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Investigator-Initiated Clinical Pharmacokinetic Studies in Resource-Limited Settings: Minimal Requirements and Practical Guidance

The Journal of Clinical Pharmacology
2025, 0(0) 1–13

DOI: 10.1002/jcph.6184

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Abstract

Clinical pharmacology studies are critical for determining the efficacy and safety of drugs. Due to the resource-intensive nature of these studies, most have been conducted in high-income countries, leading to a significant gap in clinical pharmacology data for patients in low- and middle-income countries. This paper provides an overview of the minimal requirements for performing a clinical pharmacology investigator-initiated trial (IIT), including pharmacokinetic sampling. We identify common challenges in resource-limited settings and propose strategies to overcome them. This guideline covers regulatory approval, participant recruitment, drug storage, sample collection and handling, transport, bioanalytical analysis, and data management tailored to the constraints of resource-limited settings. Strategies are proposed to minimize resource demands, including simplified study designs, the use of technologies like whole blood microsampling, and opportunities for collaboration. The goal is to provide practical guidance for those seeking to perform a clinical pharmacology IIT in resource-limited settings to improve safe and effective drug treatment for patients worldwide. Beyond the scope of this guideline is a detailed step-by-step guide on how to perform clinical pharmacology studies.

Keywords

clinical pharmacology, guideline, investigator-initiated study, low- and middle-income countries, pharmacokinetics, pharmacology

Introduction

A clinical pharmacology study investigates how a drug affects humans, focusing on how the body absorbs, distributes, metabolizes, and excretes the drug (pharmacokinetics [PK]) and understanding the effects on the body, including the mechanism of action and therapeutic efficacy (pharmacodynamics [PD]).[1,2] Clinical pharmacology studies are essential for determining the appropriate dosage, assessing safety and tolerability, identifying potential side effects, and understanding drug interactions.[1,2] They are a vital component of the

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Submitted for publication 24 September 2024; accepted 18 December 2024.

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drug development process, ensuring new medications are effective and safe for patients.[1,2] Clinical pharmacology studies can be conducted at various stages, from early-phase trials in healthy volunteers to post-marketing studies for approved drugs.[1,2]

Clinical pharmacology studies are essential for optimizing medication use across all patient populations. However, these studies are typically resource intensive, which has led to the majority being conducted in high-income countries (HICs).[3–5] This has resulted in a significant gap in clinical pharmacology data for patients in low- and middle-income countries (LMICs) with limited resources.[3–5] Considering genetic differences, lifestyle and diet variations, and distinct disease patterns between populations, conducting clinical pharmacology studies in these settings is crucial.[3,4] For example, genetic variations in the CYP2C9 and VKORC1 genes influence the metabolism and response to warfarin.[6] Studies have shown that specific VKORC1 variants are more common in Asian populations, leading to a higher risk of bleeding at standard doses of warfarin.[6] Similarly, black patients often have a higher prevalence of specific CYP2C9 variants associated with reduced enzyme activity, which can increase their risk of bleeding or reduce efficacy if underdosed. These genetic differences underscore the importance of targeted research in various populations to optimize drug dosing. Furthermore, patients in LMICs are often underrepresented in early-phase studies,[3] highlighting the need for post-marketing surveillance in these populations. Barriers to conducting clinical pharmacology studies in LMICs include high costs, competing national budget priorities, and a shortage of clinical pharmacologists.[7,8] To address this, it has been proposed that physicians be trained as clinical pharmacologists who can lead investigator-initiated trials (IITs) that focus on locally relevant issues, utilize available resources, and build local research capacity.[7] IITs are initiated and led by a researcher, the principal investigator (PI), rather than by a pharmaceutical company.[9] In IITs, the PI assumes the primary responsibility for the conception, design, execution, and management of the study.[9] Pharmaceutical companies often offer guidelines for those interested in performing IITs. Nonetheless, conducting clinical pharmacology IITs, particularly those involving PK sampling, remains challenging since this is knowledge intensive and resource demanding. Previous studies have shown that despite challenges, it is feasible.[10–16]

Recognizing the importance of conducting these studies in resource-limited settings, and given the existing barriers, we provide an overview of the minimal requirements for performing a clinical pharmacology IIT, including PK sampling. This is based on a literature review, guidelines, and expert consultation on conducting clinical trials in resource-limited settings. Beyond the scope of this paper is a detailed step-by-step guide on how to perform clinical pharmacology studies. We offer practical guidance on meeting the minimal requirements by referencing relevant good clinical practice (GCP) guideline items,[9] identifying common challenges in resource-limited settings, and proposing strategies to overcome them.

Overview of the Minimal Requirements

The minimal requirements for performing an investigator-initiated clinical pharmacology study, which includes PK sampling, are shown in Figure 1 and Table 1. The practical guidelines on how to meet these requirements are discussed as per requirement.

