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# Ethical and practical considerations in HIV drug trial closure: perspectives of research staff in Uganda

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## Abstract

There is a gap in evidence regarding how research trial closure processes are managed to ensure continuity of HIV care for HIV positive participants following trial closure within low income settings. This research aimed to establish how research staff in Uganda understood and practised post-trial care for HIV positive trial participants. A grounded theory study was conducted using in-depth individual interviews and focus group discussions with 22 research

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staff from three different trials in Uganda. The results indicated that researchers engaged in three main activities to support trial participants, including: (i) preparing for post-trial care, which included instituting trial closure guidelines, planning necessary resources, and informing trial participants about post-trial care; (ii) facilitating participants during trial exit by engaging in psychological and practical support activities and (iii) providing follow up care and support for participants after trial exit, to respond to the needs of trial participants which often arose after trial exit. This study established a need for a holistic approach to post-trial-care of HIV positive trial participants in Uganda, and the need to engage multiple stakeholders including ethics authorities.

**Keywords**
HIV, trial closure, research staff, Uganda, ethics

## Background

Tackling the HIV epidemic has required an enormous globally coordinated research effort. Much of this research has taken place in sub-Saharan Africa, due to the high prevalence of HIV, having readily available and willing volunteers, and the need to find suitable and affordable interventions for this setting (Selgelid and Jamrozik, 2018; Weigmann, 2015). There is a call for a high level of ethical regulation of research conducted in low income settings due to fears of possible unethical research practice such as coercion/undue influence and exploitation of research participants (Selgelid and Jamrozik, 2018; Weigmann, 2015). Currently, most policy guidelines on trial practice focus on issues around trial recruitment and trial conduct and provide detailed guidance on these, while the area of trial closure has received relatively less attention. Thus, areas such as recruitment, informed consent, standards of care during research, and monitoring and management of adverse effects during trial conduct receive greater attention than the issue of post-trial obligations (Nalubega and Evans, 2015). Recent research suggests that trial closure can be a stressful time for trial participants and that additional support for participants may be required during the trial closure period (Nalubega et al., 2019). Research ethical debates have, therefore, started to focus on post-trial care.

Post-trial obligations have been largely understood to mean the obligation of researchers to continue to provide a proven intervention to the respective trial participants beyond trial participation (Lawton et al., 2019). However, in some types of research, especially those involving chronic conditions, post-trial obligations may necessitate going beyond the provision of trial products/interventions, and incorporate a range of other on-going services such as continued care and management of the disease condition and related psychosocial services (Cho et al., 2018; Lawton et al., 2019). In research involving HIV infected

persons, there is need for continued/lifelong provision of HIV treatment, care and support, which requires referral and adequate linkage to alternative care facilities, and follow up beyond the period of trial closure (Cho et al., 2018). Additionally, the need for monitoring and compensation for potential adverse effects from trial interventions (Lawton et al., 2019), and provision of trial feedback (Chen et al., 2016; Schroter et al., 2019), have been key concerns in post-trial (research) ethics.

Authors in the field of HIV have recommended the need to address a range of post-trial care needs of research participants including ensuring continued access to required HIV treatments, psychosocial support and other services, (Cho et al., 2018; Nalubega et al., 2019, 2021; Vallely et al., 2009). Despite these recommendations, a gap in research regulation appears to exist whereby available policy guidelines are too generic and do not emphasise key aspects of research ethics which appear essential to some stakeholders (Kwagala et al., 2010). Where guidelines exist on some of the post-trial aspects, these provide very limited information to adequately guide practice. For example, in Uganda, the research regulatory authority, the Uganda National Council for Science and Technology points out the importance of continued post-trial care and follow-up following trial closure for an appropriate period of time (UNCST, 2007, 2014), but do not state what type of care and for how long this should be undertaken. This general guidance makes the current approach to post-trial care unclear and non-specific, and may not be suitable for guiding research practice. Authors have recommended the need for ethics authorities to ensure that specific guidelines and policies are made on how post-trial care issues, for example, access to treatments, should be approached to enable standardisation of the care provided to research participants following trial closure (Kwagala et al., 2010). Ethics review boards in particular have been urged to provide final guidance on post-trial care (UNAIDS, 2012).

