree to be recorded?

This research project was submitted to the Ethics Committee Northwest and Central Switzerland (EKNZ) and was exempted from formal ethical approval according to the Swiss Human Research Act (2014) since only managerial but no health-related data are collected. The EKNZ, however, reviewed the research project and confirmed that it fulfils the general ethical and scientific standards for research with humans and poses no health hazards.

Thank you for your time and considerations about taking part in this interview.

Angela Lazarova
PhD Student, Swiss TPH
Department of Medicine
Medicines Implementation Research Unit (MIRU)
Tel: +41 (0)61 284 89 65
Study e-mail address: **miru@swisstph.ch**

Claudia Fuchs
Master Student, University of Basel/Swiss TPH
Department of Medicine
Medicines Implementation Research Unit (MIRU)
Tel: +41 (0)61 284 89 77
Study e-mail address: **miru@swisstph.ch**

6.4 Participant information sheet in French

Swiss TPH
Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut
Institut Tropical et de Santé Publique Suisse

Associated Institute of the University of Basel

Department of Medicine
Angela Lazarova
PhD Student

Informations pour les participants

Qualité dans le cadre des études cliniques - Perspective des pays aux ressources limitées

L'entretien fait partie d'un projet de recherche axé sur le concept de qualité dans les études cliniques dans une perspective de contexte à ressources limitées. Le but de cet entretien est d'explorer l'opinion des différents intervenants (promoteurs, investigateurs et moniteurs) impliqués dans la conduite des études cliniques en Afrique subsaharienne concernant la signification et la conception du terme qualité dans le cadre des essais cliniques. Votre opinion peut nous aider à mieux comprendre quels facteurs sont jugés pertinents pour la qualité des études cliniques. En démontrant les niveaux multidimensionnels de qualité des études cliniques, nous visons à faciliter la gestion de la qualité des études cliniques dans des contextes des pays aux ressources limitées. Cet entretien n'a pas pour but de vous tester ou de vous évaluer.

Informations de confidentialité:
Votre participation à cet entretien est volontaire. Vous ne serez pas payé(e) pour votre participation. L'entretien durera environ 45 minutes. Il n'y a pas de risques connus ou prévus ni d'avantages directs.
Si vous acceptez, l'entretien sera enregistré électroniquement. L'enregistrement sera transcrit et utilisé comme base pour une analyse qualitative. Avant la transcription, les noms de fichier des enregistrements seront anonymes en attribuant un code unique. Toutes les données d'identification collectées à des fins de communication seront traitées de manière confidentielle et stockées dans un fichier séparé avec un accès restreint. Seuls les enquêteurs auront accès à ces fichiers. Si vous n'acceptez pas d'être enregistré électroniquement, vos réponses seront saisies à la main par l'enquêteur. Certaines de vos déclarations peuvent être citées dans une publication scientifique, mais ne contiendront pas votre nom, le nom de votre organisation ou toute information qui pourrait vous retracer. Vous pouvez ignorer toute question à votre discrétion et vous pouvez vous retirer de l'étude à tout moment (avant, pendant et après la collecte de données) sans donner de raison. Si vous décidez de vous retirer après l'entretien, veuillez nous en informer par un e-mail à l'adresse indiquée à la fin de cette lettre. Si, au moment du retrait, des données ont été collectées mais n'ont pas encore été soumises pour publication, elles ne seront pas incluses dans la publication. Votre acceptation, votre refus ou votre retrait de cette étude sera également confidentiel. Si vous avez des questions, veuillez nous contacter via l'adresse e-mail ci-dessous.
En acceptant de participer à cet entretien, vous confirmez que vous comprenez les informations qui vous sont fournies dans ce document. Acceptez-vous de participer à cet entretien? Acceptez-vous d'être enregistré?

Ce projet de recherche a été soumis au Comité d'éthique de la Suisse Nord-Ouest et centrale (EKNZ) et a été exempté de l'approbation éthique formelle selon la loi suisse sur la recherche humaine (2014) car seules des données managériales sont collectées et non pas les données de santé. Cependant L'EKNZ a examiné le projet de recherche et a confirmé qu'il répond aux normes éthiques et scientifiques générales pour la recherche avec les humains et ne pose aucun risque pour la santé.

Nous vous remercions de votre temps et des considérations à prendre part à cet entretien.

Angela Lazarova
PhD Student, Swiss TPH
Department of Medicine
Medicines Implementation Research Unit (MIRU)
Tel: +41 (0)61 284 89 65
Study e-mail address: **miru@swisstph.ch**

Claudia Fuchs
Master Student, University of Basel/Swiss TPH
Department of Medicine
Medicines Implementation Research Unit (MIRU)
Tel: +41 (0)61 284 89 77
Study e-mail address: **miru@swisstph.ch**

6.5 COREQ

Table S1: COREQ (COnsolidated criteria for REporting Qualitative research) Checklist

A checklist of items that should be included in reports of qualitative research. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Topic	Item No.	Guide Questions/Description	Reported on Page no.
Domain 1: Research team and reflexivity			
Personal characteristics			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	Study design and setting, last paragraph, p7
Credentials	2	What were the researcher's credentials? E.g., PhD, MD	Study design and setting, last paragraph, p7
Occupation	3	What was their occupation at the time of the study?	Study design and setting, last paragraph, p7
Gender	4	Was the researcher male or female?	Study design and setting, last paragraph, p7
Experience and training	5	What experience or training did the researcher have?	Study design and setting, last paragraph, p7
Relationship with participants			
Relationship established	6	Was a relationship established prior to study commencement?	Ethical aspects, last paragraph, p10
Participant knowledge of the interviewer	7	What did the participants know about the researcher? E.g., Personal goals, reasons for doing the research	Ethical aspects, last paragraph, p10
Interviewer characteristics	8	What characteristics were reported about the interviewer/facilitator? E.g., Bias, assumptions, reasons and interests in the research topic	Ethical aspects, last paragraph, p10
Domain 2: Study design			
Theoretical framework			
Methodological orientation and Theory	9	How were participants selected? E.g., purposive, convenience, consecutive, snowball	Methods section, first paragraph, p7
Participant selection			
Sampling	10	How were participants approached? E.g., face- to-face, telephone, mail, email	Sampling and recruitment, p7-8
Method of approach	11	How many participants were in the study?	Ethical aspects, last paragraph, p10
Sample size	12	How many people refused to participate or dropped out?	Participants, p11
Non-participation	13	What were the reasons for this?	Box 1, p8
Setting			
Setting of data collection	14	Where was the data collected? E.g., home, clinic, workplace	Study design and setting, first paragraph, p6
Presence of non- participants	15	Was anyone else present besides the participants and researchers?	Strengths and limitations, fifth paragraph, p28
Description of sample	16	What are the important characteristics of the sample? E.g., demographic data, date	Study design and setting, second paragraph, p7
Data collection			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Data collection, first paragraph, p9
Repeat interviews	18	Were repeat interviews carried out? If yes, how many?	Box 1, p8
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	Data collection, last paragraph, p9
Field notes	20	Were field notes made during and/or after the interview or focus group?	Data collection, last paragraph, p9
Duration	21	What was the duration of the interviews or focus group?	Data collection, last paragraph, p9
Data saturation	22	Was data saturation discussed?	Sampling and recruitment, p8
Transcripts returned	23	Were transcripts returned to participants for comment and/or correction?	Strengths and limitations, fifth paragraph, p28
Domain 3: analysis and findings			
Data analysis			
Number of data coders	24	How many data coders coded the data?	Data analysis, last paragraph, p10
Description of the coding tree	25	Did authors provide a description of the coding tree?	Table 4 and S2 Table
Derivation of themes	26	Were themes identified in advance or derived from the data?	Data analysis, first paragraph, p9 and Methods, p6

Software	27	What software, if applicable, was used to manage the data?	Data collection, last paragraph, p9
Participant checking	28	Did participants provide feedback on the findings?	Strengths and limitations, fifth paragraph, p28
Reporting			
Quotations presented	29	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? E.g., Participant number	S1 Table and Results, p13-24
Data and findings consistent	30	Was there consistency between the data presented and the findings?	Discussion, p24-30
Clarity of major themes	31	Were major themes clearly presented in the findings?	Results, p13-24, Table 4 and S2 Table
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	Results, p13-24, Discussion last paragraph p27

From: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. International Journal for Quality in Health Care. 2007. Volume 19, Number 6: pp. 349 – 357

6.6 Interview guides

Table S2: Interview guide in English

1. Personal and background information

a) Which **country** are you from?
b) Can you tell me about your **professional background**?
   - What did you study?
   - Where did you study?
   - What is your degree in?
   - In which institution do you work now? Where?
c) What was your **position** in the conduct of clinical trials?
   - How long have you worked in this position?
   - Have you worked in different positions related to clinical trials?
   - How long is your overall clinical trial experience?
d) What type/s of **medical intervention/s** have you tested in clinical trials?
   (Prompts: drugs, vaccines, diagnostics, etc.)

e) What was/were the **study population/s** in your clinical trials?
   (Prompts: children, adolescents, adults, elderly, pregnant, volunteers, patients, etc.)

f) Which clinical trial **phase/s** have you worked on?
   (Prompts: I, II, III, IV)

g) How **large** was/were your clinical trial/s in SSA?
   (Prompts: population size, mono- vs. multi-centre, duration)

h) In which **country/countries** have you conducted clinical trials (Prompt: in SSA and in non-SSA)?
i) In what type/s of **facility/facilities** did you conduct the clinical trial/was the clinical trial conducted?
   (Prompts: hospital, research centre, urban, rural, other)

j) Can you tell me something about the clinical trial **environment** you have worked in?
   - Was it an academic, or industrial, or other environment?

2. General questions about clinical trial quality

a) I would like to start now with a **general question**: What does clinical trial quality, as a whole, mean to you?
b) Which **factors** do you think have an influence on clinical trial quality?

3. Questions about quality in clinical trial planning

a) Can you tell me about how you usually come up with the **idea** of conducting a clinical trial? / What aspects lead to your involvement in a clinical trial conduct?
   - Why do you conduct clinical trials in SSA?

b) If you have experience in clinical trial planning:
   - What are **typical tasks** for you when planning a clinical trial?
   - How are these tasks **important** for clinical trial quality? (Prompt: what are essential tasks for clinical trial quality during the planning?)
   - How are these tasks influenced by the fact that the clinical trial takes place in **SSA**?

   If you have experience in more than one country in SSA:

   - Can you tell me more about the **variation** of these tasks from country to country in SSA?
   - Are there **common** aspects?

c) *If you have experience in different clinical trial sizes*: What effect does the **size** of the clinical trial have on the clinical trial quality?
d) Can you explain more about what effect the **facility** chosen for a clinical trial can have upon the clinical trial quality?
   - How did you **choose** the clinical trial facility/facilities?
   - How **equipped** was/were the facility/facilities? (Prompts: already established facility, new facilities were constructed for the trials)
e) *Referring to the clinical trial environment:* Who was the **sponsor** of your clinical trials? (Prompt: investigator-initiated, university-sponsor, external sponsor, industrial sponsor, consortium, product development partnership?)
f) How was/were your clinical trial/s **funded**? (Prompts: Did you have an external funder *(=funder other than sponsor)*? Did you also have clinical trials with multiple funders?)
   - *If you had an external funder/s:*
     - What kind of **expectations** did the funder/s have for clinical trial quality?
     - In how far did the expectations by the funder **guide** the clinical trial planning and conduct?

