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IMPROVING THE QUALITY OF HOST COUNTRY ETHICAL OVERSIGHT OF INTERNATIONAL RESEARCH: THE USE OF A COLLABORATIVE 'PRE-REVIEW' MECHANISM FOR A STUDY OF FEXINIDAZOLE FOR HUMAN AFRICAN TRYPANOSOMIASIS

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ABSTRACT
Developing countries face numerous barriers to conducting effective and efficient ethics reviews of international collaborative research. In addition to potentially overlooking important scientific and ethical considerations, inadequate or insufficiently trained ethics committees may insist on unwarranted changes to protocols that can impair a study's scientific or ethical validity. Moreover, poorly functioning review systems can impose substantial delays on the commencement of research, which needlessly undermine the development of new interventions for urgent medical needs. In response to these concerns, the Drugs for Neglected Diseases Initiative (DNDi), an independent nonprofit organization founded by a coalition of public sector and international organizations, developed a mechanism to facilitate more effective and efficient host country ethics review for a study of the use of fexinidazole for the treatment of late stage African Trypanosomiasis (HAT). The project involved the implementation of a novel 'pre-review' process of ethical oversight, conducted by an ad hoc committee of ethics committee representatives from African and European countries, in collaboration with internationally recognized scientific experts. This article examines the process and outcomes of this collaborative process.

I. INTRODUCTION

The obligation to seek prospective ethical review of research involving human participants is widely recognized as an international ethical and legal requirement.[1] Research ethics committee (REC) review is designed to safeguard participants' rights and well-being by ensuring that the risks of research are minimized, that risks are reasonable in relation to anticipated benefits, that the researchers have made adequate plans for obtaining

[1] World Health Organization (WHO). 2011. *Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants*. Geneva: WHO: xi. Available at: http://www.who.int/ethics/publications/research_standards_9789241502948/en/ [Accessed 16 May 2014].

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participants' informed consent, and that other ethical issues, such as confidentiality and equitable participant selection, have been appropriately addressed.[2] Ethical guidelines recommend that, when research is sponsored in one country but conducted in another, REC review should be conducted in both jurisdictions.[3] Review by a host country REC is essential because local factors are relevant to assessing risks and potential benefits,[4] evaluating the effectiveness of the researchers' proposed informed consent strategies,[5] and anticipating the potential impact of a study on the community from which participants will be drawn.[6] Recognizing the importance of local REC oversight, many countries are in the process of creating or strengthening legal frameworks requiring REC review of international collaborative research.[7] These efforts have been supported by a variety of international capacity-strengthening initiatives.[8]

Most developing country RECs, however, face numerous barriers to conducting ethics reviews effectively and efficiently.[9] Even if a country has formally established an REC system, it can be difficult to find sufficient numbers of qualified persons to serve on the committees and address all technical and ethical aspects of the review. In addition, opportunities for training and networking are often limited, and committees frequently lack essential resources, such as office space, administrative staff, and access to computers. In some developing countries, RECs may also experience explicit or implicit pressures that impede their ability to make independent decisions. For example, in countries that have come to depend on the financial or infrastructural benefits of foreign-sponsored research, RECs may be discouraged from imposing conditions on studies that could lead sponsors to go elsewhere.[10]

The fact that some RECs are unable to carry out their missions effectively raises serious concerns. In addition to potentially overlooking important scientific and ethical considerations, inadequate or insufficiently trained RECs may insist on unwarranted changes to protocols that can impair a study's scientific or ethical validity. Moreover, poorly functioning review systems can impose substantial delays on the commencement of research, which needlessly undermine the development of new interventions for urgent medical needs.

Recognizing these concerns, the Drugs for Neglected Diseases Initiative (DNDi), an independent non-profit organization founded by a coalition of public sector and international organizations, sought to develop a mechanism to facilitate more effective and efficient host country REC review for a proposed study on the use of fexinidazole for the treatment of late stage Human African Trypanosomiasis (HAT), commonly known as African sleeping sickness. The project involved the implementation of a novel 'pre-review' process of ethical oversight, conducted by an ad hoc committee of REC representatives from African countries in collaboration with the Necker Hospital REC in Paris and internationally recognized scientific experts. The objectives of the pre-review included the following:

- identifying and clarifying ethical and scientific questions;
- alerting sponsors to aspects of the study requiring further development before REC submission;
- highlighting uniquely 'local' issues to which host country RECs should pay particular attention;
- promoting international knowledge sharing and capacity development; and
- modeling good practices in ethics review for meeting participants.