Regulatory Authorities and Institutional Review Boards

Approval from an institutional review board/independent ethics committee (IRB/IEC) is mandatory before starting the study. Depending on the study site, approval from regulatory authorities such as the Pharmacy and Poisons Board(PPB) in Kenya or the South African Health Products Regulatory Authority (SAHPRA) might be necessary. Regulatory authorities are national agencies that are responsible for overseeing the safety, efficacy, and quality of drugs and clinical trials. A well-defined research question with local relevance and simplified study protocols ensure the feasibility of the study. Obtaining regulatory approval can be time consuming; it might be beneficial to contact the regulatory committee in advance to discuss important requirements or submission formats. For minor reviews in ongoing clinical trials, IRB/IECs are required to provide expedited review.[9]

Many regulatory committees request signed contracts between relevant parties. Contracts to consider include a material transfer agreement if materials are transferred between organizations, a service agreement if any services are performed by, for example, external laboratories, a data sharing agreement if any collaborating parties are involved, and a financial agreement for external funding. Furthermore, in clinical pharmacology studies, participant insurance is most likely necessary. The study should be prospectively registered in a study registry. The WHO has defined study registry criteria and lists eligible registries on its website.[17]

Recruitment of Participants

The investigator-sponsor (hereafter referred to as the investigator) must demonstrate to the IRB/IEC the potential for recruiting an adequate number of suitable participants. However, the number of patients with certain diagnoses or characteristics may be unknown. In such cases, an observational study can be conducted

Table 1. Overview of Minimal Requirements to Perform a Clinical Pharmacology Study, Including Challenges That May Be Encountered and Offered Strategies for Overcoming These Challenges

Minimal Requirement	Relevant Guideline Items (9, 59)	Challenge	Strategy
Regulatory requirements, contracts, and study registration			
Approval from regulatory authorities and institutional review board	GCP Principle 2.6	Regulatory approval has an unpredictable timeline.	Contact the regulatory committees prior to submission to discuss requirements and the use of formatted documents.
	GCP 3.3.5		In case of minor revisions, expedited review should be offered by the IRB/IEC.
Signed contracts between relevant parties	GCP 5.8.1	No templates for relevant contracts are available.	Use available online templates, customize them as needed, and discuss them with legal experts or relevant parties.
Study registration	-	Most appropriate study registry is unknown.	Select a trial registry that meets the WHO Registry Criteria (17).
Recruitment of participants			
Access to sufficient suitable participants	GCP 4.2.1	Not able to demonstrate that recruiting the required number of suitable participants is feasible.	Conduct study in which the number of patients with the diagnosis of interest is collected.
		Exact age of participants is unknown whilst this is an in- or exclusion criterion of the study.	Request birth certificate. Exclude participants of unknown age from participating (include this in study protocol).
Qualified informed consent administrator	GCP 4.2.3	Informed consent administrator has not completed GCP training.	Free GCP training: National Drug Abuse Treatment Clinical Trials Network: https://gcp.nidatraining.org/ Global Health Training Center: https://globalhealthtrainingcentre.tghn.org/ich-good-clinical-practice/
Appropriate informed consent forms	GCP 4.8.5	Multiple languages are spoken within the same site.	Provide informed consent forms in all relevant languages.
		Due to existing hierarchical structures, there might be a risk of agreeing to participate in a study to respect the hierarchy.	Request participant to summarize informed consent discussion in their own words. Conducting informed consent discussion without the treating or senior physician.
		As a consequence of participating in the study, participants have to stay overnight.	Explicitly mention this in informed consent form. Facilitate overnight stay (e.g., in hospital or nearby lodging). Develop a protocol which includes sparse rather than extensive sampling. Select sample collection method that allows for self-collection (whole blood microsampling).
	GCP 4.8.8	Participant or their legally acceptable presentative does not have a signature.	If allowed by the local regulatory authorities, make use of fingerprint signing.
	GCP 4.8.9	Participants or their legally acceptable representative are illiterate.	Include an impartial witness in the informed consent discussion.
	GCP 3.1.8	In impoverished patients, there might be a high risk of financial incentive for participating in the study.	Tailor financial compensation to actual costs through careful budgeting and inform participants about this in the informed consent form.