Thus, there is a call for further guidance and regulation to expand on existing guidelines and to provide more specific guidance on post-trial care. Despite the need, it is argued that the area of post-trial care is not sufficiently well studied to generate reliable evidence that can influence policies and practice (Pratt et al., 2012; Slack, 2014). Existing research on post-trial care has been predominantly undertaken in clinical areas such as Cancer or Diabetes (Lawton et al., 2019). There is an important gap in our understanding of HIV-related post-trial practice.

## *Study aim*

This research sought to establish how research staff understand and practice post-trial care in drug trials involving HIV positive participants in Uganda.

## Methods

The study adopted a qualitative, constructive grounded theory approach (Charmaz, 2014), which resulted in construction of a model of 'Facilitated Transition' to guide post-trial practice – reported in another paper (Nalubega et al., 2021).

### *Study setting*

We included participants from two research institutions involved in running three separate HIV clinical trials. Each of the trials was in a different geographical location. Trial 1 was conducted at an urban site in Kampala, Trial 2 at a peri-urban site in Western Uganda and Trial 3 at a peri-urban site in Eastern Uganda. Trials 1 and 3 were conducted by the same research institution.

### *Recruitment and data collection methods*

Purposive and convenience sampling approaches were employed to ensure representation of geographical sites, trial staff categories and genders. In addition, the principle of data saturation was adopted in determining the final sample size. We interviewed 22 research staff in total comprising of three trial coordinators, four clinicians, five staff related to counselling and home visiting, and ten nurses. Participants were interviewed using focus group discussions (FGDs) and key informant interviews (KIIs). In total, two FGDs were conducted. Both FGDs were from Trial 1 with one FGD having eight study nurses and another having three staff from counselling/home visiting. The remaining staff including two nurses, two counsellors, four clinicians and three trial coordinators were interviewed using key informant interviews. Research staff were approached through their supervisors, and all those approached agreed to participate. Staff were eligible to participate if they had been directly involved in exiting participants from research trials within the past 1 year. Interviews were conducted in the English language by the first author (who was a Ugandan nurse and a PhD student at the time, who had previously worked on HIV clinical trials). All interviews were conducted at research clinics where the respective staff worked. Data was collected during October 2014–August 2015.

### *Data analysis*

Interviews were transcribed and analysed using a standard grounded theory approach as described in Charmaz (2014) using open coding (line by line coding), focused coding (coding larger sections of data), axial coding (developing categories and showing their relationships between them), theoretical coding (comparing and collapsing categories) and theory construction. Other techniques that improved

our analysis included memo writing, theoretical sampling, constant comparison and diagramming. NVivo 10 was used to manage the data.

### *Maintaining rigour*

Measures to ensure rigour in the current study included constant discussions among the research team about the analysis and the resultant interpretations, use of verbatim quotes to support our interpretations and paying attention to disconfirming cases and opposing or divergent views of the participants.

### *Ethics*

Our study was approved by the University of Nottingham UK and The AIDS Support Organization (TASO) Uganda, Research Ethics Committee (REC). The study was registered with the Uganda National Council for Science and Technology (UNCST), as SS3608. We received written permission to undertake the study from both participating institutions and written informed consent was given by all respondents. Anonymity and confidentiality of all participants' information was ensured throughout the study conduct and reporting. All names used in the write up of this study are pseudonyms.

## Findings

### *Participants*

The study included 22 research staff. These were: three trial coordinators, four clinicians, five counsellors/home visitors, and ten nurses. Out of the 22 staff, 15 were from Trial 1, four were from Trial 2, and three were from Trial 3. Although we had planned to have a relatively balanced distribution of research participants across cadres and trials, this was not possible due to the diverse nature of staff composition in the included trials. The majority (72.7%) of staff were female.