- Were there any expectations bound to the fact that the clinical trial is conducted in **SSA**? (Prompts: health programs, capacity building, post-trial access to treatment)

g) What **other partners** were involved in clinical trial planning? (Prompts: contract research organisation [CRO], patient representatives, other)
- What kind of **expectations** did they have for clinical trial quality?
- In how far did their expectations **guide** the clinical trial planning and conduct?

h) Were you involved in making a clinical trial **budget plan**?
If yes:
- On what aspects were the **largest** costs usually budgeted?
- Were any **adjustments** made during the clinical trial conduct? On which item were they mostly applied?

4. Questions about quality in clinical trial design

a) Speaking further about clinical trial **design**, what are generally important components of clinical trial design? / What makes a **good** clinical trial design?
- What is a good **informed consent**?
- What is a good **case report form**?

b) *If you were involved in clinical trial designing:*
- How did you develop the **protocol**?
- What **guidelines** did you consider for the clinical trial design? (Prompt: international ones, local ones, CONSORT, ICH-GCP?)
- Was the implementation of this/these guideline/s in any way influenced by the fact that the trial is conducted in **SSA**? (Prompt: were there any challenges, when implementing the guidelines?)

c) Can you tell me more about what influence did the ethical committee/s (**EC**s) or institutional review board/s (**IRB**s) have on the clinical trial design?
- **Where** was ethical approval of the protocol received? (Prompts: One country, more countries?)

In case you have been in contact with a local EC:

- Can you tell me more about the **reach** of the EC? (Prompt: Was it an institutional, a national, or was it an international one?)
- Do you have an idea of the **workload** of this EC? About how much **time** did your approval take? How did this **affect** the clinical trial **design**? How did this **affect** the clinical trial **planning**?

d) How was it decided whether the design was **feasible**? (Prompts: informed consent [e.g., rapid assessment], protocol procedure dry run, case report form [CRF] dry run?)

5. Questions about quality in clinical trial initiation

a) Moving now towards **preparatory** steps before clinical trial initiation, what essential tasks had to be completed before the clinical trial/s was/were initiated? (Prompt: What did you have to assure before patient recruitment could be started?)
- Which steps are important for clinical trial quality?

b) How was it assured that clinical trial **staff** (Prompts: monitor, investigator, lab, nurse, pharmacy) is able to perform correctly?
- What **events** took place in this matter? **How** were they trained? **When** were they trained? (Prompts: Was an investigator meeting performed? Was a clinical trial initiation visit performed?)
- What influence does **staff experience** have on the clinical trial quality?

c) Was clinical trial initiation influenced in any way by the fact that the trial is conducted in **SSA**? (Prompts: logistics, approvals, contracts, payment schemes)

6. Questions about quality in clinical trial conduct

a) Once patient **recruitment** has started, what were typical tasks from your side?
- How are these tasks important for clinical trial quality? (Prompt: what are essential tasks for clinical trial quality during the conduct?)

b) Can you tell me more about how patient **recruitment relates to clinical trial quality**?
- How is patient recruitment influenced by the fact that the trial is conducted in **SSA**?
- How does the **informed consent** procedure influence recruitment?

c) How did you assure that everything is **going as planned** during the conduct of a clinical trial?
- Did you implement any specific **quality control**? (Prompt: monitoring?)

If monitoring was implemented:

- What **influence** did monitoring have on clinical trial quality?
- **How much monitoring** did you apply? (Prompt: was every single aspect checked, or were priorities defined?)

If priorities were defined:

- How did you **prioritize**? / Did you **weight** your monitoring/quality control activities according to anything? (Prompt: Risk of the trial, risk of specific events within a trial, risk of specific items within a clinical trial assessed?)

If other quality control measure was implemented than monitoring:

- What **influence** did this quality control method have on clinical trial quality?

d) If "risk" was mentioned:
- Have you heard or used the **label** risk-based quality management or monitoring?

- What are/could be useful **features** of risk-based monitoring?
- What could be **challenges** of risk-based monitoring?
- To what extent is risk-based monitoring applicable in clinical trials conducted in **SSA**?

7. Questions about quality in clinical trial completion

a) What were your typical tasks towards the **end** of a clinical trial?
   - How are these tasks important for clinical trial quality? (Prompt: what are essential tasks for clinical trial quality once the last patient has been followed-up?)

8. Questions about clinical trial quality reflection

a) Based on what did you **finally judge** the quality of your clinical trial/s?
b) What aspects could have been **improved** in your clinical trials? **Why**? **How** would you improve this/these aspects?
c) What aspects could have been **skipped or shortened**? Is there anything that could have been done more pragmatically? Can you explain why or why not?
d) *If you have experience in both, **academic and industrial** trials*: what **differences** do you deem important for clinical trial quality?
e) *If you have experience in both, **non-SSA and SSA** trials:* what **differences** do you deem important for clinical trial quality?
f) Have you experienced **challenges** during the process of a clinical trial you did not foresee?
   If yes:
   - Would you like to share one or more examples from your experience?
   - What did you do about it/them?
   - What could have been done to prevent it/them?

9. Questions about the stakeholders in clinical trial conduct

a) Would you **recommend** anything to other stakeholders to improve a clinical trial (Prompts: what are lessons learned from the collaborations with monitors? What are lessons learned from the collaboration with investigators*?* What are lessons learned from the collaboration with sponsors*? In case of a consortium*: What are lessons learned from the collaboration with multiple partners?)
b) How may the modes of **payment** be influencing clinical trial quality?
   - Based on what have you been paid? (Prompts: regular payments, performance-based payments, e.g., based on patient recruitment)
   - If monitors were hired: Based on what were they paid?

10. Conclusions

a) And moving to the final conclusions: How would you define clinical trial quality in **one sentence**?
b) Are there **any other relevant points** you would like to mention in relation to clinical trial quality?
c) Do you have any questions?

Table S3: Interview guide in French

1. Informations personnelles et générales

a) De quel pays venez-vous?
b) Pouvez-vous me parler de votre expérience professionnelle?
   - Qu'avez-vous étudié?
   - Où avez-vous étudié?
   - Quel est votre diplôme?
   - Dans quel type d'institution travaillez-vous?
c) Quelle était votre position dans la conduite des études cliniques?
   - Depuis combien de temps travaillez-vous dans ce poste?
   - Avez-vous travaillé dans différentes positions liées aux études cliniques?
   - Quelle est la durée de votre expérience totale?
d) Quel/s type/s d'intervention/s médicale/médicaux avez-vous testé dans les études cliniques? (Invites: médicaments, vaccins, diagnostic, etc.)
e) Quelle était la/les population/s étudiée/s dans vos études cliniques? (Invites: enfants, adolescents, adultes, personnes âgées, enceintes, volontaires, patients, etc.)
f) Sur quelle/s phase/s d'études cliniques avez-vous travaillé? (Invites: I, II, III, IV)
g) Quelle était la taille de vos études cliniques en Afrique subsaharienne? (Invites: taille de la population, mono- ou multicentrique, durée)
h) Dans quel pays avez-vous réalisé des études cliniques?
i) Dans quel/s type/s d'établissement/installations avez-vous réalisé l'étude clinique / l'étude clinique a-t-elle été effectuée? (Invites: hôpital, centre de recherche, urbain, rural, autre)
j) Pouvez-vous me parler de l'environnement d'études cliniques dans lequel vous avez travaillé?
   - Était-ce un milieu académique, industriel ou autre?

2. Questions générales sur la qualité des études

a) Je voudrais commencer par une question générale: Qu'est-ce que c'est pour vous, la qualité des études cliniques dans son ensemble?
b) Maintenant, quels facteurs ont une influence sur la/cette qualité des études cliniques selon vous?

3. Questions sur la qualité dans la planification des études cliniques

On va parler maintenant du processus d'une étude clinique et on commence avec la planification.

a) Pouvez-vous me dire comment vous envisagez habituellement de mener une étude clinique? / Quels aspects entraînent votre participation à une étude clinique?
   - Pourquoi menez-vous des études cliniques en Afrique subsaharienne?

b) *Si vous avez participé à la planification d'études cliniques* :
   - Quelles sont les tâches typiques pour vous lors de la planification d'une étude clinique?
   - En quoi ces tâches sont-elles importantes pour la qualité des études cliniques? (Prompt : quels sont les tâches essentielles pour la qualité des études cliniques ?)
   - Comment ces tâches sont-elles influencées par le fait que l'étude clinique a lieu en Afrique subsaharienne?

   Si vous avez de l'expérience dans plus d'un pays d'Afrique subsaharienne:
   - Pouvez-vous m'en dire plus sur la variation de ces tâches d'un pays à l'autre en Afrique subsaharienne?
   - Y a-t-il des aspects communs?

c) *Si vous avez de l'expérience dans différentes tailles d'études cliniques*: Comment la taille de l'étude clinique affecte-t-elle la qualité?
d) Pouvez-vous expliquer plus en détail comment l'installation choisie pour une étude clinique peut avoir un impact sur la qualité des études cliniques?
   - Comment avez-vous choisi l'installation ou les installations d'études cliniques?
   - Dans quelle mesure les installations / installations étaient-elles équipées (se référer à l'installation mentionnée)? (Invites: installation déjà établie, de nouvelles installations ont été construites pour les études)

e) Comment votre / vos étude (s) clinique (s) a / ont été financé (s)? (Invites: Avez-vous eu un bailleur de fonds externe? Avez-vous également eu des études cliniques avec plusieurs bailleurs de fonds?)
   - *Si vous aviez un bailleur de fonds externe (= bailleur de fonds autre que le commanditaire):*
     - Quel genre d'attentes les bailleurs de fonds ont-ils eu pour la qualité des études cliniques?
     - Dans quelle mesure les attentes du bailleur de fonds guident-elles la planification des études cliniques
   - Y avait-il des attentes liées au fait que l'étude clinique soit menée en Afrique subsaharienne? (Invites: programmes de santé, renforcement des capacités, accès au traitement après le procès)

f) Quels autres partenaires ont participé à la planification des études cliniques? (Invites: consortium, partenariat pour le développement de produits, organisation de recherche sous contrat [CRO], représentants des patients, autres)
   - Quel genre d'attentes ont-ils eu pour la qualité des études cliniques?
   - Dans quelle mesure leurs attentes ont-elles guidé la planification des études cliniques?

g) Avez-vous participé à l'élaboration d'un plan budgétaire pour les études cliniques?
   Si oui:
   - Sur quels aspects les coûts les plus importants sont-ils habituellement budgétés?
   - Des ajustements ont-ils été apportés au cours de l'étude clinique? (Invite: sur quel article ont-ils été principalement appliqués?)

4. Questions sur la qualité dans la conception des études cliniques

a) Pour en savoir plus sur la conception des études cliniques, quels sont les éléments généralement importants de la conception des études cliniques? / Qu'est-ce qui fait un bon plan d'étude clinique?
   - Qu'est-ce qui fait un bon consentement éclairé ?
   - Qu'est-ce qui fait un bon formulaire de rapport de cas (CRF)?

b) Si vous-avez participé à la conception d'études cliniques :
   - Comment avez-vous développé le protocole?
   - Quelles directives avez-vous envisagées pour les études cliniques? (Invites : internationale, locale, CONSORT, ICH-GCP ?)
   - Comment la mise en place des directives a-t-elle été liée au fait que l'étude clinique soit menée en Afrique subsaharienne?

c) Pouvez-vous m'en dire plus sur l'influence des comités d'éthique ou des commissions d'examen international sur la conception des études cliniques?
   - Où l'approbation éthique du protocole a-t-elle été reçue? (Invites: Nord, Sud?)

