

PERSPECTIVES PAPER

Development of Guidelines for the Conduct of HIV Research Monitoring by Ethics Committees in Nigeria

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Abstract

Nigerian research ethics committees are charged with the responsibility to monitor ongoing research to ensure compliance with ethical standards. Recent evidence from qualitative studies on research conduct however, indicate that many research studies fail to implement their protocols as written, and that this is not reported due to a failure of comprehensive monitoring. As Nigeria is in many respects a highly suitable country in which to conduct HIV biomedical prevention research, we argue there is a need to reprioritise the strengthening of the monitoring capacity of ethics committees so that such vital and ethically complex research can be conducted with confidence. We identify the need for (i) improved resourcing and training of ethics committee members, and (ii) comprehensive planning of research monitoring as part of the ethics committee protocol review process. We also highlight the significance of community collaboration and the establishment of a central pool of national monitors, as essential components for reinvigorating monitoring capacity. (*Afr J Reprod Health* 2014; 18[3]: 66-73)

Keywords: Ethics, monitoring, HIV prevention, compliance

Résumé

Les comités nigériens de recherche sur l'éthique sont chargés de la responsabilité de surveiller les recherches en cours pour assurer la conformité avec les normes éthiques. Des données récentes provenant des études qualitatives sur la conduite de la recherche indiquent cependant que de nombreuses études de recherche ne parviennent pas à mettre en œuvre leurs protocoles écrits, et que ce n'est pas signalées à cause d'une défaillance de la surveillance globale. Alors que le Nigeria est à bien des égards un pays très approprié dans lequel l'on peut mener des recherches sur la prévention biomédicale du VIH, nous soutenons qu'il est nécessaire de redéfinir les priorités du renforcement de la capacité de surveillance des comités d'éthique de sorte que cette recherche vitale et éthique complexe puisse être effectuée en toute confiance. Nous identifions la nécessité de (i) l'amélioration des ressources et la formation des membres des comités d'éthique, et (ii) la planification globale de suivi de la recherche dans le cadre du processus d'examen du protocole du comité d'éthique. Nous soulignons également l'importance de la collaboration de la communauté et la mise en place d'un pool central de moniteurs nationaux, en tant que composants essentiels pour relancer la capacité de surveillance. (*Afr J Reprod Health* 2014; 18[3]: 66-73)

Mots-clés: éthique, la surveillance, la prévention du VIH, de la conformité

Introduction

Nigeria is home to the second largest HIV epidemic globally, with 3.5 million people living with HIV and more than 300,000 new infections occurring annually^{1,2}. The high number of new infections makes Nigeria a justifiable site for HIV prevention research, particularly as there is a modest downturn in the national HIV incidence from 0.27 in 2010 to 0.26 in 2011 and 0.24 in 2012³. Such research has the potential to bring

significant benefits to Nigeria if well designed and conducted. Reports of sub-optimal research conduct, and in some instances outright misconduct^{4,5}, however, suggest that there is a need to strengthen the research monitoring framework in Nigeria to ensure that research protocols are implemented in accordance with currently recognised standards.

In 2007, the Federal Health Ministry adopted the National Code of Health Research Ethics. This Code defines 'research', the principles of ethical

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health research, the criteria for reviewing health research proposals and the constitution and scope of health research ethics committees. The code stipulates five specific monitoring activities with which research ethics committees are charged. These are (i) continuing oversight of approved research at intervals judged by the HREC as being appropriate, given the degree of risk involved in participation in the research; (ii) authority to examine all aspects and documents including consent forms, questionnaires, case report forms that are related to the research and necessary for the HREC to conduct its oversight function; (iii) annual monitoring or at least once during the lifetime of the research where the duration of the research is less than a year; (iv) authority to observe or cause to be observed on its behalf, the research and its consent process to ensure compliance with the highest scientific and ethical standards; and (v) authority to initiate the process of oversight of research in the event of receipt of complaints, information or data relevant to the research from any source⁶.

Monitoring the ethical conduct of research to ensure adherence to ethical standards is thus a clear requirement for Nigerian Health Research Ethics Committees (HRECs). This paper will consider evidence that ethics monitoring of research does not necessarily occur in practice, look at how the system could be improved to optimise monitoring by HRECs and why these issues are particularly important in HIV prevention research.

The HIV prevention research context

Since 2007, there have been a series of advances in HIV biomedical prevention that have implications for ongoing research: voluntary medical male circumcision⁷⁻⁹; pre-exposure prophylaxis (the use of antiretroviral drugs in HIV negative people at high risk of HIV to reduce risk)¹⁰⁻¹⁴; and treatment-as-prevention (treating HIV positive people with antiretroviral drugs earlier in their disease course to prevent onwards transmission to sexual partners)¹⁵. In addition, post-exposure prophylaxis reduces the risk of HIV infection if initiated within 72 hours of exposure^{16,17}.