(*Continued*)

Table 1. (Continued)

Minimal Requirement	Relevant Guideline Items (9, 59)	Challenge	Strategy
Drug storage and dispensing			
Location for drug storage	GCP 5.13.1	Designated storage location is not available due to space challenges.	Investigate drugs that already have designated space in the pharmacy. Obtain a storage box that can be placed in the pharmacy.
		Access to designated storage location cannot be limited to study personnel.	Obtain a storage box that can be locked and placed in the pharmacy.
Availability of sufficient drug	GCP 5.14.1	Study drug is not (consistently) available.	Stop participant recruitment and inclusion during stockouts. Budget for the drug and monitor the stock for the study participants. Contact pharmaceutical companies or supplier if they have the drug available for donation.
		Substandard or counterfeit study drug.	Perform a quality control of the study drug before and during the study.
Sample collection			
Access to sample site	-	No or difficult to obtain intravenous access.	Select a sample collection method that does not require intravenous access.
Qualified staff for sample collection	GCP 4.2.3	Low availability of clinical staff.	Hire dedicated staff for sampling. Select a study design that allows for sparse sampling per participant in wider time frames. Perform sampling on days when staff is known to be available. Consider self-collection of whole blood microsamples in adult participants that can be properly trained.
Transport to laboratory/storage (bed to bench)	GLP 6.1.2	Concerns about stability of the product during (time to) transport to laboratory or storage location.	Select a sample matrix that remains stable under various conditions. Validate the stability of the samples under various conditions.
Sample handling and storage			
Processing on time and under the right conditions	ICH guideline M10	Sample processing is not available on-site.	Select a sample matrix that does not require processing (DBS, VAMS). Transport the sample within the appropriate time frame to a nearby facility that does have adequate processing facilities.
		Doing sample processing within a limited time frame is not possible.	Select a sample matrix that does not require processing (DBS, VAMS). Validate the maximum time frame for sample processing.
Accurate labeling and storage under the right conditions	GLP 6.1.2	Refrigerated sample storage is not available on-site.	Select a sample matrix that does not require refrigerated sample storage (DBS, VAMS). Transport the sample within the appropriate time frame to a nearby facility that does have adequate storage facilities.
		Samples are mislabeled or get lost.	Dedicate a specific section of the storage facility to the study. Write a SOP and train the involved staff.

(*Continued*)

Table 1. (Continued)

Minimal Requirement	Relevant Guideline Items (9, 59)	Challenge	Strategy
Transport to bioanalytical laboratory			
Courier capable of shipping under appropriate conditions	GLP 6.1.2	Temperature-controlled transport is unavailable.	Select a sample collection method that does not require temperature-controlled transport.
		Concerns about stability of the product during transport to bioanalytical laboratory.	Validate the stability of the samples after transport. Check temperature logs.
Bioanalytical method			
Validated bioanalytical method	ICH guideline M10	Validated bioanalytical method is not available in the country of sample collection.	Collaborate with laboratory as close as possible. Contact pharmaceutical companies if they have equipment available for donation.
		LC-MS/MS is not available.	Use of LC with alternative detection methods (e.g., UV, fluorescence).
Availability of reference compound and internal standards		Reference compound or internal standards are not (consistently) available.	Prepare sufficient stock of reference compound and internal standards. Contact pharmaceutical companies or supplier if they have reference compound or internal standards available for donation.
Biostatistics			
Sufficient expertise in conducting biostatistical analysis	GCP 5.4.1	Insufficient expertise in the use of the software or in conducting the biostatistical analyses.	Consider performing an NCA. Contact pharmacometrics group for support.
	GCP 5.5.1		Online support. Training to build capacity.
Software for conducting biostatistical analysis	-	Software license is not available.	Make use of open-source software. Contact software company if license costs can be waivered.
Data collection			
Data collection system	GCP 4.9.1	Electronic data collection in the field is not possible (e.g., no stable internet, no devices for electronic data collection).	Select an electronic data collection system that can collect data offline (REDCap, Castor). Collect data on paper and transfer to electronic data collection system. Collect data on paper.
	GCP 4.9.3	Electronic data collection is too expensive.	Select electronic data collection system that is free or offers reduced pricing (REDCap, Castor).
Publication and local dissemination			
Publication of study results	-	Publication fees are too expensive.	Select an open-access journal with no or reduced publication fees for researchers from resource-limited settings. Include publication fees while drafting the study budget.
		Challenges in finding a journal interested in publishing the study results.	Reach out to a journal editor before beginning the study to discuss their potential interest in publishing it and inquire about the possibility of a publication fee waiver.

DBS, dried blood spots; GCP, good clinical practice; IRB/IEC, institutional review board/independent ethics committee; NCA, non-compartmental analysis; SOP, standard operating procedure; UV, ultraviolet, VAMS, volumetric absorptive microsampling; WHO, World Health Organization.