   Au cas où vous seriez en contact avec un comité d'éthique local:
   - Pouvez-vous m'en dire plus sur la portée du comité éthique? (Invite: Était-ce un comité national ou était-ce un comité international?)
   - Avez-vous une idée de la charge de travail de ce comité? Combien de temps a duré votre approbation? Comment cela a-t-il affecté la conception de l'étude clinique?

d) Comment a-t-on décidé si la conception était faisable? (Invites: consentement éclairé [par exemple, évaluation rapide], protocole, formulaire de rapport de cas [CRF])

5. Questions sur la qualité de l'initiation des études cliniques

a) Passons maintenant aux étapes préparatoires avant le lancement de l'étude clinique, quelles tâches essentielles devaient être accomplies ? (Invite: qu'aviez-vous à assurer avant que le recrutement des patients puisse commencer?)
   - Comment ces étapes sont-elles importantes pour la qualité des études cliniques?

b) Comment a-t-on assuré que le personnel des études cliniques (suggestions: moniteur, investigateur, laboratoire, infirmière, pharmacie) est capable de fonctionner correctement?
   - Quels événements ont eu lieu dans cette affaire? Comment ont-ils été formés? Quand ont-ils été formés? (Invites: Une réunion d'investigateurs a-t-elle été effectuée? Une visite d'initiation aux études cliniques a-t-elle été effectuée?)
   - Comment l'expérience du personnel a-t-elle influencé la qualité des études cliniques ?

c) Comment l'initiation des études cliniques a-t-elle été influencée par le fait que l'étude est menée en Afrique subsaharienne? (Invite : logistique, approbations, contrats, modes de paiement)

6. Questions sur la qualité de la conduite des études cliniques

a) Une fois que le recrutement des patients a commencé, quelles sont les tâches typiques de votre part?
   - Comment sont-elles importantes pour la qualité des études cliniques ? (Invite : Quelles sont les tâches essentielles pour la qualité des études cliniques pendant la conduite?)

b) Pouvez-vous m'en dire plus sur la relation entre le recrutement de patients et la qualité des études cliniques?
   - Comment le recrutement des patients est-il influencé par le fait que l'étude est menée en Afrique subsaharienne?
   - Comment la procédure de consentement éclairé influence-t-elle le recrutement?

c) Comment avez-vous assuré que tout se passe comme prévu?
   - Avez-vous mis en place un contrôle de qualité spécifique?

   Si monitoring a été mise en place:
   - Quel impact a-t-il eu sur la qualité des études cliniques?
   - Combien de monitoring a été mise en place ? (Invite : chaque aspect contrôlé, priorités ?)

   Si des priorités ont été définies:
   - Comment avez-vous priorisé? / Avez-vous pondéré vos activités de surveillance / contrôle de qualité en fonction de quoi que ce soit? (Invite: Risque de l'essai, risque d'événements spécifiques dans un essai, risque d'éléments spécifiques dans un essai clinique évalué?)

   Si autres mesures ont été mise en place :
   - Quel impact ont-elles eus ?

d) *Si "risque" a été mentionné*:
   - Avez-vous entendu ou utilisé l'étiquette de "surveillance de la qualité basée sur le risque"?
   - Quelles sont / pourraient être des caractéristiques utiles de la surveillance basée sur les risques?
   - Quels pourraient être les défis de la surveillance basée sur le risque?
   - Dans quelle mesure la surveillance basée sur le risque est-elle applicable dans les essais cliniques menés en Afrique subsaharienne?

7. Questions sur la qualité de la terminaison des études cliniques

a) Quelles ont été vos tâches typiques vers la fin d'une étude clinique?
   - Comment ont-ils influencé la qualité des études cliniques? (Invite: quelles sont les tâches essentielles pour la qualité des essais cliniques une fois que le dernier patient a été suivi?)

8. Questions sur la réflexion sur la qualité des études cliniques

a) Sur la base de quoi avez-vous finalement jugé la qualité de vos études cliniques?
b) Quels aspects pourraient avoir été améliorés dans vos études cliniques? Pourquoi? Comment amélioreriez-vous cet/ces aspect/s?
c) Quels aspects auraient pu être ignorés ou raccourcis? Y a-t-il quelque chose qui aurait pu être fait de manière plus pragmatique? Pouvez-vous expliquer pourquoi ou pourquoi pas?
d) Si vous avez de l'expérience dans des études universitaires et industrielles: quelles différences estimez-vous importantes pour la qualité des études cliniques?
e) Avez-vous eu des difficultés au cours d'une étude clinique que vous n'aviez pas prévu? *Si oui:*
   - Souhaitez-vous partager un ou plusieurs exemples de votre expérience?
   - Qu'avez-vous fait à ce sujet?
   - Qu'est-ce qui aurait pu être fait pour l'éviter?

9. Questions sur les parties prenantes dans la conduite des études cliniques

a) Recommanderiez-vous quelque chose aux autres parties prenantes pour améliorer une étude clinique (Invites: quelles sont les leçons tirées des collaborations avec les moniteurs?) Quelles sont les leçons tirées de la collaboration avec les sponsors? Dans le cas d'un consortium: Quelles sont les leçons tirées de la collaboration?
b) Comment les modes de paiement peuvent-ils influencer la qualité des études cliniques?
   - Sur la base de quoi avez-vous été payé? (Invites: paiements réguliers, paiements basés sur la performance, par exemple basés sur le recrutement des patients)
   - Si les moniteurs ont été embauchés: En fonction de quoi ont-ils été payés?

10. Conclusions

a) Et passer aux conclusions finales: Comment définiriez-vous la qualité des études cliniques en une phrase?
b) Y a-t-il d'autres points pertinents que vous aimeriez mentionner en relation avec la qualité des études cliniques?
c) Avez-vous des questions?

6.7 One-sentence clinical trial quality definitions

Table S4: One-sentence clinical trial quality definitions

Interview participant	Definition
01A	Well, for me I would call it the clinical trial is the trial that is directly related to the improvement of the life of the vulnerable population.
02A	Let's say, it's a full quality assurance management system that looks at all the aspects and try to set up systems for all these aspects, not too heavy, but that can cover many aspects and not only one. But that does not become too heavy to paralyse the whole trial, because this can be too much and then it can paralyse the whole thing. So it has to be clever, light, but very targeted to the main risks, as you said when we talked about risks, but covering several aspects and not just one, something like that. I mean not just SOP's, it goes beyond SOP's, it goes…it's also just […] Yes, how to cleverly recruit people, how to cleverly follow the data, so it has several aspects.
03A	A good quality trial is a trial that is desired by the local investigators. …No, I mean, the different thing is, the quality of a trial is, can be assessed by a lot of different things, and maybe not always all together, or, you know, kind of, for me a good quality trial can be a trial where everybody is happy, meaning the sponsor, because he got what he wanted, the CRO because...the investigators they got...the local investigators they got what they wanted...And finally the target population benefits, you know kind of, I think and benefits rather early than rather late, than if it's rather late.
04A	[Laughs] I don't know, one sentence is really difficult because it's so much, it's so many aspects I would say you cannot really define it in one sentence, it's so many interplaying aspects that come together which need to be fulfilled […] I think, I've mentioned several times before it's really these partnerships. It's the presence, the motivation, it's a good team, it's yeah all this.
05A	I cannot, define or...? Yes I think it's difficult to define but...The quality is safeguarding the integrity of clinical trial data and protecting the safety of participants in a clinical trial.
06A	Ahm...In one sentence I would say, you have not done harm and you have documented what you have formulated in your case report forms and you have met your primary objectives.
07A	Based on the quality of the clinical trial, your clinical trials data reflects this quality…and if you want to have good results, valuable results you have to have good quality.
08A	It's a huge challenge [*assumption: to conduct a good quality trial*]…but I think that…it's getting better now, also with the trial master file. Like, my first clinical trial didn't have a master file. So it's getting...now we are getting to more and more rules and stricter which might seem a bit boring and a bit too much when you are stressed in… […] Yeah, when you are on the field you are really stressed and you don't want to pay attention on signature. But I think in the end it is really important, to have something that discipline your work step by step, so only have to do this, this, this.
09A	It's a difficult task. Ok, let's try. I would say, check everything on a daily basis to make sure that...Yeah, check everything on a daily basis. Everything is what you have done as a work, your files, your patient forms, your informed consent form - check your daily work. Take time in the evening to check your daily work, so you ensure the quality.
10A	In one sentence...Clinical trial quality means ensuring that we strictly obey by the step out and that what is outlined in the methodology. Okay, I would say that the clinical trial quality is ensuring that we strictly obey by the, by the standards that we set out in the methodology.
11A	That's the most difficult question, you are asking me today [laughs]. So, clinical trial quality...Clinical trial quality is a set...I would say it's all factors that help you collect data that will help you arrive at the right conclusions, all the factors that contribute to what...the successful achievement of a correct conclusion from a study.
12A	Clinical trial quality...Yes it is [challenging]. Clinical trial quality...

	[…] Ok. Clinical trial quality...ok I can say clinical trial quality is dependent on the quality of data generated, yeah...and ensuring the safety of the participant is upheld at all times.
13A	How I would define it? Well, you can't [*define quality in one sentence*]. No, in one sentence no. We just talked about it [*referring to the whole interview. Considering also the initial question about the meaning of clinical trial quality, where the participant replied "everything", we went for "many aspects" in the analysis].*
14A	Yes, I think good clinical trial quality is a clinical trial which follows all ICH-GCP & GCLP requirements and is having a good and well trained team to perform it.
15A	I guess, I would, maybe the...in one sentence... Let's see: The rigorous execution of an important scientific question downed upon a cohort...or a clinical trial, which stresses an important hypothesis just founded upon a sound scientific premise. They are the phrases brought together in one sentence.
16A	Oh in one sentence [laughs]...Oh gosh, ok, so...I would say in one sentence...Clinical trial quality is about providing or ensuring…providing assurance that the data you collect is credible and accurate and at the same time making sure that, you know, all the safety, the wellbeing, the rights, integrity of the volunteers are taken into account or are protected.
17A	I think clinical trial quality...refers to steps taken, to ensure the smooth running, and minimisation of bias and confounding in a trial.
18A	I think I'm going to say: If…clinical trial quality depends on the design and the methodology applied to the study […] But a good quality study is a well-thought, well-planned, well-conducted study even in resource-limited settings. That's what I would say.
19A	In one sentence, the quality means that the compliance with the requirements and the credibility, so that the data which will come out of the clinical trial will be reliable.
20A	The quality after involvement is the safety...wherever the safety is and getting high quality that means that the clinical trial quality, I think, is where you applied very well all...that it takes to the safety of your participants then the quality is there. I would sum up that it's safety, quality equals safety. Quality, quality is if you have to carry out a good clinical trial, quality wise you should have a good safety awareness.
21A	Yeah, Clinical trial quality in one sentence is that...the quality is specifically, how good or close to reality, close to the truth you are with your data, in form of a clinical trials, so this would be ability to get accurate and valid information for that kind of study, and that reaches the study objectives.
01B	Quality is equal to...data integrity plus ethics.
02B	I think clinical trial quality is really critical, it's crucial, it's one of the most important aspects and it's really what ensures your data quality and ensures that you think about the patient safety first. All this quality that has to be put in place...it's difficult in one sentence, sorry [laughs]...I think, yeah…quality is a lot about patient safety and wellbeing.
03B	Ok, the quality...the quality of a clinical trial starts from the protocol. The protocol determines the end. If the protocol is complicated, then the study tools may not be clear enough to collect the kind of data that you need to answer the research question, so if the protocol is also ambiguous, then, you know, your analysis of the statistics may not be clear enough, you know, to define the end points. I think, for me it's really the protocol. The simpler the protocol, the lower the risk of having problems with quality and implementation. So more complex protocols, more ambiguous protocols, you know, risk of you having problems with quality down the stream.
04B	Integrity of data...So no matter what kind of results we get, we have to be able to reproduce by doing different analyses at the end of the day. The quality...most of the people...That's all, that's with the integrity of the data at the end.
05B	Wow...hm. Ok, I would say a trial that has been conducted adhering to the protocol, while ensuring the safety of the trial participants.