International ethical guidelines require consideration of 'state of the art' HIV prevention interventions when testing new experimental HIV prevention interventions¹⁸. Forthcoming HIV prevention research therefore needs to take these new advances into account when designing new trial protocols, and consider whether or not any or all of these interventions should be included in the standard of prevention for trial participants. Sound justifications should be provided for decisions, with evidence of consultation among key stakeholders, including the community¹⁹.

The need for ongoing research in HIV prevention remains strong, as none of the newly established interventions listed above provide an ideal form of protection. The attributes of optimal biomedical HIV prevention include: a high level of efficacy; suitability for women and men; effective for both anal and vaginal exposure; high protection achieved by a single or small number of doses; dosing not coitally dependent; low cost; and stability at room temperature²⁰. Vaccination is the intervention that would best meet these criteria, but despite some progress towards this goal, an effective HIV vaccine remains elusive²¹. In the meantime, other innovative prevention technologies, such as antiretroviral-dispensing vaginal rings and rectal microbicides, are in development²².

HIV prevention research is further complicated by the fact that in undertaking research to find more effective and user-friendly technologies, difficult decisions have to be made about the deployment of newly validated approaches like pre-exposure prophylaxis (PrEP)¹⁰⁻¹⁴ and treatment as prevention (TasP)¹⁵ within the research context, along with the provision of condoms and treatment for sexually transmissible infections. Medical male circumcision, another recently proven biomedical prevention intervention⁷⁻⁹, has already been included as standard of prevention in trials, but this is less applicable to Nigeria where 87% of men are already circumcised²³.

These newly established prevention interventions bring with them profound ethical considerations for design of future HIV prevention trials. It needs to be explicitly clear that decisions made in the protocol design, regarding the standard of prevention, have been informed by

community collaboration processes. Informed consent processes should ensure that participants fully understand and voluntarily consent to participate in the research and that they are aware of the standard of prevention provided within the trial. To ensure that informed processes are applied consistently throughout the duration of the trial, monitoring is critical.

In short, in order to conduct further research on HIV biomedical prevention that is both scientifically valid and ethically sound in protecting the interests of research participants, robust ethical/regulatory frameworks are necessary. Monitoring standards to measure compliance with the protocol is a critical aspect of this²⁴.

Elements of ethics monitoring in research

'Ethics monitoring' in research refers to processes designed to assess compliance with ethical standards, such as those set by regulatory authorities and/or international guidelines¹. These processes include monitoring and reporting of adverse events, amendments to approved protocols, renewal of approvals (annual or at another pre-specified interval), and monitoring of on-site processes for the duration of the trial. Some elements of monitoring are passive, in that they require the receipt and review of documents only. Other tasks are more active, such as on-site monitoring, which should include not just review of documents but observation of informed consent processes and trial-related work practices at the site. On-site monitoring should comprise both announced and unannounced visits by monitors, and are the most complex task and time consuming tasks for an HREC. It has been identified as one of the most effective ways of ensuring compliance with ethical standards during the conduct of research²⁵.

A recent study by Ochieng and colleagues conducted in Uganda examined research site monitoring for compliance with ethics regulatory standards²⁵, looking retrospectively at research monitoring practices. The researchers identified seven critical elements: (i) monitoring compliance with regulatory requirements; (ii) assessing the site facilities; (iii) monitoring the informed consent

process; (iv) monitoring the documentation of informed consent; (v) monitoring the reporting and management of adverse events; (vi) observing the workplace practices; and (vii) training related to the research. Monitoring these seven elements was sufficient for assessing compliance with ethical and regulatory standards, according to the authors²⁵.

Detailed guidance on the creation of a monitoring plan for ethics committees which complies with Good Clinical Practice (GCP) is available from the US Food and Drug Administration²⁶. As ethics monitoring is explicitly focused on the wellbeing and safety of participants, it needs to ensure that processes that are ethically sensitive are being followed correctly. Accordingly, actually witnessing the informed consent process while recruitment is ongoing rather than simply inspecting signed forms is critical. In recognition of the importance of community partnership in HIV research, HIV biomedical prevention research studies should also include the monitoring of community collaboration processes. New tools that help to implement the GCP guidelines are now available²⁷, including exercises that identify strengths and gaps in community participatory practice and activities that list, rank and score trial process through interaction with community members. Observing and documenting the results of these exercises would provide an HREC monitor with a great deal of valuable information about the collaborative processes utilised in the trial, and the perceived success of these.

Research monitoring in Nigeria – the legislative and policy framework

A recent audit of ethical and legal regulation of HIV vaccine research in high incidence African countries, including Nigeria, found that monitoring of ongoing research was a key concern²⁴. Despite mechanisms being in place to monitor research post-approval in Nigeria, monitoring has been identified as one of several ethically complex factors due, primarily to problems with resources and training²⁴.