The purpose of the pre-review was not to replace host country REC oversight but rather to facilitate it. Thus, the pre-reviewers were not empowered to approve or disapprove the protocol; their role was limited to making recommendations for further consideration by the sponsor of the study and host country RECs. The pre-reviewers' recommendations were advisory only. Final decisions about approval, disapproval, or modifications of the protocol would be made by host country RECs based on their standard operating procedures.

In this article, we consider the potential utility of the pre-review process as a means of improving the efficacy

[2] Ibid: 14; World Medical Association, 2008. *Declaration of Helsinki.* Available at: http://www.wma.net/en/30publications/10policies/b3/ [Accessed 16 May 2014]; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. *Good Clinical Practice*. Available at: http://ichgcp.net/ [Accessed 16 May 2014].

[3] E.g. Nuffield Council on Bioethics. 2002. *The Ethics of Research Related to Healthcare in Developing Countries.* London: Nuffield Council on Bioethics: 107. Available at: http://www.nuffieldbioethics.org/sites/default/files/HRRDC_Follow-up_Discussion_Paper.pdf [Accessed 16 May 2014].

[4] The George Institute for International Health. 2010. *Registering New Drugs: The African Context*. Sydney: The George Institute for International Health: 5. Available at: http://www.policycures.org/downloads/DNDi_Registering_New_Drugs-The_African_Context_20100108.pdf [Accessed 16 May 2014].

[5] Z.A. Bhutta. Beyond Informed Consent. *Bull World Health Org* 2004; 72: 771–777.

[6] E.J. Emanuel et al. What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research. *J Infect Dis* 2004; 189: 930–937: 932.

[7] Networking for Ethics on Biomedical Research in Africa (NEBRA). 2006. *Final Report*. Available at: http://elearning.trree.org/file.php/1/NebraReport/FinalReport-2006-english.pdf [Accessed 16 May 2014].

[8] E.g. European and Developing Countries Clinical Trials Partnership. Ethics Review Boards. Available at: http://www.edctp.org/?id=659 [Accessed 16 May 2014].

[9] N.E. Kass et al. The Structure and Function of Research Ethics Committees in Africa: A Case Study. *PLoS Med* 2007; 4(1): e3. doi:10.1371/journal.pmed.0040003. Available at: http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.0040003 [Accessed 16 May 2014].

[10] Ibid.

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and efficiency of host country ethical oversight. We begin by providing a brief overview of the nature of the HAT study and the mechanics of the pre-review mechanism. Next, we look at some of the key ethical issues brought out in the pre-review deliberations, the recommendations of the pre-reviewers, and the impact of those recommendations on the study design. Finally, we assess the merits of the pre-review process and consider its potential for broader replication.

II. BACKGROUND ON THE FEXINIDAZOLE STUDY

HAT is an exclusively African disease, with many foci over international boundaries. Those affected generally live in poor, rural areas and have little purchasing power or political impact. The disease is characterized by severe mental and physical impairments and has serious socio-economic consequences for communities. Left untreated, it is almost invariably fatal. Because signs and symptoms of the disease are non-specific, early diagnosis is often overlooked. The few drugs for HAT are either toxic or require trained clinicians to administer slow infusions.[11]

The proposed study tests a short-course oral treatment for late-stage HAT using fexinidazole, a new antiparasitic agent. This approach is a major advance over current treatments, which require 10 days of hospitalization and have important side effects. The study is designed as an open-label, randomized, non-inferiority Phase II/III trial comparing fexinidazole to nifurtimox-eflornithine combination therapy (NECT), the standard first line late stage HAT Gambiense treatment. It will involve up to 6 centers, with 60–130 participants per center, for a total of 510 participants. The primary study objective is efficacy at 18 months. Biology and safety will also be examined as secondary objectives.[12]

The study will rely on both passive and active case detection to recruit participants. In order to increase active case detection, additional ad hoc mobile teams will be organized, beyond those currently used for population screening. Persons identified with stage one HAT will be treated in their villages. Persons with stage two HAT (defined as cases in which the parasite has begun to affect the central nervous system) will be referred to the hospital, where they will be considered as potential candidates for the study. Screening related specifically to eligibility for participating in the protocol – i.e., beyond what is normally done as part of the clinical care of HAT patients – will be conducted after participants have provided informed consent to enroll in the study.