06B	Mmh, that's a good question…well, I suppose, the bottom line is. I would...You can say that the quality of the clinical trials was good, if the data are good. I mean that's...it's all about the data, unfortunately, at the end of the day it is the data.
07B	Oh my…in one sentence...clinical trial quality really comes down to good participant experience and trustworthy data.
08B	You are aspiring to demonstrate operational excellence as well as excellent quality of data but you have to be flexible to understand that they will not necessarily be perfect, and you will need to adapt and be accepting of what you find with a reason.
09B	Quality data is data that we can depend on to answer our question. To me that's what it means. Clinical trial quality, yes, it is thrilled down to data eventually, because this is what we are trying to generate.
10B	I would say...I would define clinical trial quality and that it's not well defined. I think particularly in African setting that whole quality management of clinical trials…that is something that needs to be developed as an independent unit so that it supports the trials better…and I don't see enough networking of quality people in Africa to see that they help each other very well.
11B	Clinical trial quality are all the measures that are put in place in order to protect subjects who take part in clinical trials while ensuring meaningful data generation.
12B	Clinical trial quality in once sentence...well...You need a sound protocol and an adequately trained team and taking into account the community and patients' wellbeing into consideration.
13B	Wow. I think for a good clinical trial it is important that the data that will come out of it is clear and the patient is not put at risk.
01C	I would not be able to define it in one sentence, and I will tell you why [laughs]. So I am currently dealing, or participating in a study where...which I believe was messed up by a monitor and the quality was really bad, so then our CRO was contracted to come in and try to mitigate and the quality extremely low to an extent that even enrolment logs were missing. So quality of clinical trials is that monitors' objectives still vary in sub-Saharan Africa, I would say. Largely, the quality is good, but there is still, you know, projects of very poor quality of the research than under the watch of monitors actually. So there's still quite a bit work that needs to be done.
02C	In one sentence, oh...The quality of the study is the totality of data, material, and staff that collaborates to reach this quality.
03C	In one sentence! I can't say in one sentence; I always touch a lot of whatever I have been mentioning. Maybe I would say in one word, compliance to protocols, procedures, GCP/GCLP and ethical requirements.
04C	Clinical trial quality is mandatory, it's everything... I would say clinical trial quality is not...is not…something that people could say I want to do it, I don't want, it's mandatory. If we are not adhering to the guidelines, then nobody is going to trust what we are producing. So the quality is mandatory, no discussion on quality, I say no discussion on quality, no discussion!
05C	Yes I'm saying that the quality of a clinical trial must be a trial that is conducted according to the laid out principles, as ensured in the ICH-GCP standards and according to SOPs and according to the protocol.
06C	How will I define quality? Quality is…quality is doing what you do best, sticking with the international standards.
07C	Ah…mmm! I think that's the most difficult one! […] Ok. So I will say…yeah…quality is a continuous process [laughing].
08C	Clinical trials practice is a […] set of the GCP-ICH guideline, country regulation guideline and sponsor, and site SOP.
09C	Yeah...in one sentence [laughing]...You know, the thing is that at the end of the day, the clinical trial should be able to give you the right figure, you know, the right figure of the question you are asking yourself. You need to ensure that when you are doing a clinical trial, the information you will have is the right information. I mean you need to get the right information when you are doing a trial. You do not need to have a bias, you do not need to have a, you know...a good clinical trial is a clinical trial that gives you the right information.
10C	For my expertise, doing the right thing at the right time [mentioning earlier in the interview: doing the right things right].
11C	I think there are a lot of challenges, but every person involved with this standardisation, with ICH-GCP, every person is fighting to fulfill all the requirements of ICH-GCP. I think this is a good thing.

12C	Oh my! [laughs]. Ah…Clinical trial quality…I would say that clinical trial… I mean for me just clinical trial quality means to stick to the protocol and guidelines that are required. I mean I can't think of anything else of like a summary for that. They have to follow.

A: Investigators; B: Sponsors; C: Monitors

6.8 Coding tree for resource-limited settings specific themes

Table S5: Coding tree for resource-limited settings specific themes

CT quality-promoting factors	Themes	Codes	Subcodes
Context adaptation	Population differences	Health condition	Participant compensation as frequent issue in SSA
			Represent the population flexibly
			Motivation for CT participation
			Conflicting health system developments
			Concomitant diseases
			Population type
			Concomitant medication
			Over-researched population
		Accessibility	Finding patients for follow-up can be tricky
			Recruitment strategy
		Education	Awareness
			Rapid assessment of understanding
			Trust
			Language
			Not written language
			Illiteracy
			Translating
			Simple ICF
			Short ICF
		Culture	Initial consent by community leaders/community
			Age of consent
			Appropriate representatives
			Meaning of blood
			Importance of culture
	Regional aspects	Region	Public holidays
			Seasonality
			Politics
			Weather problems
Infrastructure	Capacity	Processes take more time	RA approval takes more time
	Health authority approval	ECs example	Different requirements
			Approval time by EC
		EC approval long & unpredictable	Reasons for delays (Internal inefficiencies, limited capacity, high workload)

		Harmonise laws in West Africa	Joint review
		Latest developments	Submission process improved
		Recommendations	Anticipation, prioritisation & flexibility recommended
	Availability of guidelines	National laws and guidelines / International regulations	Followed ICH-GCP
			Disease specific guidelines
		Local guidelines	No locally modified guidelines
			Institutional guidelines / Specific local requirements
			In process of establishing guidelines
			Mainly based on ICH-GCP
	Staff qualification	Disadvantages in education system	Adequate training time
			Measures (Pilot, close monitoring, accompany)
	Facility level	Facility characteristics	Variable facility types
			Urban vs. rural
			Established facilities themselves
		Challenges with remote, rural location	Supply-chain bureaucracy
			Power and internet connectivity
		Site assessment visit / questionnaire	Reputation
Partnership	Collaboration	Local partners	Variable
		Community engagement	*Community consent (see Culture)*
		Local PIs involved (feasibility)	Early involvement in protocol development
			Routine & Schedule
			Share responsibility
	Communication	Good communication	Having a communication system for all parties
			Informing important stakeholders
			Open communication channel between sites
			Consider cultural differences
			Sponsors to engage with local collaborators
	Sustainability	Funding mechanisms	Variable funding
			Flexibility in budget
			Long-term partnership
		Capacity building	Education opportunities
			Research opportunities
			Empowerment

6.9 PRISMA Checklist from Manuscript II

Table S6: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	OK: See title (page #1).
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	OK: See (page #2-3).
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	OK: See Introduction starting from paragraph 2 (page #3-4).
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	OK: See last two paragraphs of the Introduction (page #4).
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	OK: See Material and methods section, first paragraph (page #4) and Search strategy section in Material and methods section, end of first paragraph (page #5)
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	OK: See Table 1 for the search strategy (page #5-6), Table 2 about eligibility criteria in Material and methods section (page #6-7), and text (page #4-7).
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	OK: See Table 1 for the search strategy (page #5-6) and Search strategy section in Material and methods section (page #4-6)

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	OK: See Table 1 about search strategy in Material and methods section (page #5-6) and S1 Text.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	OK: See Eligibility criteria and screening section in Material and methods section (page #6-8) and Table 3 about screening strategy (page #7-8).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	OK: See Eligibility criteria and screening section (page #6-8), as well as Data extraction and analysis section in Material and methods section (page #8).
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	OK: See Data extraction and analysis section in Material and methods section (page #8) and Result section (page #11).
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	OK: See Critical appraisal of studies section in Material and methods section (page #8).
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	OK: See critical appraisal of studies section in Material and methods section (page #8).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	OK: See separate file for Fig 1 plus caption in Results section (page #9).
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	OK: See Table 4 including study characteristics in Results section (page #9-10).
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA

Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	OK: As far as applicable presented in table including the framework of themes concerning minor parents in Results section (page #12-17).
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	OK: As far as applicable presented in table including the framework of themes concerning minor parents in Results section (page #12-17).
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	OK: As far as applicable presented in table including the framework of themes concerning minor parents in Results section (page #12-17).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	OK: As far as applicable presented in Discussion section (page #21-25).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	OK: See strengths and limitations section in Discussion section (page #24-25).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	OK: See Discussion and Conclusion section (page #21-25).
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	OK: See funding information in application system.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097.

6.10 Search strategies of the systematic review

Table S7: Search strategies

PubMed (initial search)

(((((((((informed consent*) OR (consent form*) OR "patient information" OR (consent) OR (consented) OR (consenting) OR (assent) OR (parental permission*))) **AND** ((minor*) OR (pediatr*) OR (paediatr*) OR "child" OR "children" OR "childhood" OR infant* OR (adolescen*) OR "underage" OR (under-aged) OR (under aged*) OR (teen*) OR (minor parent*) OR (minor mother*) OR (under aged* AND parent*) OR (under-aged parent*) OR (underage parent*) OR (under aged* AND mother*) OR (under-aged mother*) OR (underage mother*) OR (teenage parent*) OR (teenage mother*) OR (adolescent parent*) OR (adolescent mother*))) **AND** ((parent*) OR "proxy" OR (representative*) OR (legally acceptable representative*) OR (guardian*) OR (caregiver*) OR (care giver*) OR (surrogate*) OR (decision making*) OR (capacity) OR (capab*) OR (competen*) OR (legal competenc*) OR (legally competent*) OR (matur*) OR (emancipat*) OR (waiv*) OR (exempt*) OR ("autonomy"))) **AND** ("trial" OR "trials" OR (clinical research*) OR "clinical trial" OR "clinical trials" OR (random*) OR "RCT" OR "pediatric research" OR "paediatric research" OR (medical research*) OR ("research" AND "child") OR ("research" AND "adolescent"))) **AND** ((low income*) OR (low resource*) OR (low-resource) OR (resource-limited) OR (resource limited*) OR (resource-poor) OR (resource poor*) OR (resource restricted*) OR (resource-restricted) OR (developing countr*) OR (global*) OR (international*) OR (developing world*) OR (less developed*) OR (less-developed) OR (less advanced*) OR (less-advanced) OR (poverty-related) OR (poverty related*) OR (LMIC*) OR "low-and middle income" OR (resource*)))) **OR** ((((((("Informed Consent"[Mesh] OR "Parental Notification"[Mesh] OR "Presumed Consent"[Mesh])) **AND** ("Minors"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh] OR "Child, Orphaned"[Mesh] OR "Pregnancy in Adolescence"[Mesh] OR "Maternal Age"[Mesh] OR "Vulnerable Populations"[Mesh])) **AND** ("Parents"[Mesh] OR "Legal Guardians"[Mesh] OR "Caregivers"[Mesh] OR "Decision Making"[Mesh] OR "Judicial Role"[Mesh] OR "Mental Competency"[Mesh] OR "Comprehension"[Mesh] OR "Liability, Legal"[Mesh] OR "Personal Autonomy"[Mesh] OR "Child Welfare"[Mesh] OR "Infant Welfare"[Mesh])) **AND** ("Biomedical Research"[Mesh] OR "Clinical Trials as Topic"[Mesh] OR "Research Subjects"[Mesh] OR "Pediatrics"[Mesh])) **AND** ("Developing Countries"[Mesh] OR "Poverty"[Mesh] OR "Neglected Diseases"[Mesh] OR "Culture"[Mesh] OR "Culturally Appropriate Technology"[Mesh] OR "Global Health"[Mesh] OR "Health Resources"[Mesh] OR "Global Burden of Disease"[Mesh]))