### *Themes*

The findings revealed a number of activities that researchers engaged in, or felt were necessary, to facilitate the transition of HIV positive trial participants from research to 'usual care' facilities for continued HIV management. These activities were sorted into three major themes; (i) planning and preparing for trial closure, (ii) facilitating participants during trial exit, and (iii) care and support after trial exit.

### *Planning and preparing for trial closure*

Researchers noted that providing post-trial care required prior preparation and, ideally, should be initiated with participants during preparation for the trial and

during trial conduct. Researchers reported that they relied on ethics documents such as national and international research guidelines to prepare for post-trial care. However, they noted that most of these guidelines did not provide explicit guidance for post-trial care which made preparation difficult. For example, while areas such as informed consent and care during trial conduct were well elaborated in the guidelines, there was a lack of clear guidance on important post-trial issues such as follow up after trial closure to ensure adequate linkage to care or compensation for side effects related to trial participation. Consequently, researchers recommended the need for research guidelines to include post-trial care as an important part of trial practice.

> *If it is an obligation or if it is a policy of an institution, then they can add it (post-trial follow-up) on the budget; it can be added onto the budget and say 'for us we do this, if it is a policy of an institution. (Jane, trial coordinator)*

Activities that were seen to be important to post-trial care included establishment of trial closure guidelines, planning necessary resources and preparation of trial participants for post-trial care. Preparation of trial participants involved providing them with relevant information on trial closure and guidance on how and where to access care after leaving the trials.

> *Trial closure starts at the beginning of the study apparently. Because as we start the treatment of patients, we go through the screening, we go through the enrolment, we see them settle in, we prepare them or we tell them that there is time when the study will end so that as we start, as they settle in, they know that there is time and the trial will end. So, by the time we get to the closure, they are already into closure. (Joy, counsellor/health visitor/community mobiliser)*

Psychological support was also provided to address the emotional needs of the participants associated with trial closure. The main psychological concerns of trial participants that emerged during closure of the trials [reported in a recent publication by the authors] included loss of quality care and supportive relationships within the research setting, fear of how to find suitable care facilities after living the trials, and fear of possible side effects occurring after trial closure. To address the psychological needs of trial participants, research staff provided psychological support in form of counselling and providing relevant information to the participants during preparation for trial closure.

> *So, we start preparing them psychologically because many of our participants get attached to us and they don't want to go away from this kind of care that we have been giving them. So, we start preparing them before the real time of closure. (Nsubuga, clinician)*

## Facilitating participants during trial exit

Research staff engaged in various activities to support trial exit processes. For example, they provided continued psychological support to allay participants' anxieties associated with leaving a trial.

> *Then of course, all the time we have to talk to the patients because some we know also they become a bit anxious, they have been with you for four years, may be for how many years, now somehow the end is coming, so you have to keep preparing them. (Jane, trial coordinator)*

Research staff reported the need to support trial participants to identify and link back to healthcare facilities of their choice. However, in practice, the support provided was generally limited to providing referral letters, an approach research staff perceived as passive and insufficient to achieve appropriate linkage to post-trial care.

> *Practically it ends at giving them referral letters, though usually on the referral letter we are giving, we have contacts, we put our contacts there as well in case the health giver the other side may need more information about what we have written. (Lydia, clinician)*

Research staff felt that current practices regarding linkage to care could be improved by engaging in a more proactive researcher-led process, for example, by accompanying participants to the care facilities and assisting them to (re)register in care.

