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Taking the bull by the horns: Ethical considerations in the design and implementation of an Ebola virus therapy trial

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ABSTRACT

Ebola virus is categorized as one of the most dangerous pathogens in the world. Although there is no known cure for Ebola virus, there is some evidence that the severity of the disease can be curtailed using plasma from survivors. Although there is a general consensus on the importance of research, methodological and ethical challenges for conducting research in an emergency situation have been identified. Performing clinical trials is important, especially for health conditions that are of public health significance (including rare epidemics) to develop new therapies as well as to test the efficacy and effectiveness of new interventions. However, routine clinical trial procedures can be difficult to apply in emergency public health crises hence require a consideration of alternative approaches on how therapies in these situations are tested and brought to the market. This paper examines some of the ethical issues that arise when conducting clinical trials during a highly dangerous pathogen outbreak, with a special focus on the Ebola virus outbreak in West Africa. The issues presented here come from a review of a protocol that was submitted to the Global Emerging Pathogens Treatment Consortium (GET). In reviewing the proposal, which was about conducting a clinical trial to evaluate the safety and efficacy of using convalescent plasma in the management of Ebola virus disease, the authors deliberated on various issues, which were documented as minutes and later used as a basis for this paper. The experiences and reflections shared by the authors, who came from different regions and disciplines across Africa, present wide-ranging perspectives on the conduct of clinical trials during a dangerous disease outbreak in a resource-poor setting.
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1. Introduction

Ebola Virus Disease (EVD) caught the attention of the global community following an outbreak in West Africa in December 2013. Prior to the 2013 outbreak, there had been multiple episodes of EVD outbreaks in Africa since 1976 (Heymann et al., 1980). However, the current outbreak in West Africa is of a magnitude that has never been witnessed, with over 27,000 cases reported and more than 11,000 deaths by the end of July 2015. The case fatality was 47% and 64% for Guinea and Sierra Leone respectively (Organization WH, 2015).

Although there is no known cure for EVD, there is some evidence that the disease's severity can be curtailed using plasma from survivors (Kudoyarova-Zubavichene et al., 1999). An African-led effort, comprising of experts in different fields including infectious diseases, various subspecialties of pathology, hematology, blood transfusions, physicians, bioinformatics, bio-banking, ethics, social science, community engagement, patient advocates, logistics, engineers and government administrators, was established to rapidly organize and establish a plasmapheresis and plasma processing and storage facility in West Africa. This was to enable a clinical trial to assess the safety and efficacy of convalescent plasma harvested from EVD survivors, first for its efficacy as a therapeutic product for managing patients with EVD (Nyamathi et al., 2003), and in the future, as a preventative therapy.

Conducting studies on the use of convalescent plasma as a

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therapy for EVD patients raises important ethical and moral issues with regards to the potential risks associated with harvesting plasma from EVD survivors. There are ethical concerns around patient recruitment and the collection of plasma from EVD patients who have just recently recovered from a seriously debilitating infection; the storage, use and sharing of samples and data; the non-inclusion of pregnant women and children; the prioritization of access to therapy; appropriate study design within the context of the compassionate use of convalescent plasma for therapy; and post-trial access issues among others (Yakubu et al., 2014; Hayden, 2014; Folayan et al., 2014a).

The GET is an African-led consortium with international collaborations aimed at harmonizing the response to the outbreak through the belief systems of the community in which it has the greatest effect. The consortium includes expertise from several fields that are necessary to contain this type of outbreak. It has a governing hierarchy that oversees several working groups (Newswire). Its Ethics, Community Engagement and Patient Advocacy and Support Working Group (ECEPAS) reviewed research protocols prior to submission for institutional ethics approval. This paper highlights those ethical discussions and how determinations were reached to ensure ethical integrity in the design and implementation of a protocol that sought to evaluate the Efficacy and Safety of Ebola Virus Disease Convalescent Plasma for Treatment of EVD (hereafter referred to as target study). The protocol took into consideration, the contexts of the localities where trials would be implemented, and the validity of the research methodology.

1.1. Ethical framework for public health emergency research

There are many publications about the ethical considerations of planning and implementing research in emergency health situations (Amey, 1982; Dick, 1993; Richardson, 2005; Molyneux et al., 2013). Some authors argue against conducting research during emergency situations based on the challenges associated with operationalizing the principle of autonomy (Richardson, 2005; Morrison et al., 2009). These authors argue that individuals and the community at large have few or no options to engage with the proposed research irrespective of the level of risk associated with the research, in view of the associated mortality or morbidity of the health condition. In these situations, patients may become more vulnerable, be exposed to potential coercion and exploitation and experience limited mental capacity to make informed choices (Richardson, 2005; Largent et al., 2010).