Sort by: Relevance Filters: Humans; English; French

Embase (initial search)

('informed consent'/syn OR 'patient information'/syn OR 'parental consent'/syn OR 'parental notification'/syn OR 'presumed consent'/syn OR 'consent' OR 'consenting' OR 'consented' OR 'assent*' OR 'parental permission' OR 'informed consent' OR 'consent form*' OR 'patient information') **AND** ('minor (person)'/syn OR 'child'/de OR 'infant'/exp OR 'adolescent'/syn OR 'parental age'/syn OR 'orphaned child'/syn OR 'preschool child'/syn OR 'school child'/syn OR 'toddler'/syn OR 'paediatrics'/de OR 'adolescent pregnancy'/syn OR 'adolescent parent'/syn OR 'vulnerable population'/syn OR 'minor*' OR 'pediatric*' OR 'paediatric*' OR 'child' OR 'children' OR 'childhood' OR 'infant*' OR 'adolescen*' OR 'adolescent patient' OR 'underage*' OR 'under age*' OR 'teen*' OR 'minor parent*' OR 'minor mother*' OR 'under aged parent*' OR 'underage parent*' OR 'under aged mother*' OR 'underage mother*' OR 'teenage parent*' OR 'teenage mother*' OR 'adolescent parent*' OR 'adolescent mother*') **AND** ('parent'/de OR 'caregiver'/syn OR 'patient decision making'/syn OR 'shared decision making'/syn OR 'ethical decision making'/syn OR 'legal liability'/syn OR 'patient autonomy'/syn OR 'competence'/syn OR 'mental capacity'/de OR 'comprehension'/syn OR 'maturity'/de OR 'child welfare'/syn OR 'custodial care'/syn OR 'child advocacy'/syn OR 'parent*' OR 'proxy' OR 'representative*' OR 'legally acceptable representative' OR 'guardian*' OR 'caregiver*' OR 'care giver*' OR 'surrogate*' OR 'decision making' OR 'capacity' OR 'capab*' OR 'competen*' OR 'legal competenc*' OR 'legally competent' OR 'matur*' OR 'emancipat*' OR 'waiv*' OR 'exempt*' OR 'autonomy') **AND** ('clinical research'/syn OR 'clinical trial'/syn OR 'clinical trial (topic)'/syn OR 'randomized controlled trial'/syn OR 'randomized controlled trial (topic)'/syn OR 'drug research'/syn OR 'research subject'/syn OR 'trial' OR 'trials' OR 'random*' OR 'rct*' OR 'clinical trial' OR 'clinical trials' OR 'clinical research' OR 'pediatric research' OR 'paediatric research' OR 'medical research' OR ('research' NEAR/3 ('child' OR 'adolescent'))) **AND** ('developing country'/syn OR 'poverty'/syn OR 'cultural factor'/syn OR 'global disease burden'/syn OR 'cultural competence'/syn OR 'neglected disease'/syn OR 'resource allocation'/syn OR 'global health'/syn OR 'low income country' OR ('resource*' NEAR/1 ('restricted' OR 'limited' OR 'low' OR 'poor')) OR 'poverty related' OR 'developing world' OR 'less

developed' OR 'less advanced' OR 'lmic*' OR 'low and middle income' OR 'global*' OR 'developing countr*' OR 'international*') **AND** ([english]/lim OR [french]/lim) **AND** [humans]/lim

Embase (updated search)

('Informed Consent'/exp OR 'informed consent legal aspects'/exp OR 'Parental Notification'/exp OR 'patient information'/exp OR 'parental consent'/exp OR "patient information":ti,ab OR consent:ti,ab OR consented:ti,ab OR consenting:ti,ab OR assent*:ti,ab OR "parental permission*":ti,ab) **AND** ('minor (person)'/exp OR 'Child'/exp OR 'Adolescent'/exp OR 'Pediatrics'/exp OR 'adolescent pregnancy'/exp OR 'adolescent parent'/exp OR 'parental Age'/exp OR 'Vulnerable Population'/exp OR 'child health care'/exp OR 'pediatric hospital'/exp OR 'pediatric intensive care unit'/exp OR minor*:ti,ab OR pediatr*:ti,ab OR paediatr*:ti,ab OR child:ti,ab OR children:ti,ab OR childhood:ti,ab OR infant*:ti,ab OR newborn*:ti,ab OR "new born*":ti,ab OR baby:ti,ab OR babies:ti,ab OR neonat*:ti,ab OR perinat*:ti,ab OR postnat*:ti,ab OR kid:ti,ab OR kids:ti,ab OR boy*:ti,ab OR girl*:ti,ab OR preschool*:ti,ab OR kindergar*:ti,ab OR prepuberty*:ti,ab OR prepubescen*:ti,ab OR juvenil*:ti,ab OR youth*:ti,ab OR puber*:ti,ab OR pubescen*:ti,ab OR schoolchild*:ti,ab OR highschool*:ti,ab OR underaged*:ti,ab OR underage:ti,ab OR teen*:ti,ab OR adolescen*:ti,ab) **AND** ('Parent'/exp OR 'custodial care'/exp OR 'Caregiver'/exp OR 'Decision Making'/exp OR 'jurisprudence'/exp OR 'mental capacity'/exp OR 'Comprehension'/exp OR 'legal competence'/exp OR 'legal liability'/exp OR 'patient Autonomy'/exp OR 'Child Welfare'/exp OR 'Infant Welfare'/exp OR 'maturity'/de OR 'child advocacy'/exp OR parent*:ti,ab OR proxy:ti,ab OR representative*:ti,ab OR guardian*:ti,ab OR caregiver*:ti,ab OR "care giver*":ti,ab OR surrogate*:ti,ab OR "decision making*":ti,ab OR capacity:ti,ab OR capab*:ti,ab OR competen*:ti,ab OR legal-competen*:ti,ab OR legally-competen*:ti,ab OR matur*:ti,ab OR emancipat*:ti,ab OR waiv*:ti,ab OR exempt*:ti,ab OR autonomy:ti,ab) **AND** ('medical Research'/exp OR 'Clinical Trial (topic)'/exp OR 'Research Subject'/exp OR trial:ti,ab OR trials:ti,ab OR random*:ti,ab OR RCT:ti,ab OR placebo:ti,ab OR research*:ti,ab) **AND** ('Developing Country'/exp OR 'Poverty'/exp OR 'Neglected Disease'/exp OR 'cultural factor'/exp OR 'Appropriate Technology'/exp OR 'Global Health'/exp OR 'health care planning'/exp OR 'global disease burden'/exp OR 'resource allocation'/exp OR 'cultural competence'/exp OR "low income*":ti,ab OR low-resource*:ti,ab OR resource*:ti,ab OR resource-limited:ti,ab OR resource-poor*:ti,ab OR resource-restricted:ti,ab OR "developing countr*":ti,ab OR global*:ti,ab OR international*:ti,ab OR "developing world*":ti,ab OR less-developed:ti,ab OR less-advanced:ti,ab OR poverty-related*:ti,ab OR LMIC*:ti,ab OR low-and-middle-income:ti,ab OR angola:ti,ab OR angolan:ti,ab OR benin:ti,ab OR botswana:ti,ab OR "burkina faso":ti,ab OR "upper volta":ti,ab OR burundi:ti,ab OR "côte d-ivoire":ti,ab OR "cote d-ivoire":ti,ab OR "ivory coast":ti,ab OR cameroon:ti,ab OR camerun:ti,ab OR kamerun:ti,ab OR "central african republic":ti,ab OR chad:ti,ab OR congo:ti,ab OR zaire:ti,ab OR djibouti:ti,ab OR "equatorial guinea":ti,ab OR eritrea:ti,ab OR ethiopia:ti,ab OR gabon:ti,ab OR gambia:ti,ab OR guinea:ti,ab OR "guinea bissau":ti,ab OR kenya:ti,ab OR lesotho:ti,ab OR liberia:ti,ab OR malawi:ti,ab OR mali:ti,ab OR mauritania:ti,ab OR mozambique:ti,ab OR namibia:ti,ab OR niger:ti,ab OR nigeria:ti,ab OR nigerian:ti,ab OR rwanda:ti,ab OR senegal:ti,ab OR "sierra leone":ti,ab OR somalia:ti,ab OR "south africa":ti,ab OR "south sudan":ti,ab OR sudan:ti,ab OR swaziland:ti,ab OR tanzania:ti,ab OR togo:ti,ab OR uganda:ti,ab OR zambia:ti,ab OR sambia:ti,ab OR zimbabwe:ti,ab OR rhodesia:ti,ab OR 'Africa South of the Sahara'/exp) **NOT** (('animal'/de OR 'animal experiment'/exp OR 'nonhuman'/de) **NOT** ('human'/exp OR 'human experiment'/de))

CINAHL (initial search)

"((MH "Consent (Research)") OR (MH "Consent") OR (MH "Protection of Human Subjects") OR (MH "Parental Notification") OR (informed consent*) OR (consent form*) OR "patient information" OR (consent) OR (consented) OR (consenting) OR (assent) OR (parental permission*)) **AND** ((MM "Minors (Legal)") OR (MH "Child") OR (MH "Infant") OR (MH "Child, Preschool") OR (MH "Infant, Newborn") OR (MH "Adolescence") OR (MH "Pediatrics") OR (MH "Adolescent Parents+") OR (MH "Maternal Age+") OR (MH "Adolescent Fathers") OR (MH "Adolescent Mothers") OR (MH "Special Populations") OR (minor*) OR (pediatr*) OR (paediatr*) OR "child" OR "children" OR "childhood" OR (infant*) OR (adolescen*) OR (underaged) OR (under aged*) OR "underage" OR (teen*) OR (minor parent*) OR (under aged* AND parent*) OR (under-aged parent*) OR (underage parent*) OR (under aged* AND mother*) OR (under-aged mother*) OR (underage mother*) OR (minor mother*) OR (teenage parent*) OR (teenage mother*) OR (adolescent parent*) OR (adolescent mother*)) **AND** ((MH "Parents+") OR (MH "Guardianship, Legal+") OR (MH "Caregivers") OR (MH "Decision Making, Patient") OR (MH "Decision Making, Family") OR (MH "Decision Making, Ethical") OR (MH "Liability, Legal") OR (MH "Patient Autonomy") OR (MH "Competence (Legal)") OR (MH "Child Advocacy") OR (MH "Child Custody") OR (MH "Child Welfare") OR (parent*) OR ("proxy") OR (representative*) OR (legally acceptable representative*) OR (guardian*) OR (caregiver*) OR (care giver*) OR