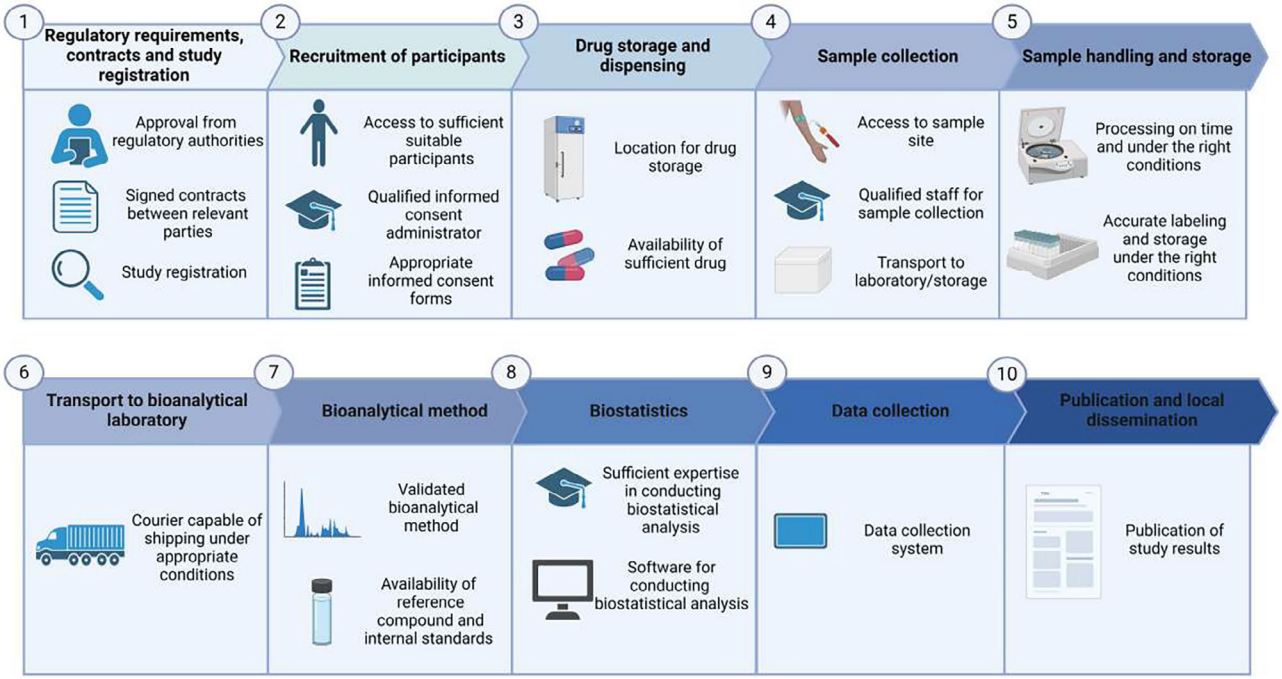

Figure 1. Flowchart of the minimal requirements for performing an investigator-initiated clinical pharmacology study, including PK sampling. Image created with Biorender.com.

to collect the baseline characteristics of the patient population of interest.[18–20]

Informed consent administrators should be qualified to conduct the informed consent discussion. If unqualified, training should be done before the study begins. They can also register for free online GCP courses, such as the Global Health Network's ICH GCP course (available at https://globalhealthtrainingcentre.tghn.org/ich-good-clinical-practice/).

In resource-limited settings, suitable participants might be vulnerable subjects. This includes impoverished patients. Their decision to participate might be unduly influenced by expectations of benefit from participation or fear of negative consequences if they choose to refrain from participating.[9] To avoid financial incentives, any financial compensation should be closely aligned with actual costs made by the participant, such as travel costs. A detailed breakdown of these costs in the informed consent form can help mitigate financial incentives. Additionally, the informed consent discussion should be conducted without senior or treating physicians to avoid hierarchical pressure,[21] and it should be clearly communicated that standard care will continue regardless of participation.

Malnutrition is a public health concern in LMICs, where it accounts for up to 50% of mortalities in children below 5 years of age.[22] Conditions such as Kwashiorkor may cause physiological changes such as hypoalbuminemia,[23] reduced hepatic basal metabolic rate,[24] and glomerular filtration rate (GFR).[25] These changes significantly alter the pharmacokinetics of drugs, leading to reduced efficacy or increased toxicity.[22] Investigators in LMICs should be aware of the impact of malnutrition on the pharmacokinetics of drugs and account for these effects when designing their studies.

Practical challenges may also hinder patient participation. If a participant is illiterate, an impartial literate witness should be present during the informed consent discussion.[21] They should read the informed consent form and any other written information to the participant and confirm their understanding of the study.[9] However, instead of witnesses guiding the study participants to make informed decisions, they most often influence them based on personal perspectives.[26] To avoid this, recruit and train impartial witnesses or have the participants choose a trusted individual to witness for them.[26]

Some LMIC countries, such as India, now require audiovisual evidence of the informed consent process in low-literacy settings.[21] This poses several challenges, including subjects refusing to be recorded and the process being tedious and time consuming.[27] Investigators also need to be aware of the cultural differences in LMICs. Gender hierarchy and decision-making processes may differ significantly when compared to HICs. For instance, in pediatric patients, male caregivers may make the final decision on whether a child can join a study or not.[28] Fathers are more likely to ask questions during consenting, and there is more participation during the

consenting process if both caregivers are present.[29] While it may not be easy, investigators should put more effort into ensuring that both caregivers are present during the consenting process. Investigators should also seek to understand the culture of their study population so that they can design their informed consent process appropriately.