Examples of emergency health crises that necessitate conducting research during an outbreak include Influenza, SARS, and Avian flu. This is because these health conditions present extraordinary risks not only to the infected individuals but also to the general public at large and due to their extremely fatal and high infectious rate. In addition, they occur suddenly and unexpectedly, and require urgent responses to minimize their devastation. According to the Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada (Tri Council Policy Statement Canadian-TCPS 2) panel on research ethics, emergency health crises tend to be time-limited and require authorities to exercise special responsibilities and powers to deal with the situation (Canadian TCPS, 2015).

The Ebola virus outbreak in West Africa is another global health crisis. In this condition, patient management involves confinement and restricted movement and contact with patients to reduce transmission of the virus through direct physical contact (Lowe et al., 2015; Southall and MacDonald, 2014; Yamin et al., 2015). The emergency crisis caused by the epidemic necessitates the need to conduct research for drugs and vaccines that can cure and or prevent EVD infection. Unfortunately, the situation on the ground makes the conduct of research during the epidemic ethically challenging. For example, affected persons have unattended personal, physical and emotional needs, the health system is severely constrained with lack of effective treatment, making individuals infected with EVD lack access to acceptable standards of care (Nusbaum, 2015; Wiwanitkit et al., 2015). These conditions increase the vulnerability of individuals in the affected region as they are exposed to more fragile negotiations; with volunteers likely to enroll in research as a sole means to obtain medical care (Amey, 1982; Richardson, 2005; Morrison et al., 2009). Similarly, EVD patients in West Africa may experience desperation for any form of life-saving therapies, irrespective of its known efficacy level. The fragile psychological status of affected individuals may limit their ability to make informed choices about participation in EVD research or clinical trials that offer some hope of EVD remedy. Their ability to make an informed decision about the potential for immediate or lifelong adverse effects of their participation may be severely diminished or impaired (Morrison et al., 2009; Burke, 2014; Schmidt et al., 2004).

Despite these ethical challenges, the need to conduct research during rare epidemics such as the EVD outbreak in West Africa is inevitable. Candidate products, including preventive and therapeutic interventions, must continue undergoing rigorous clinical trials to determine their efficacy and effectiveness and their ability to prevent hazards to the community in line with the precautionary principle (Adebamowo et al., 2014; Gonzalvo-Cirac et al., 2013). The need to test these therapeutic and preventive candidate products is based on the need to generate robust evidence on the safety and efficacy of products before being used widely (Gonzalvo-Cirac et al., 2013). Public health crisis situations may thus call for flexibility in the rigor with which therapies are tested and brought to the market. Supporting this view; in her article on the ethics of clinical science in a public health emergency, Sarah Edwards contends that conducting clinical research under the usual regulatory constraints may be difficult or even impossible during a public health emergency (Edwards, 2013). She further argues that, “despite the fears associated with conducting research in an emergency situation, there has been little effort to consider the process by which scientifically robust data can be ethically gathered in such situations” (Edwards, 2013, see page 3). An important question linked to this concern is: how can new interventions for treating dangerous pathogens be tested and evaluated ethically?

1.2. Framework for conducting research in a public health emergency situation

Despite the general consensus on the importance of conducting research during epidemics (Morrison et al., 2009), opinions are divided as to what framework should be used when conducting such research. Some authors have underscored the importance of a robust review of the protocol by competent and independent Ethical Review Boards (ERB), and suggested the need for the ERB to grant a waiver of informed consent under certain circumstances. (Petrini, 2013; Hill et al., 2011; Lemaire, 2007; Triner et al., 2007). Others have argued that the tightly controlled, rigorously staged, and cautiously distributed process by which therapies are normally evaluated is not appropriate in pandemic situations (Vaslef et al., 2006; Kipnis et al., 2006) as responses to sudden public health emergencies need to be both effective and extremely prompt, and the time required to implement most research protocols in the most rigorous manner is often not compatible with the timeline required to respond to an emergency situation and bring diseases under control (Petrini, 2013). To this end, Sarah Edwards proposed a different methodological approach of using cluster randomized

control trials in which both the therapy's safety and efficacy are simultaneously studied within a population by randomly allocating the intervention under investigation to groups of people rather than randomly selected individuals (Edwards, 2013). Similarly, Cohen et al. proposed the use of a stepped-wedge cluster as an alternative to using a randomized control trial design for the development of Ebola virus vaccines (Cohen and Kupferschmidt, 2014) to overcome the ethical dilemmas associated with the continued compassionate use of experimental drugs that have been shown to be safe for use in phase I studies (Joffe, 2014; Hantel and Olopade, 2015). In this design, a new investigational vaccine or other treatment would be introduced to selected groups at a chosen time with those waiting for the treatment acting as control groups. As more of the drug is manufactured, groups acting temporarily as control groups could be included in the study (Edwards, 2013). The phase III Ebola ça Suffit trial which tested a recombinant, replication-competent vesicular stomatitis virus-based vaccine expressing a surface glycoprotein of Zaire Ebola virus (rVSV-ZEBOV) and whose results, released on 31 July 2015; showed 100% effectiveness, was based on an adapted stepped-wedge cluster design (Henao-Restrepo et al., 2015).