The audit also identified the need for greater clarity around institutional responsibilities,

particularly a need to ensure that institutions carry out responsibilities regarding monitoring trials post HREC approval. Researchers who failed to adhere to guidelines faced a disciplinary committee⁶, but there appeared to be no consequences for institutions that failed to carry out monitoring tasks.

Research conduct is dealt with at several levels in the Nigerian legal system²⁴. Firstly, general provisions in the Constitution acknowledge the right not to be subjected to torture or to cruel, unusual or degrading treatment. Secondly, there is law at the national level enacted by the national assembly and the senate, responsible for legislation including the National Bill of Health, which established the committees detailed below that have oversight of research. Thirdly there is the policy level, where national plans and research codes sit, including the HIV Vaccine Plan and the National Code of Health Research Ethics.

The National Agency for Food and Drug Administration and Control (NAFDAC) is the body responsible for the registration of new drugs and the regulation of clinical trials. The NAFDAC and the National Health Research Ethics Committee (NHREC) technically have oversight of the research conduct, but in practice the responsibility for ethics review and monitoring of clinical research protocols is delegated to institutional HRECS. HRECs are expected to review clinical research protocols to ensure both the scientific validity and ethical integrity of the study. The research protocol is then submitted to NAFDAC for review of the pharmacological elements of the study following approval of the study by the Institutional HREC. All clinical trials are expected to receive clearance from both the local HREC and NAFDAC before commencement of the study. In addition, the institutional HREC that provides ethics clearance and NAFDAC are expected to monitor the conduct of the clinical trials. The functions of NAFDAC and HRECs with respect to research oversight functions are articulated in the National Health Bill of 2009²⁴

Nigeria also has a National HIV Vaccine Plan, which has had two iterations – one in 2001 and the second in 2012²⁸. Under the Vaccine Plan, it is stipulated that data in HIV biomedical prevention trials are to be monitored by an independent Data

Safety Monitoring Board (DSMB), appointed specifically to oversee matters relating to adverse events and the efficacy (or lack thereof) of the experimental intervention. The role of the DSMB can be seen as complementing, rather than replacing, the monitoring responsibilities of the NAFDAC and HRECs²⁹.

One of the key goals of the National Vaccine Plan is, “to enhance policies surrounding HIV vaccine trial execution and regulation by creating strategies for Nigerian regulatory agencies to work together to improve coordination and integration of their activities, strengthen capacity for the review of HIV vaccine protocols and ensure the safety of all trial volunteers”²⁸. This is clearly relevant to the issue of monitoring ongoing trials to ensure compliance with ethical standards.

One of the main challenges that have limited the ability of HRECs to conduct monitoring activities has been financial resources²⁵. A qualitative study conducted by Agunloye and colleagues found that some HRECs relied entirely upon fees charged to researchers for handling protocol review to finance their operations, while others accessed institutional funding³⁰. This study found that while HRECs followed guidelines from the NHREC with respect to protocol review, only one HREC met the requirement to monitor projects after approval. This post-approval monitoring was funded entirely from the fee charged for protocol review. Training was also a barrier to optimal functioning, with less than 30% of HREC members having formal training in research ethics³⁰.

The limited research monitoring of HRECs in Nigeria may therefore be related to both capacity needs and financial needs. Folayan and colleagues³¹ demonstrated that a 3 day capacity building training for 13 ethics committee resulted in five (38.5%) of the HREC instituting monitoring activities for approved research protocols. The eight other committees also discussed the need to institute these measures to monitor approved research protocols. They identified however finance as a constraint for non-initiation of monitoring activities. The efficacy of training to improve capacity to address ethical issues in resource limited settings has also been highlighted by Ajuwon and Kass³².

In the case of developed countries such as the United Kingdom, where the regulation of biomedical research is well developed, challenges are also faced with onsite monitoring of research, which may be linked to committee members being voluntary³³, as they are in Nigeria. Pickworth noted that many ethics committee members may be unable to add monitoring to their workload, despite recognition of the importance of monitoring research implementation as a means of improving compliance with ethics standards which also deters deliberate unethical practices³³. It is therefore important to identify ways to enable ethics committees perform their role as research monitors while recognising their limitation with respect to time to invest in the process.

One possible way to address this is to have HRECs develop a comprehensive monitoring plan for each protocol approved, giving consideration to the full range of logistical details including timing of site visits, plans for data transmission, and transport and housing requirements for on-site monitors²⁹. The HRECs can then delegate this responsibility to independent bodies that are accredited to play this role. The Nigeria National Health Research Ethics Committee which is currently responsible for coordinating the functions of the HREC, could be charged with the responsibility of accrediting research monitors who can perform site visits efficiently and independently. Research monitors would need to take an accreditation course organised by a certified institution in the country. The HREC could then employ the services of these individuals. Active on-site monitoring not only allows for detection of protocol deviation, it also provides an opportunity for the HREC to interact with researchers and allow for education and information sharing³⁴.

