Review

Qualitative Exploration of Ethical and Regulatory Review of Herbal Remedy Trials in Tanzania: A Case Study of the *Maytenus Senegalensis* Clinical Trial

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Abstract

Background: Herbal remedies are vital worldwide and 80% of Africans rely on them. However, the limited number of well-designed clinical trials in Tanzania emphasizes the necessity for specific ethical and regulatory guidance. This research article examines the *M. senegalensis* clinical trial as case study to highlight ethical and regulatory review process in Tanzania.

Methods: A single intrinsic case study design was employed to gain insight into the ethical and regulatory review process of the *M. senegalensis* trial in Tanzania. A qualitative desk review was utilized, and searches were conducted using PubMed, ScienceDirect, Google Scholar databases, and gray literature. Thematic analysis was used for the data analysis.

Results: The document screening identified valuable sources, including three regulatory authority guidelines, five peer-reviewed journal articles, one organizational report and guideline, and five submission packages for the *M. senegalensis* trial protocol. It also included responses from ethics committees and regulatory authorities. The study found that the essential information for the ethical and regulatory review of herbal remedy trials in Tanzania encompasses nonclinical and clinical studies, anecdotal and ethnomedical evidence, study design, population, endpoints, scientific name, plant extraction details, product type (e.g., raw (fresh or dry), extract), extraction solvent, moisture content, identification of raw material, chemical profile, dose determination, and adverse event monitoring.

Conclusions: The majority of essential information identified focuses on the standardization and quality assurance of the tested herbal product to ensure its verifiability and reproducibility. The findings can guide the review process and create specific herbal trial guidelines in Tanzania and beyond.

Key words: Clinical trials, Regulatory and ethical review, Herbal medicine, Tanzania

Introduction

Herbal remedies, widely used worldwide to treat diseases and symptoms, have long been used by both rural and urban communities in Africa before the advent of modern medicine (1;2). Recent estimates indicate that about 80% of the African population uses herbal remedies. The global COVID-19 pandemic has significantly increased the interest of certain African governments, including the Tanzanian government, in herbal remedies (3;4). Herbs are plants or parts of plants that are used for their taste, fragrance, or medicinal purposes and can be obtained in different forms, such as fresh or dried plants, tablets, capsules, powders, teas, and extracts (2).

As the use of herbal remedies increases, safety concerns are also growing. Serious adverse reactions, including hypersensitivity and organ toxicity, as well as interactions with conventional drugs, have been associated with the use of herbal remedies. Furthermore, there is a limited number of rigorous trials of these remedies (5–7). In 2005, the World Health Organization (WHO) issued guidelines of regulatory requirements for clinical trials of herbal products (8). According to this guideline, a clinical trial can only be initiated if the regulatory authorities of the relevant country are

satisfied with the quality of the submitted data on herbal medicine safety and efficacy, the detailed clinical trial protocol, and the capacity of both the investigator and the sponsor.

In Tanzania, the regulatory landscape involves the Tanzania Medicines and Medical Devices Authority (TMDA), which oversees the conduct of phase I-IV clinical trials. Regulatory approval is contingent upon approval by the National Health Research Ethics Committee (NatHREC) (9). The NatHREC reviews research proposals to ensure participant protection and provides national-level ethical approval for health research in Tanzania. NatHREC also supports institutional ethics committees (10). If the research involves a foreign researcher, an additional approval is required from the Tanzanian Commission for Science and Technology (COSTECH) (11). Despite the existence of ethical and regulatory framework, Tanzania lacks specific guidance for the review of herbal clinical trials.

The Tanzanian government enacted the Traditional Medicine Act in 2002, and in response to this Act, the Ministry of Health established the Traditional Medicine Unit. The objective of this unit within the ministry is to promote the integration of traditional and complementary medicine into the healthcare system (12). Furthermore, a recent study in Tanzania revealed the willingness of study participants to participate in herbal medicine trials (13). However, there is still a limited number of well-designed trials to evaluate the safety and efficacy of herbal remedies in Tanzania. This limitation may be due to the lack of specific ethical and regulatory review guidelines for clinical trials of herbal remedies, which hinders the design and review process (14;15). Herbal remedies pose unique challenges due to their complex composition, potential interactions, and lack of standardized formulations. The safety and effectiveness of herbal products can be influenced by variations caused by seasonal changes, harvesting methods, and environmental conditions (16;18). Ensuring batch-to-batch uniformity of the tested herbal and its constituent compounds is essential to demonstrate the safety and efficacy of herbal medicine in clinical trials. These challenges raise ethical and regulatory concerns that require the presence of specific guidelines to ensure consistent quality of herbal remedy, participant safety, and informed consent in herbal remedy clinical trials.