> *For example, these patients we work with, some have challenges that we don't write in the exit reports, for example a patient is having psychosocial issues, a patient is having adherence issues, a patient is having may be some health issues or medical issues, that would be discussed doctor to doctor. So I believe it would be good when we move, we see those health workers, we discuss with them on the way forward of the patient other than giving them exit reports that don't explain more" (Favour, counsellor/home visitor).*

In addition, due to the low economic status of many trial participants, staff felt strongly the need for some continued financial/material support to address the socio-economic needs of the participants after trial closure. This need was partly attributed to an ethical obligation of researchers to compensate trial participants for their contribution in the trials and partly seen as a moral obligation to support those who were in need and who had become accustomed to receiving benefits during the trial.

> *So, me my appeal to researchers is to always at the end of the study to extend some help to those people, because they give in a lot. (Favour, counsellor/home visitor)*

### *Care and support after trial exit*

Upon leaving the trial, research staff reported the need for participants to be supported as they established themselves back into 'usual' health and care routines. At a minimum, staff felt that participants should be supported for a period of 12 months, during which time a number of activities should be undertaken to provide psychological and socioeconomic support to enable participants to adjust to life after the trial.

> *'It makes a lot of sense to follow them up because for some drugs, the reactions or side effects may come a little later than within the defined study period. So it is important to follow them up and see if anything came up that would still be associated with the drugs, but it is not done. At least we don't do it as an institution'. (Wambo, clinician)*

In addition, all staff saw it as their duty to provide feedback on trial outcomes. Despite this desire however, dissemination of trial results had not been done in any of the included trials. Staff cited bureaucratic reasons, such as trial regulatory issues, as sometimes interfering with timely delivery of trial results. They recommended that a mechanism should be provided in which participants can receive interim results as they wait for the final trial feedback.

> *. . . you know these regulatory issues, because sometimes it depends on which scientific conference we are going to present. So you cannot disseminate results before the scientific conference has. . .(Destiny, nurse)*

Additionally, accessing participants for trial dissemination after trial exit was reportedly difficult due to changes of contacts or relocations of participants.

Research staff reported that despite their willingness to offer support after trial exit, it was practically difficult. This was because post-trial care activities are usually not planned for, and hence were not budgeted for. Without the requisite resources, no follow up could take place.

> *The reason as to why it (post-trial follow-up) is not done is because the sponsors facilitate the study up to the date of exit, we stop there. (Favour, Counsellor/home visitor)*

Overall, the support provided to trial participants after trial exit was minimal and relied upon the individual initiatives of the staff. It was strongly suggested that the implementation of post-trial care would require a collaborative approach between a range of stakeholders. Stakeholders would include the researchers, health facility workers, local NGOs, the community, the Government, and ethics bodies. These would play key roles in streamlining the provision of post-trial care, from instituting policies to actual provision of care and monitoring of participants until they settle into post-trial care facilities.

*So bringing people on board where we are referring is also important, which has not been there, we do plan other things, we do plan the end of trial as researchers this side, and it is only at the time of exit that we do give them this letter as an introduction, these people are unaware of what else has been happening, we really need to put these people on board before closure. (Alloy, trial coordinator/nurse)*

## Discussion

This study aimed to establish how research staff understand and respond to the needs of HIV positive trial participants during closure of the trials. Researchers reported a number of activities that are needed to address the needs of the participants and to facilitate their smooth transition from research to 'usual' care facilities. To prepare participants for trial exit, researchers placed great importance on the role of counselling and emotional support in addressing the post-trial care needs of the participants. This approach was considered important to reduce negative emotional effects associated with trial closure (Lawton et al., 2019), and to offer guidance to participants on the next steps in accessing HIV care.