Additionally, clinical pharmacology studies often require extended hospital stays for participants due to PK sampling schedules. Participants may live far from the hospital in resource-limited settings, making overnight stays necessary. Participants should be informed of this in the consent form. Overnight stays should be accommodated (e.g., in the hospital or in nearby lodging). If this is not feasible, a sparse sampling strategy could be employed, allowing participants who cannot stay to leave while collecting necessary time points from those who can stay longer or are already admitted. Alternatively, a sample collection method that permits self-collection could be chosen if this is considered appropriate for the selected patient population (see section "Sample collection").

Drug Storage and Dispensing

The investigator establishes standard operating procedures (SOPs) for handling the study drug (investigational product [IP]) in accordance with GCP. The SOPs must outline the manufacturer's specific storage requirements, including temperature and humidity logs. Equipment such as thermometers should be kept up to date with temperature logs and calibration records. The study site should have a secure pharmacy, staffed by a qualified pharmacist, which meets the minimum requirements, including a designated area for the study drug. Having a designated storage location is only sometimes feasible due to space challenges. This can be overcome by using study drugs already stored in the pharmacy. Another strategy is to use a storage box within the pharmacy, with access restricted to the study pharmacist, who will monitor the storage conditions.

All pharmacy staff handling the study drug should be thoroughly trained. A pharmacy SOP on handling and dispensing the study drug should be developed and regularly reviewed. Good dispensing SOPs should be followed with adequate records of the details of the drug dispensed and the recipient of the drug.

In resource-limited settings, a common challenge is frequent stockouts of the study drug. During stockout periods, participant recruitment might be temporarily halted. However, it is preferred that the study drug stock be budgeted and monitored for study participants. Alternatively, pharmaceutical companies or suppliers could be contacted for potential donations. The Access to Medicine Foundation compiles the Access to Medicine Index, listing companies that actively work to make their products more accessible in LMICs.[30] Moreover, the risk of substandard or counterfeit drugs in resource-limited settings has been reported.[31–33] To mitigate this risk, quality control measures should be implemented before and during the study, following methods such as those outlined in the European Pharmacopoeia (Ph. Eu.).[34]

Sample Collection

The sampling schedule in a clinical pharmacology study is determined by the study design and the specific research questions being addressed. Generally, two standard study designs are used for PK studies: full-profile sampling, analyzed using non-compartmental analysis (NCA), and sparse sampling, analyzed using population PK modeling.

In full-profile sampling, fixed sampling time points are established based on key PK parameters, such as the maximum concentration (C_{max}), trough concentration (C_{trough}), and half-life ($T_{1/2}$).[35] This approach requires intensive sampling from all participants, with relatively few participants typically included in the study.[35] The analysis hinges on the availability of samples collected precisely within the pre-determined time windows; missing or mistimed samples can significantly impact the reliability of the results.[35] However, NCA is a straightforward method that does not require specialized software, making it accessible for many researchers (see section "Biostatistics"). Sparse sampling, in contrast, offers greater flexibility by allowing sampling at various time points across participants.[36] In both sampling methods, measurements are combined into a population PK model, which accounts for variability between individuals and provides a more comprehensive understanding of the drug's behavior in the population.[36] In sparse sampling, missing samples are permissible as the model can still generate meaningful insights from the available data.[36] However, population PK analysis is more complex, requiring advanced statistical methods and specialized software, which demands more significant resources than NCA (see section "Biostatistics"). The choice between full-profile and sparse sampling depends on the study's objectives.[37] Full-profile sampling is ideal for studies aiming to precisely define PK parameters in a small group, while sparse sampling and population PK modeling are better suited for understanding drug behavior across a broader population, particularly when individual sampling schedules need to be flexible.[37]

Access to the sample site depends on the selected sample matrix. PK sampling is typically done using blood. If plasma is the final product, intravenous access is required. In resource-limited settings, central venous access through peripherally inserted central catheters (PICCs) or tunneled or non-tunneled central venous

catheters (CVCs) is often not feasible. Therefore, peripheral intravenous cannulas are often the only option for obtaining intravenous access. However, blockage may occur because clinical pharmacology studies often involve frequent sampling. Replacement of peripheral intravenous cannulas should be avoided as much as possible because it may cause complications and is burdensome. Furthermore, plasma samples require cold-chain transport and storage.