The absence of specific guidelines for the ethical and regulatory review of herbal clinical trials in Tanzania can lead to approval delays or rejections. Consequently, the generation of evidence for the safety and efficacy of potentially beneficial herbal remedies is delayed and burdens researchers (19). This research article examines the *M. senegalensis* clinical trial as a case study to highlight the ethical and regulatory review process of herbal clinical trials in Tanzania. The information shared in this research article can improve the quality of herbal clinical trials, expedite the ethical regulatory approval process, and increase the availability of evidence for herbal remedies in Tanzania.

Methods

Study Design

A single intrinsic case study design was utilized to gather information on the ethical and regulatory review process of the M. senegalensis trial conducted in Tanzania. An intrinsic case study focuses on understanding the unique characteristics of the case itself, which requires a detailed description (20). The objective of this specific case study was to thoroughly investigate and understand the ethical and regulatory review process of herbal remedy trials in Tanzania, using the M. senegalensis trial as a lens.

Description of the M. senegalensis clinical trial

The trial aimed to assess the safety and efficacy of M. senegalensis, a herbal remedy used for the treatment of uncomplicated malaria, comparing it with Artemether-lumefantrine in Tanzanian adults aged 18 to 45 years old. The trial consisted of two stages: stage one involved a dose-escalation study that evaluated safety and tolerability in healthy individuals, followed by stage two, which employed a phase IIa randomized controlled study design to examine safety, tolerability, and efficacy in individuals with uncomplicated malaria. The trial was carried out at the Bagamoyo Clinical Trial Facility, located 74 km north of Dar es Salaam, in the Coast region of Tanzania. The trial was registered with clinicaltrials.gov (NCT04944966).

Data collection method.

The study utilized a desk review methodology to collect information on the ethical and regulatory review process of herbal remedy trials globally, with a specific focus on Tanzania. A qualitative desk review involves the researcher analyzing relevant materials to provide context and perspective on the investigated topic (21;22). Any text-based material can serve as a source of information for qualitative research (23). Reputable databases such as PubMed, Science Direct, and Google Scholar, as well as gray literature sources, were used to search for relevant information. The scope of the review included various guidelines and documents on the conduct of clinical trials in the context of herbal medicine, herbal products, or herbal remedies. The inclusion criteria included documents related to the M. senegalensis clinical trial, published guidelines, peer-reviewed journal articles, and gray literature. The search terms used covered a wide range of combinations, specifically targeting the ethical and regulatory aspects of clinical trials involving herbal

medicine. The search terms used were "ethics review" or "regulatory review" in combination with "herbal remedy clinical trials", or "herbal product clinical trials", or "herbal medicine clinical trials", or "herbal medicine ", or "herbal product " or "herbal Remedy". Furthermore, the search terms "guidelines" and "conduct clinical trials" were used alone or in combination with "herbal medicine", or "herbal medicine", or "herbal product", or "herbal remedy". Furthermore, the searches were limited to documents published or created between January 1, 2002, and January 1, 2022. Incomplete documents were also excluded as reliable sources of information.

Data Analysis

The data analysis process involved extracting pertinent information from each identified document and documenting it in a structured extraction form. The data extraction form categorized information by source type, authorship, title, publication date, and relevant details extracted for research purposes. The extraction of information from the documents was carried out by two researchers independently. In addition, a harmonized summary was produced through consensus between these two researchers, and the third researcher was consulted if there was still a disagreement. Thematic analysis was chosen as the approach for data analysis in this study, as it is consistent with the existing literature (22). The analysis in this study aimed to categorize the extracted data into themes, identifying patterns and recurring concepts.