Participants in the study will undergo 10 days of treatment, followed by 3–7 days of post-treatment. During the post-treatment phase, participants will be hospitalized. After post-treatment, participants will be followed on an outpatient basis for up to two years. Participants will undergo a variety of interventions beyond those they would receive if they underwent HAT treatment outside of a study, including one additional lumbar puncture at the end of treatment in order to assess the immediate efficacy of the drug and its concentration in the cerebrospinal fluid.

Because transportation to the hospital is an obstacle to obtaining care and follow up, transportation costs will be reimbursed. Food will be provided to both study participants and those who do not consent to participate or who do not meet the inclusion/exclusion criteria. In addition to serving as a token of appreciation, providing food is necessary for scientific reasons, as the fexinidazole must be administered with food in order to be absorbed properly. Additional benefits to participants, including payment for wages lost because of follow-up visits, will be at the discretion of local RECs.[13]

For participants who cannot read, the consent process will be observed by a witness chosen by the participant. Witnesses will be independent from the study team and must be able to read and write. Information provided to participants and witnesses will use lay language and will be translated into the local language. Information will be explained orally by the investigator or delegated staff, and participants will be given time for reflection if necessary. A signature or fingerprint will be obtained before any trial procedure is initiated and before the first dose of medication is provided. Participants will have the opportunity to withdraw their participation at any time without prejudice. Participants who withdraw will be offered treatment with NECT as needed.

Fexinidazole will be considered an acceptable treatment if the difference in response as compared to NECT is no more than 13%. Some difference in response rates between fexinidazole and NECT is considered acceptable because the ability to administer fexinidazole orally provides a treatment advantage. The decision to accept a difference of up to 13% was based on a survey of HAT clinicians.

A data safety and monitoring board (DSMB) will be created for the study, consisting of at least three members (a clinician, an epidemiologist-statistician, and a cardiologist). The DSMB will be independent from the sponsor and will hold scheduled and ad hoc meetings. It will be responsible for futility analysis and safety surveillance. The sponsor will also be responsible for pharmacovigilance.

[11] Drugs for Neglected Diseases Initiative (DNDi). *Human African Trypanosomiasis: Global View*. Available at: http://www.dndi.org/diseases-projects/diseases/hat.html. [Accessed 16 May 2014].

[12] Further information about the study is available at ClinicalTrials.gov, available at: http://clinicaltrials.gov/ct2/show/NCT01685827?term=fexinidazole&rank=3. [Accessed 16 May 2014].

[13] In fact, none of the RECs to which the protocol was ultimately submitted were in favor of making such payments.

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Study results will be provided to the village community via mobile teams, to investigators (through meetings, reports, and publications), and HAT stakeholders (through the HAT platform,[14] information letters, and scientific meetings).

III. ESTABLISHING THE PRE-REVIEW PROCESS

The initial impetus for establishing a pre-review process for this study came from the sponsor, DNDi. Having previously sponsored international collaborative studies, DNDi was familiar with the ethical complexities of conducting research in resource-poor settings. In order to ensure that the ethical issues in the HAT study were fully considered, it reached out to the Ethics and Health unit of the World Health Organization (WHO) for technical assistance. In response, WHO recommended convening an expert meeting with participants from African countries that would potentially be hosts of the study, or that had experience in protocol reviews, in collaboration with an established REC outside the region with experience in international collaborative research.

The initial plan was to host the meeting in Brazzaville or another site that would likely be participating in the HAT study. However, the meeting organizers were unable to arrange a meeting site in Africa due to a variety of logistical and security issues. When the Ethics Committee of the Faculty of Medicine of the University of Paris, Descartes ('University of Paris Ethics Committee') volunteered to host the meeting within the necessary timeframe, it was therefore decided to move the meeting to Paris. An advantage of this move was that all of the members of the University of Paris Ethics Committee attended the meeting and contributed to the discussion. Unfortunately, as a result of problems obtaining visas, REC members from the Democratic Republic of the Congo (DRC) (the country where most of the trial participants will be recruited) were forced to participate in the meeting by teleconference. In addition, representation from the CAR (the second key study site) was insufficient, as representatives of the main committee in charge of reviewing clinical research were unable to attend.