Community experience of research conduct

The findings of the Nigeria ethical and legal audit described earlier, which highlighted concerns with monitoring of ongoing trials after ethical approval, were echoed by qualitative research conducted by the New HIV Vaccines and Microbicides Advocacy Society (NHVMAS)⁴. NHVMAS conducted Community Dialogue meetings and

found that community members reported a perception that informed consent standards were generally low. The following specific concerns were raised: (i) failure to implement consent processes that have approved as part of the study protocol; (ii) overemphasis on the potential benefits of research and avoidance of talking about risks when providing information on studies during consent processes; (iii) insufficient information given about the purpose of research during consent (iv) use of highly technical language in consent forms; (v) failure to translate consent forms into local languages; (vi) participants not given enough information about their right to not participate and their right to withdraw from research if they choose to do so; and (vii) negotiation of compensation occurring during recruitment of participants rather than prior to protocol approval. NHVMAS found that such breaches were reported in trials that appeared to meet ethical standards on paper. The implementation of agreed standards is thus the issue, hence the importance of monitoring and reporting systems to document whether or not standards are actually met in practice.

As previously noted, community collaboration is a critical element in negotiating standards in research, and communities ought to be engaged in monitoring processes to ensure that researchers are accountable for their community engagement practices. The feasibility of community involvement in the monitoring of biomedical HIV prevention research had been previously demonstrated by NHVMAS³⁵. The organisation has reported on its initiation and implementation of a monitoring plan of five research sites engaged with a number of biomedical HIV prevention technologies (two cellulose sulphate and SAVVY microbicide research study sites respectively, and one site engaged with the TMC120 preparatory study in Nigeria in 2005). The process helped community representatives who participated in these monitoring visits understand the research process better. It also enabled researchers at the site to understand community needs, interests and concerns. Very little has been seen in the way of replicating this process in the field despite the prescription by ethics guidance documents such as the Good Participatory Practice Guidelines¹⁹ that

promote community engagement in the monitoring of research process.

Also, as due consideration is been given to building capacity of HRECs to monitor research, critical attention should be given to how the process would engage community representatives. The collaboration between HRECs and community representatives for research monitoring could be strengthened through the engagement of the laypersons on HRECs to play the role of community representatives³⁶. Such representation would however, only be valid if the layperson on the HREC was nominated by the community to play this role on their behalf. Unfortunately, this is often not the case. Otherwise, where research Community Advisory Boards (CAB) exists, HRECs could work closely with such CAB to conduct joint monitoring of research activities. Community Advisory Boards are volunteers or elected community members who represent the community in the which a trial is taking place. Their role is to help researchers understand and respect local customs and practices, to advocate for participants' interests and to work with researchers on locally appropriate information provision.

Moving forward

The landscape for the conduct of HIV prevention research is expanding in Nigeria. Recently, a four year HIV vaccine trial research preparedness project was conducted³⁷. This study intended to highlight the inadequacy in clinical trial research capacity and to supplement other HIV vaccine related efforts in the country. A two year formative preparedness research project on PrEP has also recently concluded and could help develop national understanding of the appropriate model for promoting PrEP use for HIV serodiscordant couples in Nigeria³⁸. Past biomedical HIV prevention research conducted in Nigeria to date includes the cellulose sulphate, SAVVY phase II clinical trial, TMC120 preparatory study and the nonoxynol 9 acceptability study³⁹.

The multi-centre and multi-national in designs of most HIV prevention research requires and engages rigorous scrutiny and monitoring of research site practices by external research

monitoring and auditing bodies. Yet, active engagement of national research regulatory agencies in the monitoring of the conduct of these trials is still essential. Such internal audit and monitoring processes promotes transparency in the collaborative nature of the conduct of these trials. This highlights the importance of building local capacity for research monitoring and the need to address gaps where they exist.

One essential step for the research community is to reach agreement on a set of guidelines that HRECs should follow when conducting monitoring visits for biomedical HIV prevention research. The guidelines should have standards that are clear and attainable, and promote shared understanding regarding the importance that compliance (to the protocol) has to research participant safety. Attention needs to be given to the more complex aspects of monitoring, such as on-site monitoring of informed consent processes and adherence to the specific research protocol. Where there is evidence of non-compliance with HREC approved research protocols, remedial processes should be considered prior to disciplinary measures for the researcher. Moreover, feasible monitoring processes must be aligned with community collaborative processes, to ensure that these are actively maintained through the life cycle of the research.

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