Results and Discussion

Document characteristics

In this desk review, the reviewed documents were categorized into three groups. The first group included local and international ethical and regulatory authority guidelines that provide information on herbal clinical trial reviews. The second group consisted of peer-reviewed journal articles that offer scholarly perspectives. The third group contained submission packages for the M. senegalensis clinical trial protocol and responses from ethics committees and regulatory authorities, which offer specific information on this case study. After screening for alignment with search criteria, three regulatory authority guidelines, five peer-reviewed journal articles, one organizational report and one organizational guideline, along with five submission packages for the M. senegalensis clinical trial protocol and the corresponding responses, were identified as valuable sources of information. See the table S1 in the supplementary material for more detailed information.

Essential Information to Support Ethical and Regulatory Review of Clinical Trials for Herbal medicines elsewhere.

Table 1 presents essential information to support the ethical and regulatory review of clinical trials for herbal products elsewhere. Clinical trials are crucial for herbal medicines to survive in the international market and gain endorsement alongside modern medicine. In an evidence-based pharmaceutical era, clinical trials for herbal medicine contribute significantly to the integration of these drugs into modern healthcare practices. However, the development, ethical and regulatory review processes, as well as the conduct of clinical trials for herbal medicine, require adjustments due to their unique properties. Information on standardization and quality assurance for consistency and reproducibility is necessary to support the ethical and regulatory review of clinical trials for herbal medicines. The essential information to support the ethical and regulatory review of clinical trials for herbal medicines includes plant description, product information, type, processing, purity testing, removal of unwanted components, analysis of active ingredients and constituents, and chemical fingerprinting (24). The clinical trial protocol should include essential elements such as trial registration, scientific validity, risk-benefit assessment, subject selection criteria, and long-term follow-up procedures (8;24;32). These elements ensure transparency and assess safety and efficacy throughout the trial. Compliance with good manufacturing practices and good agricultural practices is essential to maintain high standards for herbal medicines obtained through cultivation. Furthermore, the review of the literature indicates that the Uganda National Drug Authority has made significant efforts to formulate specific guidelines for conducting clinical research on herbal medicine products. Furthermore, the Kenyan Pharmacy and Poisons Board has incorporated a dedicated section for herbal medicine products into its guidelines for the conduct of clinical trials in Kenya (24;28). The steps taken by regulatory bodies in East Africa, such as the Uganda National Drug Authority and the Kenyan Pharmacy and Poisons Board, to establish specific guidelines for herbal clinical trials, mark a crucial step forward. The efforts of these regulatory bodies lay a foundation for harmonized approaches, fostering ethical and standardized practices in herbal clinical research throughout the region.

Table 1: Essential Information to Support Ethical and Regulatory Review of Clinical Trials for Herbal Products Elsewhere

Themes	Subthemes
Rationale for conducting clinical trials for herbal medicine.	Survival herbal medicine in international market and endorsement alongside modern medicine Acceptance and integration into evidence-based healthcare
Rationale for adjusting the development, protocol review and conduct of clinical trial of herbal medicine	Unique properties of plant-based materials
Standardization and quality assurance of herbal product for consistency and reproducibility.	Scientific name of the herbal plant Cultivars and plant varieties Growing conditions of the herbal plant Harvesting methods and time of harvest of the herbal plant Parts of herbal plant harvested to produce extract or product Region(s) or country(ies) of origin of the herbal plant Type of herbal product used (raw fresh or raw dry or extract) Herbal plant drying and mechanical disruption procedures Type and concentration of solvent used for extraction Herbal drug to extract ratio Special testing for pesticides, herbicides, and heavy metals, etc. Methods used for removal of unwanted components Analysis of putative active ingredient(s) and chemical constituents. Chemical fingerprinting and testing description (methods used, and the laboratory responsible; and retention sample information) Proprietary herbal product name or extract name (brand name) Name of the manufacturer of herbal product Storage conditions of herbal product
Detailed study protocol and other supportive information to ensure standardization of procedure	Ethical and legal considerations information Evidence that demonstrates the scientific validity of the trial Risk-benefit assessment details Subject selection criteria Trial registration to ensure transparency and accountability Long term follow-up of participants to assess safety and efficacy overtime Previous nonclinical and clinical studies (existing data on toxicity, dosage form, and potential adverse effects of herbal drugs should support and justify clinical trials) Qualified study investigator Capability of the trial sponsor Adhere to Good Agriculture Practices (GAP) during herbal cultivation Adherence to Good Manufacturing Practices (GMP) during herbal product manufacture