Invitations to the meeting were extended to REC representatives from a variety of African countries, as well as international experts in HAT. REC representatives included, but were not limited to, individuals from countries likely to be selected as host sites for the study. One of the key considerations in selecting invitees was to ensure that different types of ethics review systems would be represented in the discussion. For example, individuals were invited from both national committees sponsored by governmental agencies and local committees housed in research institutions. Invitations were issued by the University of Paris Ethics Committee, with input from WHO's Ethics and Health unit. As sponsor of the study, DNDi paid for the meeting expenses through a direct transfer of funds to the Faculty of Medicine of the University of Paris, Descartes. DNDi was not involved in the selection of meeting participants.

Before the day of the meeting, participants received the same documents that would normally be included in an REC application, including the protocol, participant information forms, and the investigator's brochure. All of these documents were distributed in both English and French. The meeting itself was also conducted in both languages, with simultaneous interpretation provided by professional interpreters. Meeting participants commented that allowing participants to speak in their native language reduced inhibitions and resulted in a richer discussion.

The day-long meeting was held at the University of Paris, Descartes. It began with presentations from an expert about historical approaches to the management of HAT, followed by presentations by DNDi about the rationale and approach of the proposed intervention and critical ethical considerations relevant to the project. After a question-and-answer session, DNDi representatives left the room to allow participants to deliberate and develop recommendations. At the end of the day, the DNDi representatives were invited back into the room and the recommendations were presented, following which all participants engaged in an open discussion.

A rapporteur took notes at the meeting and prepared an extensive report, which was disseminated to meeting participants and included in DNDi's subsequent submission to RECs in the DRC and the Central African Republic (CAR). In addition, the report was submitted to the ethics review board at Médecins sans Frontières (MSF), as several selected trial sites were managed by MSF operations. In light of the report's recommendations, DNDi made several changes to the protocol, as discussed further below.

IV. KEY ETHICAL ISSUES THAT EMERGED FROM THE PRE-REVIEW PROCESS

Scholars have identified the following hallmarks of ethically acceptable research in developing countries: collaborative partnership; social value; scientific validity;

[14] The HAT Platform is 'a clinical research and access-supporting network that brings together key regional actors involved in the control of HAT in endemic countries, notably Ministries of Health, National Control Programmes, regulatory agencies, academia, clinicians, the World Health Organization (WHO) and NGOs.' Drugs for Neglected Diseases Initiative (DNDi). 2011. *Human African Trypanosomiasis Platform*. DRC: DNDi. Available at: http://www.dndi.org/images/stories/strengthening_capacities/HATbrochure.pdf. [Accessed 16 May 2014].

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fair selection of study population; favorable risk-benefit ratio; independent review; informed consent; and respect for recruited participants and study communities.[15] All of these issues were addressed in the pre-review process. Rather than attempting to provide an exhaustive summary of the entire meeting, the discussion that follows highlights some of the key issues that resulted in substantive recommendations to the sponsor.

1. Local Values and Attitudes: The Issue of Pregnancy and Contraception

Even though the potential for teratogenicity has been ruled out in animal studies, the teratogenic risk associated with the study medication in humans has never been tested. Therefore, the protocol required women of child-bearing potential to undergo urine pregnancy testing before enrollment. Women determined to be pregnant would be excluded from participation. In addition, any woman of child-bearing potential who enrolled in the study would be required to agree to use a medically-proven method of contraception (including abstinence) from the day of consent through the post-treatment phase.

While meeting participants recognized the scientific rationale for excluding pregnant women from the study, several of the African representatives emphasized the potential negative social consequences of a positive pregnancy test result, particularly for minors. They also questioned the appropriateness of requiring women to discuss and affirmatively agree to use contraception, given the cultural sensitivity of the issue. Some of the scientific experts observed that the likelihood participants would become pregnant during the study was extremely low, both because HAT has a negative effect on fertility[16] and because participants would likely be too ill to engage in sexual activity.[17] The group concluded that it was appropriate to maintain the pregnancy test requirement provided that strict limitations were imposed on the disclosure of test results. However, it recommended eliminating the required discussion about contraception. DNDi accepted these recommendations and changed the protocol accordingly.

2. Social Value of the Research

As noted above, the protocol provided for the provision of food to participants along with the medications, in part because the fexinidazole must be administered with food in order to be properly absorbed. Some of the African representatives at the meeting questioned whether this requirement – although clearly justified in the context of the study – could potentially undermine the relevance of the study results in real-world settings, where individuals with HAT do not always have stable access to food. This concern was phrased in terms of the ultimate value of the research to the local population. Specifically, would establishing the safety and efficacy of fexinidazole taken with food benefit the local population if a large portion of the population will not necessarily be able to take the medication with food?