(surrogate*) OR (decision making*) OR (capacity) OR (capab*) OR (competen*) OR (legal competenc*) OR (legally competent*) OR (matur*) OR (emancipat*) OR (waiv*) OR (exempt*) OR ("autonomy")) **AND** ((MH "Experimental Studies+") OR (MH "Clinical Research") OR (MH "Research Subjects") OR "trial" OR "trials" OR (clinical research*) OR "clinical trial" OR "clinical trials" OR (random*) OR (RCT*) OR 'pediatric research' OR 'paediatric research' OR (medical research*) OR ("research") OR ("research" AND "child") OR ("research AND adolescent")) **AND** ((MH "Developing Countries") OR (MH "Poverty+") OR (MH "Cultural Values") OR (MH "Culture") OR (MH "Cultural Competence") OR (MH "Low and Middle Income Countries") OR (MH "Resource Allocation+") OR (MH "World Health") OR (low income*) OR (low resource*) OR (low-resource) OR (resource-limited) OR (resource limited*) OR (resource-poor) OR (resource poor*) OR (resource restricted*) OR (resource-restricted) OR (developing countr*) OR (global*) OR (international*) OR (developing world*) OR (less developed*) OR (less-developed) OR (less advanced*) OR (less-advanced) OR (poverty related*) OR (poverty-related) OR (LMIC*) OR ("low-and middle income") OR ("resource")) Human on 2017-07-28 05:14 AM"

CINAHL (updated search)

((MH "Consent (Research)") OR (MH "Consent") OR (MH "Protection of Human Subjects") OR (MH "Parental Notification") OR TI "patient information" OR AB "patient information" OR TI consent OR AB consent OR TI consented OR AB consented OR TI consenting OR AB consenting OR TI assent* OR AB assent* OR TI "parental permission*" OR AB "parental permission*") **AND** ((MH "Minors (Legal)") OR (MH "Child+") OR (MH "Adolescence+") OR (MH "Pediatrics+") OR (MH "Maternal Age+") OR (MH "Adolescent Parents+") OR (MH "Special Populations") OR (MH "Child Health Services+") OR (MH "Hospitals, Pediatric") OR (MH "Intensive Care Units, Pediatric+") OR TI minor* OR AB minor* OR TI pediatr* OR AB pediatr* OR TI paediatr* OR AB paediatr* OR TI child OR AB child OR TI children OR AB children OR TI childhood OR AB childhood OR TI infant* OR AB infant* OR TI newborn* OR AB newborn* OR TI "new born*" OR AB "new born*" OR TI baby OR AB baby OR TI babies OR AB babies OR TI neonat* OR AB neonat* OR TI perinat* OR AB perinat* OR TI postnat* OR AB postnat* OR TI kid OR AB kid OR TI kids OR AB kids OR TI boy* OR AB boy* OR TI girl* OR AB girl* OR TI preschool* OR AB preschool* OR TI kindergar* OR AB kindergar* OR TI prepuberty* OR AB prepuberty* OR TI prepubescen* OR AB prepubescen* OR TI juvenil* OR AB juvenil* OR TI youth* OR AB youth* OR TI puber* OR AB puber* OR TI pubescen* OR AB pubescen* OR TI schoolchild* OR AB schoolchild* OR TI highschool* OR AB highschool* OR TI under-aged* OR AB under-aged* OR TI underage OR AB underage OR TI teen* OR AB teen* OR TI adolescen* OR AB adolescen*) **AND** ((MH "Parents+") OR (MH "Guardianship, Legal+") OR (MH "Caregivers") OR (MH "Decision Making+") OR (MH "Jurisprudence+") OR (MH "Autonomy+") OR (MH "Child Welfare+") OR (MH "Child Advocacy") OR TI parent* OR AB parent* OR TI proxy OR AB proxy OR TI representative* OR AB representative* OR TI guardian* OR AB guardian* OR TI caregiver* OR AB caregiver* OR TI "care giver*" OR AB "care giver*" OR TI surrogate* OR AB surrogate* OR TI "decision making*" OR AB "decision making*" OR TI capacity OR AB capacity OR TI capab* OR AB capab* OR TI competen* OR AB competen* OR TI legal-competen* OR AB legal-competen* OR TI legally-competen* OR AB legally-competen* OR TI matur* OR AB matur* OR TI emancipat* OR AB emancipat* OR TI waiv* OR AB waiv* OR TI exempt* OR AB exempt* OR TI autonomy OR AB autonomy) **AND** ((MH "Research, Medical") OR (MH "Clinical Research") OR (MH "Research Subjects+") OR TI trial OR AB trial OR TI trials OR AB trials OR TI random* OR AB random* OR TI RCT OR AB RCT OR TI placebo OR AB placebo OR TI research* OR AB research*) **AND** ((MH "Developing Countries") OR (MH "Poverty") OR (MH "Neglected Diseases") OR (MH "Culture+") OR (MH "Cultural Competence") OR (MH "Low and Middle Income Countries") OR (MH "Resource Allocation+") OR (MH "World Health") OR TI "low income*" OR AB "low income*" OR TI low-resource* OR AB low-resource* OR TI resource* OR AB resource* OR TI resource-limited OR AB resource-limited OR TI resource-poor* OR AB resource-poor* OR TI resource-restricted OR AB resource-restricted OR TI "developing countr*" OR AB "developing countr*" OR TI global* OR AB global* OR TI international* OR AB international* OR TI "developing world*" OR AB "developing world*" OR TI less-developed OR AB less-developed OR TI less-advanced OR AB less-advanced OR TI poverty-related* OR AB poverty-related* OR TI LMIC* OR AB LMIC* OR TI low-and-middle-income OR AB low-and-middle-income OR TI angola OR AB angola OR TI angolan OR AB angolan OR TI benin OR AB benin OR TI botswana OR AB botswana OR TI "burkina faso" OR AB "burkina faso" OR TI "upper volta" OR AB "upper volta" OR TI burundi OR AB burundi OR TI "côte d'ivoire" OR AB "côte d'ivoire" OR TI "cote d'ivoire" OR AB "cote d'ivoire" OR TI "ivory coast" OR AB "ivory coast" OR TI cameroon OR AB cameroon OR TI camerun OR AB camerun OR TI kamerun OR AB kamerun OR TI "central african republic" OR AB "central african republic" OR TI chad OR AB chad OR TI congo OR AB congo OR TI zaire OR AB zaire OR TI djibouti OR AB djibouti

OR TI "equatorial guinea" OR AB "equatorial guinea" OR TI eritrea OR AB eritrea OR TI ethiopia OR AB ethiopia OR TI gabon OR AB gabon OR TI gambia OR AB gambia OR TI guinea OR AB guinea OR TI "guinea bissau" OR AB "guinea bissau" OR TI kenya OR AB kenya OR TI lesotho OR AB lesotho OR TI liberia OR AB liberia OR TI malawi OR AB malawi OR TI mali OR AB mali OR TI mauritania OR AB mauritania OR TI mozambique OR AB mozambique OR TI namibia OR AB namibia OR TI niger OR AB niger OR TI nigeria OR AB nigeria OR TI nigerian OR AB nigerian OR TI rwanda OR AB rwanda OR TI senegal OR AB senegal OR TI "sierra leone" OR AB "sierra leone" OR TI somalia OR AB somalia OR TI "south africa" OR AB "south africa" OR TI "south sudan" OR AB "south sudan" OR TI sudan OR AB sudan OR TI swaziland OR AB swaziland OR TI tanzania OR AB tanzania OR TI togo OR AB togo OR TI uganda OR AB uganda OR TI zambia OR AB zambia OR TI sambia OR AB sambia OR TI zimbabwe OR AB zimbabwe OR TI rhodesia OR AB rhodesia OR (MH "Africa South of the Sahara+")) **NOT** ((MH "animals+") **NOT** (MH "humans+"))

Google Scholar (initial search)

1. consent ("minor parent" OR parental OR "adolescent parent" OR "teenage parent") (representative OR proxy OR guardian OR "caregiver" OR surrogate OR mature OR emancipated OR autonomy) ("clinical trial" OR "clinical trials") "developing countries"
2. consent ("adolescent mother" OR "minor mother" OR "teenage mother" OR "underage mother") ("clinical trial" OR "clinical trials") "developing countries"
3. Search for related papers of "McAdams JJ 2013, Determining the Consenting Capacity of Minors"
   Limit all searches to languages (Engl & French)

Google Scholar (updated search)

1. consent ("minor parent" OR parental OR "adolescent parent" OR "teenage parent") (representative OR proxy OR guardian OR "caregiver" OR surrogate OR mature OR emancipated OR autonomy) ("clinical trial" OR "clinical trials") "developing countries"
2. consent ("adolescent mother" OR "minor mother" OR "teenage mother" OR "underage mother") ("clinical trial" OR "clinical trials") "developing countries"
3. Search for related papers of "McAdams JJ 2013, Determining the Consenting Capacity of Minors"
   No limitations

6.11 Inaccessible documents from Manuscript II

Table S8: Articles, conference abstracts, and books not analysed due to missing access or systematic exclusion

Author	Titel	Journal/Publisher	Access	Type
(1974)	Biomedical technology - the ethical dilemmas	JSAC Grapevine	No access	Journal Article
(1993)	Recommendations of the International Symposium on Contraceptive Research and Development for the Year 2000 and Beyond	Progress in Human Reproduction Research	No access	Conference Abstract
Abdulah Aziz et al. (2011)	Acceptability of short-course AZT prevention regimen by HIV infected pregnant women; should VCT in the Antenatal setting be modified	Sexually Transmitted Infections	No access	Conference Abstract
Addissie and Mitiku (2017)	Validating and promoting 'rapid ethical assessment' as a practical method for enhancing ethical conduct of tropical disease research projects in developing countries	Tropical Medicine and International Health	No access	Conference Abstract (Poster)
Anne-Laure et al. (2009)	Clinical research in less economically developed countries: The ethical challenges	Tropical Medicine and International Health	No access	Conference Abstract
Bachenheimer and Brescia (2007)	Reinventing patient recruitment: revolutionary ideas for clinical trial success	Gower Publishing, Ltd.	No access	Book
Ballantyne and Rogers (2016)	Pregnancy, vulnerability, and the risk of exploitation in clinical research	Springer		Book Section
Barnabas et al. (2008)	HIV/AIDS Vaccine Research	Springer	No access	Book Section
Barrett et al. (2016)	Public health research	Springer	No access	Book Section
Baud et al. (2017)	Dosage regimen of biperiden to treat haloperidol-induced severe facio-troncular dystonic syndrome in children	Annals of Intensive Care	No access	Conference Abstract
Behrman and Field (2004)	Ethical conduct of clinical research involving children	National Academies Press		Book (Booklet)
Benedetti and Kesselheim (2016)	Ethics in Pediatric Oncology	Springer		Book Section
Benson and Roth (1988)	Trends in the social control of medical and psychiatric research	Law and mental health		Book Section
Bentley et al. (2013)	The breastfeeding, antiretrovirals, and nutrition (BAN) study in Malawi: Use of qualitative methods to guide study design and evaluation of a randomized controlled trial	Annals of Nutrition and Metabolism	No access	Conference Abstract
Berg (2005)	Children and placebos	Ethics and Research with Children: A Case-Based Approach		Book
Berman and Field (2004)	The ethical conduct of clinical research involving children	National Academies Press		Book