Ethical and Regulatory Approvals for the Clinical Trial of M. senegalensis Herbal Protocol in Tanzania

The *M. senegalensis* clinical trial sought approval from three ethics committees and one regulatory authority. The first step involved obtaining ethical approval from the review boards of the affiliated institutions of the principal investigator, including the institutional review boards (IRBs) of the Ifakara Health Institute (Ref. IHI/IRB/AMM/No: 13-2020) and the Ethical Review Board of the Muhimbili

University of Health and Allied Sciences (Ref. No. DA.282/298/01.C/30). After receiving approval from both IRBs, subsequent applications were submitted and approved by the National Ethics

Committee (NIMR/HQ/R.8a/Vol. IX/3639), followed by the national drug regulatory authority, the Tanzania Medicines and Medical Devices Authority (TMDA) (Ref. No. TMDA0020/CTR/0013/03).

Post-Submission Data Requests by Regulatory and Ethics Committees for M. senegalensis Clinical Trial

In reviewing the M. senegalensis trial, ethics committees and the regulatory authority requested additional information and raised concerns (Table 2). Some recommendations were made to improve the clarity of the study documents, while others pointed out the need for corrections. After addressing all concerns and submitting additional information, the study obtained approval from Tanzanian ethics committees and the regulatory authority.

Nonclinical and Clinical Studies

Ethics committees and regulatory authorities require safety and efficacy data for the herbal remedy in nonclinical and clinical studies. Despite the long-standing use of traditional healers, reviewers are looking for scientific evidence to supplement the human experience. They place particular emphasis on nonclinical studies to ensure a comprehensive safety assessment, especially with respect to chronic toxicity, which may arise from prolonged use. Given the wide range of traditional uses, both scientific and anecdotal evidence are necessary to facilitate a comprehensive risk assessment. However, certain plant extracts that initially showed promise in preclinical studies did not demonstrate any benefit in Phase II trials (33;34).

Anecdotal and Ethno-Medical Evidence

Ethics committees require a summary of anecdotal and ethnomedical evidence regarding the safety and efficacy of the herbal remedy. This summary is rooted in the cultural beliefs and practices of specific ethnicities. A long history of human use and culturally accepted ethnomedical evidence can complement preclinical data (35). Additionally, understanding the historical and cultural context in which the herbal remedy has been used can be useful in making decisions about the risks and benefits of the clinical trial of herbal medicine (35). However, it can be challenging to consider cultural differences when making decisions about risks and benefits (36).

Study Methods

Study Endpoints

The regulatory authority sought precise parameter values that function as indicators for the safety and effectiveness of the herbal medicine. It is crucial to establish accurate and specific outcome measures to evaluate the effects of the herbal remedy in clinical trials of herbal remedies. Considering the variations in disease criteria between conventional and traditional medicine, it is advisable to clarify whether the outcome measures are derived from traditional or modern medicine (37). However, literature recommends utilizing outcome measures derived from modern medicine in clinical trials involving herbal remedies (38).

Table 2: Additional Data requested by Regulatory Authority and Ethics Committees for M. senegalensis clinical trial

Themes	Subthemes	Ethics Committees	Regulatory Authority
Nonclinical and clinical studies		○	○
Anecdotal and ethno-medical evidence		○	-
Study methods	Study design	○	-
	Study population	○	○
	Study endpoints	○	○
Standardization and quality assurance of the herbal product	Scientific name of herbal plant	○	-
	Part of plant used to produce the extract.	○	-
	Type of product used (eg, raw (fresh or dry), extract)	○	-
	Type and concentration of extraction solvent used	○	○
	Moisture contents of the product	-	○
	Identification of starting raw material of the product.	○	-
	Product's chemical profile (fingerprint)	-	○
	Product dose determination	-	○
Adverse event monitoring		○	-

In this table 2, the cycle symbol (○) indicates the presence of a theme or subtheme under the ethics committees or regulatory authority category. This means that during the analysis, these themes or subthemes were identified based on the extracted relevant information from the ethics committees or regulatory authority. The bullet symbol (-) indicates the absence of a theme or subtheme under the ethics committees or regulatory authority category. This means that during the analysis, these themes or subthemes were not found or did not emerge from the extracted relevant information from ethics committees or regulatory authority.