An alternative approach is whole blood microsampling, where small volumes of blood (10–30 μL) are collected, typically through a prick on the finger, heel, or earlobe.[38] This method is particularly advantageous for frequent sampling or dealing with children or critically ill patients, as it minimizes the required blood.[39] Additionally, whole blood microsampling is less painful and uncomfortable for the patient; in some cases, it can be performed by the patient themselves.[39] Whole blood microsampling can be done through capillary microsampling, which collects blood in a capillary tube coated with an anticoagulant.[40] Like plasma sampling, this method produces a liquid sample, which usually requires cold-chain transport and storage. Alternatively, blood can be collected on dried materials, such as dried blood spot (DBS) cards, or through volumetric absorptive microsampling (VAMS) technologies.[41,42] These methods do not require cold-chain transport or storage, as the samples can be stored at ambient temperature.[41,42] While DBS cards can be affected by hematocrit levels, this is less of an issue with VAMS.[41,42] Of note is that most PK studies report plasma values. Whole blood and plasma analyte concentrations are not directly comparable, and this distinction should be carefully considered when interpreting the results.

Samples need to be collected by qualified clinical staff. In resource-limited settings, clinical staff often juggle multiple responsibilities and may not always be available to collect samples at precise time points. If hiring dedicated staff is not feasible, a sparse sampling design might be considered. Alternatively, sampling could be scheduled for days when clinical staff availability is higher. For adult study participants, self-collection of whole blood microsamples can be an option if participants can be adequately trained.

The sample must be transported to the laboratory or the storage location under appropriate conditions. Selecting a sample collection method with minimal transport requirements, such as dried microsampling, can simplify logistics. Alternatively, during the validation of the bioanalytical assay, a more comprehensive range of conditions could be assessed (e.g., whether the sample can be transported within a wider time frame or without temperature control).

Sample Handling and Storage

Venous samples must be processed on-site to obtain plasma, typically requiring a refrigerated centrifuge. This can be challenging when such equipment is unavailable due to high costs or unreliable electricity. One option is to select sites with the necessary equipment or collaborate with nearby facilities that can provide processing and storage facilities. However, this may necessitate cold-chain transport of samples, which can be expensive. It may be worth exploring whether the processing time frame can be extended without compromising the validity of the study results. This could reduce costs by allowing the collection of more samples before transporting them to the laboratory rather than making frequent trips with smaller batches. An alternative approach is to use whole blood-dried microsampling methods like DBS or VAMS, which do not require centrifugation and cold-chain transport and storage.[41,42]

Samples may need to be stored for days, months, or even years until analysis. Liquid samples must be kept at −20°C or −80°C, depending on whether they are stored short term or long term.[43] Maintaining them at these temperatures is critical as it ensures that the drug concentrations are accurate and no further drug decomposition occurs. Many study sites in resource-limited settings do not have freezers that can maintain these temperatures, requiring samples to be transported by professional dry ice carriers to other facilities with adequate storage facilities. Choosing an alternative sampling matrix such as DBS or VAMS eliminates this need.

Samples may get lost. This may be due to a number of factors, including uncontrolled access to the samples at the storage facility. Allocating a dedicated section of the storage facility to the study can mitigate this challenge. Sample mislabeling may occur, which can be prevented by creating an SOP and training the involved staff.

Transport to Bioanalytical Laboratory

If the bioanalytical method is unavailable at the sample collection site, the samples must be transported to the bioanalytical analysis laboratory. This may still present a challenge as the cost depends on the number of trips done and the distance covered. Costs may be lower if the distance covered is short and the number of trips is small. Essential documentation for a clinical pharmacology study includes shipment dates, method of shipment, shipment conditions, and sample labels.[9] Transport conditions depend on the sample collection method and the validated bioanalytical method. For example, liquid samples typically require cold-chain transport and are considered biohazardous, requiring special consideration and documentation. If this is not

feasible (e.g., due to high costs), a sample collection method that does not require temperature control and is not considered biohazardous, such as dried microsampling, could be used. The chosen courier should be capable of maintaining the appropriate conditions and providing the required documentation, such as temperature logs. Several companies offer specialized services for the transport of medical goods.

Bioanalytical Method

A validated bioanalytical method corresponding to the sample matrix must be available. Suppose such a method is unavailable at the site or country of sample collection. In that case, it is preferable to collaborate with the nearest laboratory to minimize transport costs and facilitate capacity building. Alternatively, pharmaceutical companies could be contacted whether bioanalytical equipment might be available for donation. To operate the bioanalytical equipment, technicians should be trained appropriately, with which pharmaceutical companies might be willing to assist.