Continuity of care after trial closure requires that there are appropriate processes in place to support trial participants to be linked to alternative facilities (Odero et al., 2018). In HIV and other chronic disease research, appropriate linkage to care is important, given the potential negative consequences of treatment interruptions or treatment failure (Odero et al., 2018). Participants in the current study reported using referral as the main strategy for linking participants to post-trial care, but they considered this to be a somewhat passive and unreliable approach to facilitating successful linkage. Established relevant local and international ethics guidelines (Rennie and Sugarman, 2009; UNAIDS, 2012; UNCST, 2014) consider referral as an acceptable approach to post-trial care. However, this approach has been criticised by various authors who confirm this study's finding that a more practical, proactive and staff-facilitated approach to HIV care linkage is required (Koduah Owusu et al., 2019). For example, a more proactive approach has been successfully used to link HIV positive individuals to care following HIV testing and research has demonstrated higher rates of linkage to, and retention in HIV care (Elul et al., 2017). Such an approach could be adopted for HIV trial closure.

The possibility of negative side effects occurring after trial closure was a major concern for researchers in this study. Many cited a need for ongoing monitoring of trial participants for some time following trial exit. The same concern has been expressed by several other authors (Bukenya et al., 2020; Lawton et al., 2019) who demonstrate that additional follow up and support of HIV positive clients following linkage to care significantly improved their general outcomes. Further still, the need to compensate trial participants for their engagement in research was another issue raised in the current study and is also supported in literature (Kwagala et al.,

2010). However, the whole area of compensation after a trial remains under-researched with knowledge gaps related to the appropriate amounts and the impacts of financial benefits for otherwise resource constrained individuals.

Dissemination of trial results to participants was also cited as an important responsibility for researchers. Nevertheless, although an important part of clinical trials, some authors have reported that most volunteers never receive trial feedback (Chen et al., 2016; Schroter et al., 2019). In this study, hindrances to dissemination were reported to include trial regulatory issues (e.g. where dissemination of interim results was not allowed until the final results had been concluded as was the case in Trial 1) and access issues (as many participants could not be contacted post-study). These findings indicate the need for early dissemination of trial results and for provision of interim results where possible, before participants are finally exited from the trials. Moreover, limited documented evidence exits on the practice of trial feedback in HIV research which calls for more research.

Our study showed that post-trial follow-up and monitoring of trial participants was rarely undertaken by the researchers, and where it was done, it was an individual researchers' effort rather than a protocol driven activity. This was attributed to a lack of planning for the activity and no financial facilitation for its implementation. Our study highlighted the need to establish plans for post-trial care of the participants during trial planning and incorporating these in research protocols, a finding that other authors support (Odero et al., 2018). It is also recommended that in order to improve post-trial care, specific guidelines should be incorporated in research ethics policies and enforced by the ethics authorities (Lawton et al., 2019; Pratt et al., 2017). This study also identified a need for stakeholder involvement in HIV post-trial care. Various stakeholders including health facilities, local leaders and NGOs could be essential for managing trial participants after they leave research related care (Tso et al., 2016).

Current practice and policies tend to limit the implementation of post-trial care to a few aspects such as linkage to care facilities (through referral), providing the trial medication and/or provision of trial feedback. In addition to these, research staff in this study have recommended the need for: more person-centred post-trial care taking into account the psychological needs of participants; a more active researcher-led linkage to care approach; researcher (and other stakeholder) engagement with trial participants following trial exit; and a more person-centred approach to the provision of trial feedback. The proposed approach is further detailed in *the Model of Facilitated Transition in HIV Drug Trial Closure* (Nalubega et al., 2021) and is recommended for HIV trial closure practice in Uganda and related settings.

## Conclusion

This study aimed to investigate how research staff understood, experienced and practised post-trial care for HIV positive trial participants in Uganda. The findings revealed a number of activities that researchers engaged in or felt were necessary to facilitate the transition of HIV positive trial participants from research to usual care facilities for continued HIV management. In addition to ensuring continued access to trial medications (through referral back to routine care) and providing trial feedback, the research identified other critical needs for post-trial care, including follow-up care and monitoring, and financial support. There was general recognition of the need to involve various stakeholders at different points of the transition process, and ethics authorities were viewed as important actors in the implementation of post-trial care. The proposed approach for ethical post-trial care depicts holistic and person-centred care and is recommended for HIV trial closure practice in Uganda and related settings.

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