Study Population

The ethics committees required justification for the exclusion of women participants in the proposed herbal clinical trial. The TMDA guideline for conducting clinical trials in Tanzania emphasizes the importance of including a representative sample of women in drug trials that target women or heterogeneous populations. The inclusion of all women, including postmenopausal women and those with reproductive potential, in early clinical trials is crucial for identifying and addressing potential sex-related variations when designing pivotal Phase III trials (9).

Study Design

The ethics committees recommended changing the trial phase from Phase 1 to Phase 2b in the study design section of the protocol. They stated that Phase 1 studies typically focus on dose escalation to determine the maximum tolerated dose (MTD). They emphasized that Phase 1 primarily consists of healthy individuals and only three individuals per dose group, with exceptions for terminally ill patients with incurable diseases. The researchers' decision to categorize the study as Phase 1 was based on the fact that M. senegalensis would be administered to humans at the proposed dose for the first time, despite its previous use by traditional healers. Traditional healers in the Kagera region use M. senegalensis to treat malaria, fever, pain, and

chronic diseases (39). Furthermore, the bark of M. senegalensis roots has been used for various diseases in Africa, including Benin, Côte d'Ivoire, Kenya,

Senegal, Sudan, Zambia, and Zimbabwe (39–42). Understanding the clinical trial phases is essential because it helps gauge the extent of knowledge about the drug being tested (43).

Standardization and Quality Assurance of the Product

The Tanzanian ethics committees and regulatory authority provided recommendations to ensure the quality, verifiability, and reproducibility of herbal remedies tested in the clinical trial. Previous literature has highlighted that maintaining product quality and standardization poses common challenges across different batches of the same herbal products (43;44).

Use of Scientific name of herbal remedy

The ethics committees have recommended using the scientific name, rather than the common name, for the tested herbal remedy to minimize the risk of future misidentification. Herbal product local names can vary, and different nomenclatures exist, including Latin scientific names, vernacular names, pharmaceutical names, or specific herbal remedy names (45). The accurate verification of herbal constituents relies on the correct naming of the ingredients included in the herbal product. Misidentification of other plant-related species and subsequent mislabeling can lead to severe consequences, as seen in the 1993 Belgian clinic incident, where toxic Aristolochia fungi were mistaken for Stefania tetrandra in a slimming treatment, resulting in over 100 women experiencing renal failure (47;48).

Part of Plant Used to Produce the Extract and Type of product used

The ethics committees requested the researchers to specify the specific part of the herbal plant used to create the extract. Different parts of the same herbal plant, such as leaves, stems, buds, flowers, roots, or tubers, may exhibit different pharmacological activities (48;49) In addition, the ethics committees requested that the researchers specify the type of product used, whether it is in its raw form (fresh or dried) or as an extract. Providing information on the characteristics of the herbal remedy used is necessary to provide reviewers with scientific data on the herbal product. According to the trial guidelines developed for herbal medicines, the effectiveness of herbal medicines depends on the specific part of the plant used, the type of extract (aqueous, alcoholic, glycerin), and the form of administration (50).

The type, concentration of extraction solvent used and preparation method

The regulatory authority requested information about the extraction process, including the type and concentration of the solvent, as well as the preparation method. In addition, the regulatory authority requested the herbal drug-to-extract ratio. Herbs from different parts can undergo various processing methods and can be used either in raw form or as extracts. Alcohol, glycerol, acetone, or water can be used as a solvent during extraction, and the resulting extract can take the form of tablets, capsules, liquid tinctures, or teas. Different extraction methods can produce different chemical compositions, which can affect the pharmacological activity of the final herbal product (48;50). Furthermore, the ethics committees recommended describing the dose by weight instead of volume. This recommendation led to a change in the product formulation from liquid to capsules. Capsules ensure standardized dosing and minimize variations in dosing.

Moisture contents of the product

The regulatory authority requested data on the moisture content of the tested batch of herbal remedies. In the pharmaceutical industry, determining the moisture content is crucial for quality control, as it guides inspections of raw materials and in-process tablets and capsules. It is measured as a percentage of the original wet weight and indicates the amount of water in the sample. A low moisture content improves drug stability, highlighting its significance in pharmaceutical manufacturing processes (51).