Although liquid chromatography-tandem mass spectrometry (LC-MS/MS) is the golden standard for most bioanalytical assays, the use of LC with alternative detection methods (e.g., UV, fluorescence) can be an excellent and cost-effective option.[44] These methods are often less expensive and easier to operate while maintaining the required sensitivity and specificity for the compound of interest. Selecting these methods over LC-MS/MS allows bioanalytical analysis to be conducted at the site or within the country of sample collection. If the sampling is performed with whole blood microsampling, a validated bioanalytical method capable of analyzing these tiny volume samples must be available. Most existing bioanalytical methods are based on plasma as a sample matrix. As the use of whole blood microsampling expands, more bioanalytical methods for these matrices are likely to become available.[45,46]

Reference compound and internal standards are needed for calibration curves and quality control. Due to stockouts, these might only sometimes be consistently available. Before starting the study, it is advisable to prepare sufficient stock, although this depends on the stability of the reference compound and internal standards. Similar to study drug stockouts, pharmaceutical companies or suppliers could be contacted for potential donations (see section "Drug storage and dispensing").

Biostatistics

Pharmacometrics is a scientific discipline that integrates pharmacology, mathematics, and statistics to analyze PK and PD data through modeling and simulation.[47] This field includes techniques such as population PK analysis. For those new to pharmacometrics, seeking guidance from more experienced professionals can be beneficial. If local expertise is unavailable, one can contact a pharmacometrics organization. This includes (but is not limited to) Pharmacometrics Africa,[48] the African Institute for Mathematical Sciences (AIMS), the Asian Pharmacometrics Network,[49] Population Approach Group Europe (PAGE), Pharmacometrics Network Benelux, and the Stockholm Uppsala Pharmacometrics (SUP) group.

Various software options are available for population PK analysis, such as Nonlinear Mixed Effects Modeling (NONMEM) and Phoenix. NONMEM is one of the most widely used programs, often in conjunction with Perl-speaks-NONMEM (PsN).[50,51] Graphical user interfaces for NONMEM include Pirana[52] and Finch Studio.[53] Helpful tutorials about using NONMEM with PsN and Pirana have been published.[54–57] For Phoenix software, Certara may provide access to designated academic centers of excellence (at no cost). The University of Namibia is listed as a center of excellence in Africa. Students may also request a license granted on a case-by-case basis. Licenses for FINCH studio are free for academic research. Another licensed option for population PK analysis is Monolix.[58] R offers open-source packages such as "nlmixr."[59,60]

NCA analyzes drug concentration–time data without assuming a specific compartmental model. It calculates vital PK parameters directly from observed data per participant. Open-source options for NCA include the R packages "ncar" and "NonCompart"[61] and the Excel add-in PKSolver.[62] Of note, the performed analysis should ideally be readily reproducible, which can be more easily managed with some options (e.g., R) than with others.

Data Collection

Study data are collected in case report forms (CRFs), which can be standardized documents or electronic data systems (eCRFs).[9] Many trials collect data through an electronic data collection system. Suppose electronic data collection is not feasible in the field (e.g., due to a lack of stable internet connection or electronic devices). In that case, data may be collected on printed CRFs and transferred to eCRFs. To avoid transcription errors, the transcribed data should be verified by a second researcher.

Furthermore, some electronic data collection systems (REDCap and Castor) offer offline data collection options to mediate connectivity issues. Data could also be solely collected on printed CRFs, although this may be challenging for data analysis. However, collecting or storing data electronically is not a GCP criterion.

When using electronic data collection systems, it is essential to ensure that the selected system meets the required criteria (e.g., audit trails, data entry and

validation, user access control, and data encryption). REDCap, compliant with GCP, allows for online and offline data collection and is free for non-profit organizations that join the REDCap Consortium.[63,64] Castor, also GCP compliant, offers offline data collection.[65] The Castor for Impact Program offers discounted or free access to academic institutions with limited funding, smaller research companies and those researching underserved communities, neglected tropical diseases, preventative medicine, women's health, and ultra-rare diseases. To qualify for the Castor for Impact Program, applications must be reviewed and approved first. Castor and REDCap can utilize an Application Programming Interface (API), enabling integration and interaction with other systems and tools, such as electronic health records, laboratory information management systems, and data analysis platforms (e.g., R).

Publication and Local Dissemination

Ideally, the study results should be published as open access so that the obtained scientific knowledge can be shared and the findings can be disseminated to local health authorities, allowing for integration into local health policies. However, publication fees or article processing charges (APCs) may form a barrier. If these fees were not accounted for in the study budget, researchers can consider submitting to journals that offer no or reduced fees for those from resource-limited settings.[66] Many journals and publishers provide fee reductions or waivers, typically based on the author's institutional location and country classification by organizations such as the World Bank or the Research4Life initiative.[67] Furthermore, if finding a journal interested in publishing the results is difficult, it is helpful to contact journal editors early in the process to inquire about their interest and to discuss the possibility of a fee waiver before submission.