Bhutta and Offringa (2015)	Standards of Research for Clinical Trials in Low-and Middle-Income Countries	Springer		Book
Bogie et al. (2015)	Non-invasive haemoglobin measurements for assessing anaemia in Kenyan school children as part of an integrated school health and nutrition programme	Archives of Disease in	No access	Conference Abstract
Bonsall et al. (2018)	HIV genotyping and phylogenetics in the HPTN 071 (PopART) study: Validation of a high-throughput sequencing assay for viral load quantification, genotyping, resistance testing and high-resolution transmission networking	Journal of the International AIDS Society	No access	Conference Abstract
Caporale and Pavone (2018)	International Biolaw and Shared Ethical Principles (by Caporale), The Universal Declaration on Bioethics and Human Rights as a landmark in the development of global bioethics (by Henk Ten Have)	Routledge	No access	Book Section
Chaponda (2012)	Ethical challenges in the conduct of the study-evaluation of four artemisinin-based combinations for the treatment of uncomplicated malaria in African children at the Ndola site	Tropical Medicine and Health	No access	Conference Abstract
Chi et al. (2014)	Risk-Benefit Assessment	Research Ethics in Africa: A Resource for Research Ethics committees		Book
Chi et al (2014)	10 Risk-benefit Assessment	-		Book
Clarke et al. (2005)	Research with children	A Handbook of Research Methods for Clinical and Health Psychology	No access	Book Section
Clarke et al. (2012)	A new approach for malaria control in schools: Results of a randomized trial of intermittent parasite clearance	American Journal of Tropical Medicine and Hygiene	No access	Conference Abstract
Close (2010)	The effect of probiotics in reducing the duration of acute infectious diarrhea in children: a literature review	International Journal of Probiotics & Prebiotics	No access	Journal Article
Coffin and Nelson (2005)	Optimizing Risks and Benefits: The Case of Rotavirus Vaccine	Ethics and Research with Children: A Case-Based Approach	No access	Book Section
Corneli and Borasky (2014)	Research Ethics and Working With Institutional Review Boards	Public Health Research Methods	No access	Book Section
Coughlin (2013)	Ethical issues in cancer epidemiologic studies	Cancer Epidemiology: Low-and Middle-Income Countries and Special Populations		Book
Darabi et al. (2013)	The effect of vitamin D supplementation over asthma outcome	Iranian Journal of Allergy, Asthma and Immunology	No access	Journal Article
de Zulueta (-)	HIV in pregnancy: ethical issues in screening and therapeutic research	Maternal-fetal medicine	No access	Journal Article
Dhai (2002)	Clinical Research in Africa	-	No access	Journal Article
Dickert and Grady (2008)	Incentives for research participants	Clinical Research Ethics	No access	Book Section
Duke (2016)	Randomised trials in child and adolescent health in developing countries	-		Book

Ferris and Marquis (2005)	Bioethics in scientific research: Conflicts between subject's equitable access to participate in research and current regulations	The Journal of nutrition	No access	Symposium Abstract
Field and Behrman (2004)	The necessity and challenges of clinical research involving children	Institute of Medicine Committee on Clinical Research Involving Children		Book
Field and Boat (2012)	Ethical Issues in Pediatric Drug Studies	-		Book
Fletcher (1995)	Gene therapy in mental retardation: ethical considerations	Mental retardation and developmental disabilities research reviews	No access	Journal Article
Fletcher and Richter (1996)	Ethical issues of perinatal human gene therapy	J Matern Fetal Med	No access	Journal Article
Foxcroft (2017)	Ethical Issues in Conducting Child Development Research in Sub-Saharan Africa	Springer	No access	Book Section
Friele (2012)	3.2 Die Deklaration von Helsinki und die Regelung des Informed consent–Zur Berücksichtigung interkultureller Aspekte nach der Revision von	Die Deklaration von Helsinki: Revisionen und Kontroversen	No access	Book Section
Gangestad and Salata (2012)	Ethical issues in microbicide clinical trials for HIV prevention	Current HIV research	No access	Journal Article
Glover and Nwomeh (2017)	Ethical Considerations in Pediatric Surgery	Pediatric Surgery		Book Section
Goodman and Prineas (1996)	Toward an ethics curriculum in epidemiology	Ethics and epidemiology	No access	Book
Halac et al. (2017)	Workshop: "clinical research in vulvar disease: A multidisciplinary approach"	Journal of Lower Genital Tract Disease	No access	Workshop Abstract
Hamed (2007)	Early Delivery versus Expectant Management in Patients with Preterm Prelabour Rupture of Membranes at 34-37 weeks of Gestation.	The scientific J of Elminia Faculty of medicine	No access	Journal Article - Arabic
Hartnett (2011)	Minority research: building trust project aims to improve participation and strengthen capacity for investigators and IRBs	Research Practitioner	No access	Journal Article
Helmchen et al. (2014)	From exclusion to inclusion: improving clinical research in vulnerable populations; memorandum	-		Book
Hicks (2015)	Ethical and regulatory considerations in the design of traumatic brain injury clinical studies	Elsevier	No access	Book Section (Handbook)
Holzemer (2010)	Responsible conduct of research	Improving health through nursing research		Book Section
Hurst and Elger (2011)	New issues facing IRBs	J Med		Book Section
Ibia and Binkowitz (2016)	General Principles and Considerations in Multiregional Clinical Trials for Simultaneous Global New Drug Development	Multiregional Clinical Trials for Simultaneous Global New Drug Development	No access	Book Section

Ip (2016)	A Relational Account of Global Egalitarian Justice	Springer	No access	Book
Kahn et al. (1998)	Beyond consent: Seeking justice in research	Oxford University Press on Demand	No access	Book
Kartikeyan et al. (2007)	Human Rights, Legal, and Ethical Issues	HIV and AIDS: Basic Elements and Priorities	No access	Book Section
Kasule et al. (1995)	A clinical trial of Exluton, a progestogen only contraceptive pill containing 0.5mg lynestrenol amongst lactating Zimbabwean women	British Journal of Family Planning	No access	Journal Article
King and Nicholson (1986)	Informed consent	Bulletin (Institute of Medical Ethics (Great Britain))	No access	Journal Article
Kleiderman and Knoppers (2017)	Minors and incompetent adults: A tale of two populations	Neuroethics: Anticipating the Future	No access	Book Section
Knoppers and Sprumont (2000)	Human Subjects Research, Ethics, and International Codes on Genetic Research	Encyclopedia of Ethical, Legal and Policy Issues in Biotechnology		Book
Koch and Raschka (2002)	Ethical principles for clinical trials in children	MMW-Fortschritte der Medizin	No access	Journal Article
Kodish (2018)	Oncology Group from 2002 to 2008 and was an appointed member of the Committee on Bioethics of the American Academy of Pediatrics from 1999	Ethics and Research with Children: A Case-Based Approach (2nd Edition)	No access	Book
Kopelman (2000)	Human Subjects Research, Ethics, and Research on Children	Encyclopedia of Ethical, Legal and Policy Issues in Biotechnology		Book
Kruger (2010)	Ethical issues in clinical trials in the developing world	Pediatric Blood and Cancer	No access	Conference Abstract
Kruse-Jarres et al. (2013)	Regional factors influencing participation in clinical trials in hemophilia in the United States of America and South Africa	Journal of Thrombosis and Haemostasis	No access	Conference Abstract
Lambert and Barry (2003)	10 Future challenges for vaccines	The Vaccine Book	No access	Book
Levison and Levison (2001)	Women's health and human rights	Women, Gender, and Human Rights: A Global Perspective, ed. Marjorie Agosin	No access	Book
Lo et al. (2001)	Addressing ethical issues	Designing clinical research		Book
Loue and Okello (2000)	Research bioethics in the Ugandan context. II: Procedural and substantive reform	The Journal of law, medicine & ethics: a journal of the American Society of Law, Medicine & Ethics		Book Section
Loue (2002)	Governing Principles	Legal and Ethical Aspects of HIV-Related Research		Book Section
MacDonald et al. (2019)	193. Ethical Aspects of Involving Children And Adolescents In HIV Research: A Systematic Review of The Empiric Literature	Journal of Adolescent Health	No access	Conference Abstract

Maklehemena (1998)	Voices of women	Integration	No access	Conference Abstract
Manning et al. (2009)	Ethical implications of informed consent in emergent clinical situations in a "Bush Hospital" in Mali	American Journal of Tropical Medicine and Hygiene	No access	Conference Abstract
Maple et al. (2018)	Assessing strategies and capacity for gender integration in HIV biomedical research	AIDS Research and Human Retroviruses	No access	Conference Abstract (Poster)
Marshall (2007)	Ethical challenges in study design and informed consent for health research in resource-poor settings	World Health Organization		Book
Mathuna (2012)	Ethical considerations in designing intervention studies	Intervention research: Designing, conducting, analyzing and funding		Book Section
Maticka-Tyndale (2004)	Dilemmas for obtaining consent when working with children in high AIDS prevalence regions	NCEHR Commun	No access	Journal Article
Miller (2007)	Ethical considerations in multiple sclerosis clinical trials	Multiple Sclerosis Therapeutics, 3rd ed. London, UK: Informa Healthcare		Book Section
Miller (2005)	Ethics in Research	Wiley StatsRef: Statistics Reference Online	No access	Book
Moin (2013)	New ethical and legal challenges and issues in pediatrics	Iranian Journal of Allergy, Asthma and Immunology	No access	Conference Abstract
Mulberg et al. (2013)	Pediatric drug development	John Wiley & Sons	No access	Book
Munir and Earls (1992)	Ethical principles governing research in child and adolescent psychiatry	Journal of the American Academy of Child & Adolescent Psychiatry	No access	Journal Article
Munro (2018)	18.6 Conducting Interventions in Acute Care Settings	Intervention Research and Evidence-Based Quality Improvement: Designing, Conducting, Analyzing, and Funding	No access	Book
Mwale (2017)	Risk, Rewards, and Rational Consent in Healthy Volunteering	Springer		Book Section
Nakalega et al. (2018)	Ethical considerations for involving adolescents aged 16-17 in HIV prevention clinical trials: Community perspectives from Uganda	AIDS Research and Human Retroviruses	No access	Conference Abstract
Nalugoda et al. (2009)	Is there coercion or undue inducement to participate in health research in developing countries? An example from Rakai, Uganda	Journal of Clinical Ethics	No access	Journal Article
Nelson and Classic (2015)	Informed Consent in Radiation Medicine Practice and Research	Radiation Protection in Medical Imaging and Radiation Oncology		Book Section
Nelson and Roth-Cline (2015)	Ethical considerations in the design of pediatric clinical trials in low-and middle-income countries	Springer		Book

O'Mathúna (2018)	Ethical considerations in designing intervention studies	Intervention Research and Evidence-Based Quality Improvement: Designing, Conducting, Analyzing, and Funding	No access	Book Section
Obi (2017)	Global Clinical Research	Springer	No access	Book Section
Oluremi and Moses (2016)	Knowledge and willingness of young adults to participate in early HIV vaccine trials and contraceptive practices in Southwestern, Nigeria	AIDS Research and Human Retroviruses	No access	Conference Abstract (Poster)
Onwuatuelo (2012)	Adolescents' perception of HIV vaccine trials in Nigeria	Tropical Medicine and Health	No access	Conference Abstract
Ott et al. (2013)	Ethics and Vulnerability in International Research with Adolescents	Turkish Archives of	No access	Journal Article
Pedreira Massa (1998)	Research activities in child and adolescent psychiatry: Ethical approach and informed consent	Anales de Psiquiatria	No access	Journal Article
Perrey and Ymba (2009)	From information to the decision: the motives of consent to a vaccine trial for hepatitis B in the Ivory Coast	Journal de bioéthique		Book Section
Petrini (2016)	8 Ethical and deontological issues in paediatric clinical studies: An analysis of documents from national and international institutions	Neurotechnology and Direct Brain Communication: New insights and responsibilities concerning speechless but communicative subjects	No access	Book
Plomer (2013)	The law and ethics of medical research: international bioethics and human rights	Routledge-Cavendish	No access	Book
Pope (2010)	Legal briefing: Informed consent	Journal of Clinical Ethics	No access	Journal Article
Powers et al. (2010)	Patient and parent awareness and concerns with participation in clinical trials	Pediatric Pulmonology	No access	Conference Abstract
Rahimzadeh et al. (2017)	Minors and incompetent adults: A tale of two populations	Neuroethics: Anticipating the future	No access	Book Section
Ravinetto et al. (2016)	Pooling knowledge and experience to improve clinical research standards in low-and middle-income countries: The experience of the switching the poles network (2008-2016)	American Journal of Tropical Medicine and Hygiene	No access	Conference Abstract
Ravinetto et al. (2009)	Informed consent, decision-making capacity and vulnerability in resource-constrained settings	Tropical Medicine and International Health	No access	Conference Abstract
Ravitsky et al. (2009)	The Penn Center Guide to Bioethics	Springer Publishing Company	No access	Book
Rivera et al. (2009)	Research ethics training curriculum	Academy for Educational Dev		Book
Rogowska-Szadkowska and Chlabicz (2008)	Microbicides in HIV infection prophylaxis–not only ethical challenges	HIV & AIDS Review	No access	Journal Article
Roth-Cline et al. (2011)	Ethical considerations in conducting pediatric research	Springer		Book