Identification of starting raw material of the product

The ethics committees requested information regarding the raw material used in the herbal remedy. In particular, they were interested in knowing whether the raw material of the herbal remedy was cultivated or obtained from the wild, the time of year when the raw material harvest was carried out (during the rainy or dry season), and how the raw material was stored. It is important to note that the pharmacological potency of the product can vary depending on factors such as the location where the plants were grown, the timing of harvest and the duration of storage (48;52). Furthermore, the pharmacological potency of plant products and their active ingredients can fluctuate from year to year due to climate-related factors such as rainfall, sunlight and genetic variations. Long-term storage of raw material can increase the risk of microbial contamination (48;49).

Product's chemical profile (fingerprint) of the extract

The regulatory authority requested specific details about the herbal product in order to determine its identity, purity, and other quality-related parameters. They sought information about a product description, the limit of detection (LOD) of milled powder, the particle size distribution of the milled powder, microbial contamination, aflatoxin content, and heavy metal content. Variations in phytochemical content can occur due to factors such as seasons, harvest times, methods, geographic origins, environmental conditions, agricultural practices, storage conditions, and processing/manufacturing methods, all of which can significantly impact safety and efficacy (16;18;53). Environmental conditions can influence the presence of certain elements, such as heavy metals, depending on the conditions of water, soil, and air in a given area (54–58). Heavy metals such as lead, mercury, arsenic, and cadmium can cause human poisoning if present in herbal products at levels that exceed the maximum limits set by the World Health Organization (59–61). The mechanism of heavy metal toxicity involves free radicals that cause oxidative stress and damage biomolecules such as enzymes, proteins, lipids, crucial nucleic acids and DNA, which are essential for the development of cancer and neurotoxicity.

Moreover, microbial contamination of herbal remedies can occur during the collection, storage, and processing of raw materials or finished products. Certain microbial species, which are commonly found in the environment, have the potential to contaminate finished products as a result of inadequate hygiene and quality control practices (62). Drying herbs immediately after harvest helps reduce the risk of microbial growth (61). However,

excessive drying can result in the loss of thermo-labile bioactive ingredients (54;63). Contaminated herbal products can contain allergens, pollens, toxins (aflatoxin, mycotoxins, brevetoxin B, yessotoxins, pectenotoxins, digoxin, sikimitoxin), as well as microbes such as Escherichia coli, Salmonella and Listeria monocytogenes (64–66). Furthermore, preparations such as extracts and decoctions can vary between batches and manufacturers due to differences in solvents, temperature, and extraction time (67).

The chemical profile provides information about the chemical constituents in the trial batch, which is crucial for future comparisons and quality control. Variations in herbal ingredients present challenges for quality control and standardization, raising concerns.

Product Dose Determination

The regulatory authority requested information used to determine the dose of the herbal extract tested. Since there are no documented clinical trials for M. senegalensis, the dose of 1600mg/kg body weight from the animal study was considered the No Observed Effect Level (NOEL) dose (68). The maximum recommended starting dose (MRSD) in humans, extrapolated from the NOEL dose in animals, is 7800mg/10=780mg, 800mg. The US FDA guideline for estimating the maximum safe starting dose guided the extrapolation of the animal dose to a human dose for the herbal product (*M. senegalensis*) (69). This FDA guideline is crucial for providing a standardized framework to determine the initial dose in clinical trials, ensuring participant safety by minimizing the risk of adverse effects. Adherence to this guideline helps researchers and regulatory authorities ensure ethical conduct of clinical trials and safeguard the well-being of participants.

Adverse event monitoring

The ethics committees sought clarification regarding the monitoring of adverse events. It is crucial to consider monitoring adverse events due to potential issues related to herbs, such as variations in herb quality, misidentification of plant species, insufficient manufacturing processes, improper cultivation and storage, non-standardization of the herb used, drug-herb interactions, and herb side effects (70–73). The WHO guideline for traditional medicine in Africa guided the monitoring of adverse events for the clinical trial of M. senegalensis due to limited safety data. A list of signs and symptoms, developed using the guideline, was used to assess systemic solicited adverse events within seven days post-administration (74). This approach ensured a comprehensive assessment of potential adverse effects.