As a potential solution to this problem, meeting participants suggested that, if fexinidazole is ultimately determined to be an appropriate treatment for HAT, it should be packaged and distributed with food substitutes that could be administered with the medication. Some participants suggested that national regulatory authorities could require the inclusion of food substitutes as a condition of granting marketing authorization. One of the recommendations that emerged from the meeting was that DNDi 'should work with public health authorities to ensure that, once the medication receives marketing approval, it will be provided with sufficient food to ensure proper absorption.'

The recommendation to engage regulatory authorities and public health officials in finding a solution to the problem was an important outcome of the meeting. Individual RECs, which have limited legal mandates, may have been less likely to consider this kind of recommendation to be within the scope of their authority. The open-ended, non-binding nature of the pre-review process encouraged the participants to adopt a broader approach.

3. Informed Consent

One of the strongest conclusions to emerge from the meeting was the need to improve the approach to obtaining informed consent from participants. Emphasizing the social context in which the study would be conducted, the recommendations called for the draft consent form to be 'completely revised so that it is understandable by potential participants, taking into account the fact that the study population has high rates of illiteracy and is vulnerable in many respects.' Participants also insisted on greater clarity on the overall process by which consent would be obtained – for example, who will obtain consent, what information will be shared with participants' families, and what visual information will be used.

A clear message was conveyed that the existing plans for obtaining participants' informed consent were inadequate and that the process would have to be

[15] Emanuel et al., *op cit*. note 6, p. 931.

[16] World Health Organization (WHO). 2013. *Control and Surveillance of Human African Trypanosomiasis*. Geneva: WHO: 4. Available at: http://apps.who.int/iris/bitstream/10665/95732/1/9789241209847_eng.pdf?ua=1 [Accessed 16 May 2014]; B.O. Ikede et al. Reproductive Disorders in African Trypanosomiasis: A Review. *Acta Tropica* 1988; 45: 5–10.

[17] World Health Organization (WHO), *op cit.* note 16, p. 106.

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reformulated and simplified. It is unclear whether a local REC would have felt empowered to request a foreign study sponsor to make such extensive revisions to the process of obtaining informed consent. The informed consent discussion demonstrates the potential for local RECs working together to have a greater impact than a single REC acting on its own.

In response to these suggestions, DNDi has substantially rewritten and shortened the consent form and created a toolkit of drawings illustrating key information about the study and the interventions to be used. It has also prepared a detailed description of the procedures to be used in obtaining informed consent.

4. Payments to Participants

Participants discussed the appropriateness of offering payments or other remuneration to study participants, noting the complexity of determining the line between legitimate compensation for time, effort, and inconvenience, on the one hand, and undue inducement, on the other. For example, some people suggested that it might be appropriate to pay participants who come to follow-up visits, on the theory that such payments could not constitute undue inducements because they would only be offered after study enrollment. Others worried that such payments might create pressure on participants not to withdraw. The discussion revealed that a range of reasonable perspectives exists on these issues. The group concluded that there was no universally 'correct' definition of undue inducement and that RECs should therefore resolve issues of payment according to their own local norms.

5. Attention to Local Legal Considerations

Participants discussed the challenges of obtaining informed consent from adolescents and persons who might have limited decision-making capacity due to psychiatric complications of the disease being studied. They pointed out that legal issues surrounding consent by minors and decisionally impaired individuals vary considerably within African jurisdictions. The group urged the sponsors to investigate these issues further in consultation with legal experts. In addition, the group emphasized the importance of complying with local laws regarding the storage, destruction, and transfer of biological specimens.

6. Impact of the Research on Local Health Systems

An important question concerning research in developing countries is whether the resources devoted to carrying out a study will be taken away from other pressing healthcare needs. For example, as part of this study, participants will spend 3–7 additional days as hospital inpatients, which could take away beds, staff, and equipment from other patients in need of hospital care. To address these concerns, DNDi has pledged to make efforts to increase staff at local hospitals during the study as needed and to leave equipment on site after they leave. The pre-review process provided a valuable opportunity for DNDi to express these commitments publicly and in a manner that will apply to all study sites, not just those whose RECs take the initiative to raise the issue.

7. The Importance of Developing a Genuine Collaborative Partnership

Much of the discussion at the meeting focused on steps DNDi could take to involve host country researchers and community members in a genuine partnership. For example, participants emphasized that review by host country RECs, while necessary, is not in itself sufficient to ensure community engagement. Most REC members typically have professional backgrounds, and even 'community representatives' on RECs do not necessarily speak for the most vulnerable segments of society. Participants suggested that DNDi engage in community consultation to inform and exchange ideas with the local leaders. In addition, they affirmed the importance of DNDi's decision to include host country scientists in leadership roles in the study, as well as to increase local representation on the DSMB.