Royer (1982)	Ethics and pediatrics	Concours Medical	No access	Journal Article
Hurst and Elger (2010)	Research and publication	Clinical Ethics in Anesthesiology: A Case-Based Textbook	No access	Book Section
Sass (2006)	Towards Risk Factor Health Assessment and Education	Springer		Book
Sass (1988)	Dependency on raw nature by building homes, farms, and machines, by healing diseases and developing drugs to treat them, and by establishing	The Use of Human Beings in Research: With Special Reference to Clinical Trials	No access	Book
Simar and Fowler (2010)	Consent and Assent in Paediatric Clinical Trials	Karger Publishers		Book Section
Simon (-)	Clinical Research Ethics	Clinical Research	No access	Journal Article
Sirisena et al. (2016)	The Provision of Medical and Health Genetics and Genomics in the Developing World	Elsevier	No access	Book Section
Slack et al. (2003)	Guidelines on Ethics for Medical Research	South African Medical Research Council		Book
Sullivan et al. (2017)	Malawian women's experiences of rules regarding participation in HIV prevention and treatment clinical trials during pregnancy	American Journal of Obstetrics and Gynecology	No access	Conference Abstract (Poster)
Thorne (1997)	Vancouver Summaries: Children	AIDS Care	No access	Journal Article
Thornthwaite et al. (2016)	Peroxybioflavonoids (MALSUP): A possible cure for severe cases of plasmodium falciparum malaria infection in Nigeria	European Journal of Immunology	No access	Conference Abstract
Totri and Eichenfield (2015)	Clinical Research in Pediatric Dermatology	Springer		Book
Tremellen and Belford (2010)	Ethical Issues in Clinical Research	Pharmaceutical Sciences Encyclopedia	No access	Book
Urato and Lurie (-)	Health and Safety	-	No access	Journal Article
Van Den Bent et al. (2017)	Evaluation of depatuxizumab mafodotin (ABT-414) in children with high grade glioma (HGG) and diffuse intrinsic pontine glioma (DIPG)	Neuro-Oncology	No access	Conference Abstract
VanGeest and Cummins (2008)	International Research Ethics	Global Health Care: Issues and Policies	No access	Book
Wasunna and Bukusi (2014)	6 A Stepwise Approach to Protocol Review	Research Ethics in Africa: A Resource for Research Ethics committees		Book
Watcha et al. (2010)	Validation of the baxter animated retching faces (BARF) scale for measuring nausea in children	Anesthesia and Analgesia	No access	Journal Article
Wawer (2001)	Developing Countries	Epidemiologic Methods for the Study of Infectious Diseases		Book

Weeks (2012)	Community-based use of misoprostol for pph prevention: Snapshot from a pilot study in Uganda documenting self-administration of misoprostol in a home delivery setting	International Journal of Gynecology and Obstetrics	No access	Conference Abstract (Poster)
Williams (2010)	Ethical Challenges in HIV Research and Clinical Care	HIV/AIDS Related Communication, Hearing and Swallowing Disorders	No access	Book Section
Williams (2014)	Capacity building in cancer management in Africa: Envisioning a future from past challenges	Cancer Research	No access	Conference Abstract
Wright and de Chesnay (2015)	Research with Vulnerable Populations: Implications for Developed and Developing Countries	Caring for the Vulnerable	No access	Book Section

6.12 PRISMA Checklist from Manuscript III

Table S9: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	OK: See title (page #1).
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	OK: See (page #2).
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	OK: See Background starting from paragraph 2 (page #3-4).
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	OK: See last paragraph of the Background section (page #4).
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	OK: See Methods section, first paragraph (page #4).
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	OK: See Eligibility criteria (page #5).
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	OK: See Search strategy (page #5).

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	N/A as previously published. Described and referenced in second paragraph of Methods (page #4) and under Search Strategy (page #5).
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	OK: See Eligibility criteria (page #5).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	OK: See Data extraction and analysis (page #5-6).
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	OK: See Data extraction and analysis (page #5-6).
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	OK: See strength and limitations section first paragraph (page #18)
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	OK: See Figure 1 in Results (title on page #7, figure in separate file).
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	OK: See Table 1 including study characteristics in Results section (page #7-9).
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA

Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	OK: As far as applicable presented in Table 2-4 in Results section (page #9-13).
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	OK: As far as applicable presented in Table 2-4 in Results section (page #9-13).
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	OK: As far as applicable presented in Discussion section (page #13-18).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	OK: See strengths and limitations section in Discussion section (page #17-18).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	OK: See Conclusion (page #18).
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	OK: See Funding (page #19).

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

6.13 Inaccessible documents from Manuscript III

Table S10: Articles and conference abstracts not analysed due to missing access

Author	Titel	Journal/Publisher	Access	Type
Baud et al. (2017)	Dosage regimen of biperiden to treat haloperidol-induced severe facio-troncular dystonic syndrome in children	Annals of Intensive Care	No access	Conference Abstract
Bogie et al. (2015)	Non-invasive haemoglobin measurements for assessing anaemia in kenyan school children as part of an integrated school health and nutrition programme	Archives of Disease in	No access	Conference Abstract
Bonsall et al. (2018)	HIV genotyping and phylogenetics in the HPTN 071 (PopART) study: Validation of a high-throughput sequencing assay for viral load quantification, genotyping, resistance testing and high-resolution transmission networking	Journal of the International AIDS Society	No access	Conference Abstract
Clarke et al. (2012)	A new approach for malaria control in schools: Results of a randomized trial of intermittent parasite clearance	American Journal of Tropical Medicine and Hygiene	No access	Conference Abstract
Close (2010)	The effect of probiotics in reducing the duration of acute infectious diarrhea in children: a literature review	International Journal of Probiotics & Prebiotics	No access	Journal Article
Darabi et al. (2013)	The effect of vitamin D supplementation over asthma outcome	Iranian Journal of Allergy, Asthma and Immunology	No access	Journal Article
Hamed (2007)	Early Delivery versus Expectant Management in Patients with Preterm Prelabour Rupture of Membranes at 34-37 weeks of Gestation.	The scientific J of El-minia Faculty of medicine	No access	Journal Article
Kasule et al. (1995)	A clinical trial of Exluton, a progestogen only contraceptive pill containing 0.5mg lynestrenol amongst lactating Zimbabwean women	British Journal of Family Planning	No access	Journal Article
Thornthwaite et al (2016)	Peroxybioflavonoids (MALSUP): A possible cure for severe cases of plasmodium falciparum malaria infection in Nigeria	European Journal of Immunology	No access	Conference Abstract
Van Den Bent et al. (2017)	Evaluation of depatuxizumab mafodotin (ABT-414) in children with high grade glioma (HGG) and diffuse intrinsic pontine glioma (DIPG)	Neuro-Oncology	No access	Conference Abstract
Watcha et al. (2010)	Validation of the baxter animated retching faces (BARF) scale for measuring nausea in children	Anesthesia and Analgesia	No access	Journal Article
Weeks (2012)	Community-based use of misoprostol for pph prevention: Snapshot from a pilot study in Uganda documenting self-administration of misoprostol in a home delivery setting	International Journal of Gynecology and Obstetrics	No access	Conference Abstract (Poster)

6.14 Examples and interpretations of proxy decision-maker definitions

Table S11: Examples of proxy decision-maker definitions and interpretations in various guidelines and contexts

Decision-maker	Legal interpretation	Examples of definitions

Parent	Decision-making authority (right to give permission for child participation) recognised by law	- Defined by national law:
		  - "Parent" includes an adoptive parent (South African Children's Act 38 of 2005 [1])
		  - "Foster parent" (if there is no parent or guardian): per order of Children's Court (South African Children's Act 38 of 2005 [1])
		- May be used in a broader context: "Throughout this report we use the term 'parents' to refer to one or more adults taking on this role of parental responsibility whether or not they have a biological connection with the child. In the UK context, for example, this will include legally appointed guardians and also many others, such as grandparents, who have acquired parental responsibility through a parental responsibility order or residence order." (Nuffield 2015 [2])

Guardian	Decision-making authority exercised by proxy, typically with legal power when permission is delegated to a guardian who is legally appointed (recognised as legal representative, e.g., court-appointed).	- May be a short form for "legal guardian":
		  - "Permission of a parent or legally authorized representative: The researcher must obtain the permission of at least one parent or guardian." (CIOMS 2016 [3])
		  - "[…] permission of a parent, legal guardian or other duly authorized representative." (CIOMS 2016 [3])
		  - "Parental (legal guardian) consent/permission: Expression of understanding and agreement by fully informed parent(s) or legal guardian to permit the investigator/sponsor of a clinical study to enrol a child in a clinical investigation." (ICH-E11 2017 [4])
		  - If "guardian" also equals "legal guardian" interpreted in the sense of "legally acceptable representative" as defined by the ICH-E6 2016 guideline, it relates to any individual authorized under applicable law to consent on behalf of the child, which also covers "parents".
		- May be defined by national law: "Guardian" (if there is no parent): either court-appointed OR as indicated by the parent in a will (South African Children's Act 38 of 2005 [1]).
		- May be used in a broader context: "In accordance with relevant national regulations, the permission of an immediate family member or other person with a close personal relationship with the individual must be sought […] in situations where a legally authorized representative is not available to allow for timely enrolment, researchers may obtain the permission of a representative who is socially accepted but not formally recognised before the law." (CIOMS 2016 [3])

Caregiver	Informal or formal (when recognised as legal representative, e.g., court-appointed) decision-making authority exercised by proxy	- May be short for primary caregiver: "[…] a qualitative study was conducted to explore caregiver and community perceptions […] primary caregivers (i.e., mothers and fathers) of eligible infants […]" (Achieng et al. 2020 [5]). - May be defined by national law: "Caregiver" (if there is no parent, guardian, or foster parent) "[…] any person other than a parent or guardian, who factually cares for a child and includes - a) a foster parent; b) a person who cares for the child with the implied or express consent of a parent or guardian of the child; c) a person who cares for the child whilst the child is in temporary safe care; d) the person at the head of a child and youth care centre where a child has been placed; e) the person at the head of a shelter; f) a child and youth care worker who cares for a child who is without appropriate family care in the community; and g) the child at the head of a child headed household' (South African Children's Act 38 of 2005 [1])

References

1. Slack CM, Strode A. But is this really the ‘parent’ or ‘guardian’? Practical strategies for consent to child research in South Africa. 2016;9:35–8.
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