Study Limitations

The main limitation of this study is that the reviewed documents were not designed based on research agendas. Therefore, they might not have provided all the necessary information to perfectly answer the research questions of this study. The extensive searches were conducted through databases such as PubMed, ScienceDirect, and Google Scholar to obtain relevant information from Tanzania and beyond to mitigate this limitation. Furthermore, the review included all submission packages for the M. senegalensis clinical trial protocol and responses from ethics committees and regulatory authorities, ensuring a comprehensive examination of the topic. Another limitation is the possibility of bias in the documents and the researchers. Therefore, to mitigate the risk of bias, the extraction of information from the documents was carried out by two researchers independently. In addition, a

harmonized summary was produced through consensus between these two researchers, and the third researcher was consulted if there was still a disagreement.

Conclusion

This research article provides crucial information for ethical and regulatory review process of herbal clinical trials, using the M. senegalensis clinical trial as a case study. The essential information for ethical and regulatory review of herbal clinical trials in Tanzania covers various aspects, including nonclinical and clinical studies, anecdotal and ethnomedical evidence, study design, study population, study endpoints, scientific name of the herbal remedy, part of the plant used for extraction, type of product, extraction solvent, moisture content, identification of raw material, chemical profile, determination of product dose, and adverse event monitoring. Further analysis of this identified essential information reveals that most of it focuses on the standardization and quality assurance of the evaluated herbal product to ensure its verifiability and reproducibility. This research article can be used as a guide for ethics committees and regulatory authorities in reviewing herbal clinical trials in Tanzania. In addition, this research article can prompt discussions about establishing specific regulatory and ethical guidelines for herbal clinical trials in Tanzania and beyond, addressing the unique challenges associated with herbal remedy clinical trials.

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Author contributions

KRK, FAM, JJO, AO, SJ, BN, and SA developed the study concept and design; KRK, FAM, and JJO were responsible for the acquisition of data; KRK, FAM, JJO, GN, LM, OL, NB, AH, MR, HM, AO, SJ, BN, and SA performed the analysis and interpretation of the data; KRK wrote the original draft of the manuscript; KRK, FAM, JJO, GN, LM, OL, NB, AH, MR, HM, AO, SJ, BN, and SA wrote, reviewed, and edited the manuscript; All authors read and approved the final manuscript.

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Competing interests

All authors declare that they have no commercial or other associations that may pose a conflict of interest.

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Supplementary Material

1. Table S1: Source and Relevant Information to Support Ethical and Regulatory Review of Clinical Trials for Herbal Products in Tanzania and beyond.

Data Type	Author(s)	Title	Document date	Relevant Information
Regulatory authority Guideline	Pharmacy and Poisons Board (1)	Guidelines for the Conduct of Clinical Trials in Kenya	2022	- Conventional drug processes and controls may not apply to herbal products, which requires adjustments to accommodate the unique properties of plant-based materials. - Manufacturing herbal products requires additional adaptations, such as identifying and standardizing plant material, employing appropriate extraction methods, implementing quality control measures specific to herbs, and ensuring consistency and reproducibility of the final product. - Information needed to support a regulatory evaluation of a proposed herbal substance phase 1/2 clinical trial. (i) Description of the plant: genus, species (cultivar where appropriate); region(s) and country(ies) of origin; time of harvest; parts to be harvested (ii) Plant processing: drying, mechanical disruption, solvent extraction (aqueous or organic solvents, others) (iii) Isolation, identification and purification of active ingredients (iv) Analytical procedures(v) Specification (vi) Storage conditions
Regulatory authority Guideline	Tanzania Medicines and Medical Devices Authority(2) .	Guide Lines for Applications to Conduct Clinical Trials in Tanzania Tanzania Food and Drug Authority Guidelines for Application to Conduct Clinical Trials in Tanzania	2020	- The Tanzania Medical Devices Authority (TMDA) serves as the regulatory authority in Tanzania. - TMDA is responsible for the approval of clinical trials and the grant of marketing authorisation for medicines, medical devices, diagnostics, and other products. - The guideline does not provide explicit requirements for the authorisation of clinical studies involving herbal drugs.
Regulatory authority Guideline	Uganda National Drug Authority(3)	Guideline on Clinical Research on herbal medicine products	2020	- As evidence-based pharmaceuticals dominate modern healthcare, the demand for herbal remedies persists. Modern science allows herbal products to be formulated in different dosage forms. To gain acceptance in healthcare practice, rigorous research is crucial to demonstrate the safety and efficacy of herbal remedies in modern formats for prescription and dispensing.