Capacity Building and Funding

Clinical pharmacology studies are only sometimes done in resource-limited settings. Building capacity in those settings is crucial to address this. Various training opportunities are available for investigators seeking to expand their expertise in clinical pharmacology. These include short in-person or online courses covering different aspects of clinical pharmacology, such as PK studies and the practical use of relevant software. For example, Radboud University offers a 4-week online summer course that teaches various techniques for describing and predicting PK and PD, along with their applications in research, with a reduced fee for participants from LMICs.[68] The National Institute of Health (NIH) provides a free online lecture series on the principles of clinical pharmacology, focusing on rational drug development and therapeutic utilization.[69] Like those offered by Pharmacometrics Africa, Fellowship programs provide graduate students with immersive training in pharmacometrics.[48] Another option is to pursue a funded PhD in clinical pharmacology, enabling graduates to become experts in the field. Mentorship is another valuable pathway, where researchers from resource-limited settings collaborate with established experts in clinical pharmacology from other regions. Through this collaborative work, researchers receive on-the-job training and, over time, can become proficient in clinical pharmacology and PK studies.

Additionally, clinical pharmacology researchers who have been mentored or trained can consider involving aspiring researchers as co-investigators in grants or studies to support capacity building and encourage similar research efforts. Public–academic–private partnerships offer another route of collaboration, resulting in capacity building. For instance, a partnership between a pharmaceutical company and research institutions in African countries focused on developing expertise and infrastructure for conducting clinical pharmacology studies, particularly phase I or II trials.[70] This collaboration included pre-workshop activities, a face-to-face workshop, post-workshop gap analyses, and the clinical trial phase. As a result, two successful phase I clinical studies were conducted, demonstrating the potential of such partnerships. Others could replicate this model to achieve similar outcomes.

Securing funding is often one of the most challenging aspects of conducting clinical pharmacology studies in resource-limited settings. Researchers can seek financial support from their institutions and organizations dedicated to global health or clinical pharmacology. For example, the Wellcome Trust funds research on infectious diseases.[71] TDR (the Special Programme for Research and Training in Tropical Diseases) is a global initiative that funds research projects targeting diseases of poverty, such as infectious diseases.[72] The International Union of Basic and Clinical Pharmacology (IUPHAR) reviews clinical pharmacology study proposals from researchers in resource-limited settings, provided these are co-organized with IUPHAR divisions or sections/subcommittees.[73] As discussed earlier, pharmaceutical and software companies may be approached for donations or collaborations to provide drugs, equipment, or software. Additionally, investigators in resource-limited settings often face time constraints that hinder their ability to conduct and complete studies. International collaboration can help alleviate this issue by bringing in staff, such as PhD students or research nurses, to handle the practical aspects of the study, allowing the investigator to focus on a coordinating role.

Ethics

The IRB/IEC assesses the ethics of the study design. When designing the study, it is essential to consider several questions. First, it should be evaluated whether limited resources should be directed toward conducting a clinical pharmacology study. The ethics of this decision depend on the context; in settings with severely limited resources, where many patients have limited or no access to care, priorities may lie elsewhere. However, clinical pharmacology studies are crucial for determining optimal dosing strategies, which have traditionally been underresearched in patient populations in resource-limited settings. Investing resources in these studies can lead to better use of drugs that have limited availability. Improving drug efficacy or reducing toxicity can lower the burden on a strained healthcare system and improve patients' survival and quality of life. Thus, investing in a clinical pharmacology study has the potential to provide significant clinical benefits to a larger group of patients.

Extra precautions are necessary since participants in resource-limited settings are often considered vulnerable subjects. Special measures during the informed consent process and financial compensation are discussed in Recruitment of Participants. Additionally, stockouts of the study drug can occur in resource-limited settings. A strategy for managing study drug stockouts should be established before the study begins. Access to a drug due to study participation could be an unethical advantage, both as an unethical motivator for participation and for non-participants receiving care at the same site. To address this, consider ensuring access to the study drug for all patients at the site during the study. If this is not possible, halt participant inclusion during stockouts so that drug access remains equal for all patients receiving care at the facility.

Conclusion

Conducting clinical pharmacology studies in resource-limited settings is crucial to enhancing healthcare outcomes for all patients. These studies are essential for ensuring that drug treatments are effective, safe, and appropriately tailored to diverse populations, considering differences in genetics, lifestyle, diet, and disease patterns.

This practical guideline was designed to support and encourage researchers interested in undertaking a clinical pharmacology IIT, including PK sampling in resource-limited settings. By addressing common challenges and offering practical solutions, this guideline aims to aid researchers in overcoming barriers often encountered in these settings. The ultimate goal is to contribute to a more equitable distribution of high-quality clinical pharmacology data, thereby improving healthcare for patients in all world regions.

Acknowledgments

The authors thank Ibrahim El Salih and Jochem Simonsz for critically reviewing the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Funding

No funding was received.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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