DNDi agreed to these recommendations and is working to develop additional techniques for community engagement. For example, in the DRC and CAR, they are working with existing mobile teams that go into villages to provide HAT screening.

8. Ensuring Compensation for Injured Participants

Several participants raised questions about the availability of compensation for participants who sustain injuries as a result of the research. It was noted that DNDi's insurance might not be considered applicable in cases of malpractice and that local researchers are unlikely to have individual insurance of their own. Some African countries now require clinical trial sponsors to provide insurance coverage for research-related injuries, but these requirements are not uniform.[18] The group was unable to come to a definitive recommendation on this issue, other than to call on DNDi to provide additional

[18] J. Hedgecock. 2005. *Insurance in Clinical Trials*. Buckinghamshire: The Institute of Clinical Research.

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information about the availability of insurance to host country RECs.

V. REFLECTIONS ON THE PRE-REVIEW PROCESS

Participants in the pre-review process were uniformly satisfied with the experience. At the most basic level, the process itself helped satisfy one of the fundamental ethical guidelines for research in developing countries – developing a collaborative partnership between research sponsors from the North and host countries in the South. Participants at the meeting included a wide range of representatives of African countries, including both REC members and also local scientific experts. This provided the opportunity for knowledge sharing not only between the sponsors and host countries but also among host countries themselves. Moreover, because the meeting occurred at an earlier stage of the protocol development process than a typical REC submission, participants' suggestions had a greater likelihood of influencing the final study design.

By bringing together multiple African country representatives in a coordinated process, the meeting also altered the power dynamics that frequently arise in international collaborative research. As noted above, some developing country RECs may be reluctant to impose too many conditions on research for fear that sponsors might take their studies elsewhere. By allowing potential host countries to speak in a single voice, this concern was substantially reduced.

Another benefit of the meeting was that it offered the participants a model of a well-organized and rigorous process of ethical deliberation. In a sense, it served as a sort of experiential education in ethics review for all meeting participants. This kind of learning-by-doing is undoubtedly a more effective means of capacity building than more passive forms of training such as lectures and conferences.

Finally, the meeting helped streamline the subsequent process of host country ethics review by providing RECs with a set of pre-discussed issues and the pre-reviewers' recommendations. These materials avoided the need for the kind of back-and-forth discussions that frequently lead to delays in completing the REC process. In fact, when DNDi submitted the study to RECs in the DRC and CAR, the study was approved in only 2.5 and 3 months, respectively. This is substantially less time than would normally be expected for the first pivotal trial in patients of a totally new chemical entity.[19] Moreover, no significant new issues were raised at the local RECs; all of the major issues had already been thoroughly considered as a result of the pre-reviewers' recommendations.

While the pre-review process appears to have had clear benefits in this particular study, questions about the long-term sustainability of this process still need to be explored. First, convening an international meeting of REC representatives is expensive and time consuming. As such, it is an option that most sponsors may not be in a position to consider. Second, the process's success was due in large part to WHO's role in convening the meeting, but it is not realistic to expect WHO to play this role in every collaborative international trial. In order for the process to be used on a wider scale, other mechanisms for convening and hosting these meetings will need to be found. Third, the impact of the process on local REC review should be carefully monitored. Experience with DNDi's submission of the fexinidazole study in the DRC and CAR suggested that the pre-review was beneficial, but it is possible that the pre-review recommendations will have less of an impact on other RECs' assessment of the study or on the speed of the review process. Moreover, even though the pre-review process was designed to be advisory only, there is a risk that some countries' RECs may view it is a seal of approval, leading them to be less rigorous in their review process than they might otherwise be.

Overall, this experience with pre-review suggests that it is a promising avenue for improving the quality of ethical oversight of research in developing countries. Further efforts will be required to adapt this model to other studies and to develop sustainable models for its regular use.

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Biographies

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[19] Anecdotal evidence from TB vaccine trial sites in Uganda and Mozambique suggest that REC approval typically takes approximately 5 months. H. Geldenhuys et al. Analysis of Time to Regulatory and Ethical Approval of SATVI TB Vaccine Trials in South Africa. *SAMJ* 2013; 103: 85–89:88.

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