Published article from a peer-reviewed journal	Koonrungsesomboon and Karbwang(4)	Ethical considerations in clinical research on herbal medicine for the prevention of cardio vascular disease in the ageing	2016	- Clinical research on herbal drugs should adhere to the same ethical standards as other research on product development. - Ethical considerations in clinical research on herbal medicine for the prevention of cardio vascular disease in ageing include scientific validity, risk-benefit assessment, subject selection, vulnerability, and informed consent.
Published article from a peer-reviewed journal	Nut Koonrungsesomboon(5)	Ethical considerations and challenges in herbal drug trials with The focus on scientific validity and risk assessment	2020	- Scientific validity is crucial for ethical herbal drug trials to produce scientifically valid results and social value. - Challenges in herbal drug trials include justification of study design and methodology as well as the ascertainment quality control and standardization of the herbal drug under investigation. - Risk assessment is crucial for ethical research involving human subjects. Existing data on the toxicity, dosage form, and potential adverse effects of herbal drugs should support and justify clinical trials. Trials should minimize risks to subjects and have reasonable anticipated benefits.
Clinical trial correspondence between investigator and regulatory authority: Feedback on protocol review.	Regulatory authority	Correspondence regarding the approval of the study titled "Evaluation of the Safety and efficacy of Maytenus Senegalensis for the Treatment of Uncomplicated Malaria Episodes in Adult Patients aged 18 to 45 years compared to Artemether-lumefantrine" (ClinicalTrials.gov Identifier: NCT04944966).	2019-2020	- Provide preclinical safety studies from animal studies. - The cited references only mention experiments conducted in non-pregnant mice, which cannot be extrapolated and used by female participants to reduce teratogenic risk. - Provide the parameter values that will be used as indicators for the safety and efficacy of the investigational product. - Provide preclinical studies that support the proposed herbal dose. - The filled product should include a signed and dated specification that is extensive enough to establish identity, purity, and other quality-related parameters. At a minimum, the specification should include the following: product description, LOD (limit of the detection) of milled powder, particle size distribution of the milled powder, microbial contaminations, aflatoxin content, and heavy metal content.
Clinical trial correspondence between investigator and Ethics Committees: Feedback on protocol review.	Ethics Committees	Correspondence regarding approval of the study titled "Evaluation of the safety and efficacy of Maytenus Senegalensis for the Treatment of Uncomplicated Malaria Episodes in Adult Patients aged 18 to 45 years old	2018- 2020	- It appears that there is not enough information provided regarding the background on the safety of the new product. Please consider including toxicity studies of the product." - It is suggested that you document the toxicology studies that have been conducted on animals regarding the product. - The study design was not specified by the investigators. It is crucial to clearly identify and explain the study design. - This study does not fit the characteristics of a phase 1 trial. It appears to be a phase IIa study exploring clinical effectiveness with a small number of patients. - Study population: Why will only males be included in the trial?

		compared to Artemether-lumefantrine" (ClinicalTrials.gov Identifier: NCT04944966).		- Use the correct scientific name of the plant. - Provide a concise summary of the relevant anecdotal and ethnomedical evidence for the tested herbal product. - Include information specifying which part of the plant was used to prepare the extract. - Provide clarification on the type of product utilized as a raw material for the investigational product? Specifically, is it in raw form (fresh or dry) or an extract? - Provide information on the type and concentration of extraction solvent used, as well as the specific preparation method used for the herbal product used in this study. Also, include the herbal drug-to-extract ratio in your submission. " - The study design was not specified by the investigators. It is crucial to clearly identify and explain the study design. - Under Posology and Administration, it is suggested to use weight instead of volume. - The findings of the phase 1 studies should appear vividly in the proposal

Reference

1. Republic of Kenya Pharmacy and Poisons Board. Guidelines for Applications to Conduct Clinical Trials in Kenya. 2022.
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