1.3. Key ethical considerations in public health emergency research

While the need to be flexible with the design of clinical trials of therapeutic and preventive candidate products during emergency health crisis has been established, the flexibility of clinical trial designs should in no way, compromise the ethical integrity of the research conduct just as much as the scientific validity of the research process is not compromised. Articles 6.22 and 6.23 of the revised edition of the TCPS2: Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (Humans T-CPSECoRI, December 2010) notes that, "basic ethical principles that apply to research with human subjects during the conduct of routine clinical research also apply to the conduct of research during public health emergencies," with due consideration for the preservation of the values, purpose and rights of extremely vulnerable research participants (Cohen and Kupferschmidt, 2014). Waivers are however possible in precisely identified, circumscribed, and exceptional circumstances (Research CIoH, 2010).

The declaration by the Nigerian National Ethics Committee on the use of non-validated treatments to rapidly respond to the current emergency (National Health Research Ethics Committee N, August 9th 2014) and the declaration by the World Health Organization on the appropriateness of offering unproven interventions with due respect for the ethical principles that govern research (WHO, 2014) are guidelines that have changed the trajectory of the clinical trial design and implementation during public health emergencies associated with high case fatality. This change in trajectory of clinical trial design are in line with the arguments by Folayan and colleagues (Folayan et al., 2014a) and Adebomowo et al. (Adebamowo et al., 2014) on the need for clinical trials for EVD therapies and vaccines not to preclude access to compassionate drug use during the EVD epidemic. Rather, alternative trial designs with the potential to generate the needed efficacy data quickly and with greatest social and ethical acceptability should be explored.

The ethical dilemma that resulted from the need to save lives, control the prevailing outbreak and simultaneously develop an effective therapy for disease management and for improved preparedness against future possible outbreaks implies that the study designs used during epidemics may require new thinking beyond the current research framework. Subsequently, we discussed how the various ethical dilemmas associated with experimentation on the use of convalescent plasma for the management of EVD were addressed.

1.4. Experimentation on the use of convalescent plasma for treating in Liberia

Indicators of the efficacy of convalescent plasma for treating EVD was established by Mupapa and colleagues (Mupapa et al., 1999) in 1999 during an Ebola virus outbreak in Zaire in which the investigator treated eight patients with whole blood; seven survived. However, all the patients received supportive care with intravenous fluids and other components of whole blood, such as platelets and coagulation factors, all of which have a potentially beneficial effect, thus confounding the interpretation of the immune therapy's efficacy. There is also a prior report about a laboratory scientist who received convalescent plasma and survived, but this patient also received other therapies including interferon (Emond et al., 1977). The ad hoc use of convalescent blood and plasma has continued during the current epidemic with little documentation of its efficacy (Folayan et al., 2014b).

The effectiveness of convalescent serum and plasma in the management of viral diseases had been established for many years and for several viral and bacterial infectious agents, with recent attention to Spanish influenza (Luke et al., 2006), severe influenza A H1N1 2009 (Hung et al., 2011), severe acute respiratory syndrome caused by coronavirus (Soo et al., 2004), and Argentine hemorrhagic fever (Maiztegui et al., 1979). Experiments in non-primates and non-human primates have demonstrated the efficacy of convalescent plasma in the management of Ebola virus infection (Kudoyarova-Zubavichene et al., 1999; Mikhailov et al., 1994; Dye et al., 2012). However, the efficacy and appropriate dosage of convalescent plasma for the management of Ebola virus infection in humans remain unknown, although some extrapolations were made from Mupapa et al. (Mupapa et al., 1999) to suggest that a dose as low as 200 ml of plasma from convalescent Ebola virus donors may have been effective in curtailing the severity of the infection. More recent preliminary data on the compassionate use of convalescent plasma suggests that similar doses have been used, but there is limited data on the quantity of specific anti-EBOV immunoglobulins that were infused. There are thus many unanswered questions that justify the need to design a clinical trial about the use of convalescent blood for managing Ebola virus infections.

Even though standard plasma is an established therapy worldwide used to treat bleeding and immunological disorders, and even though plasma has been listed on the World Health Organization (WHO) Essential Medicine List (Klein, 2013), there are public discussions on the long-term viability of this form of therapy. This is in view of the known challenges associated with the transfusion of plasma, especially in countries or regions in which the local blood services have inadequate infrastructure for proper donor screening, donation testing and plasma freezing and storage (Burnouf et al., 2014). These challenges include the potential for transmitting viral infections, the limited current potential to scale up this form of therapy, the potential for blood groups ABO transfusion reactions, and the potential for transfusion-related complication in study participants, among others. Despite failure to reach consensus during a meeting convened by the World Health Organization on 11th of August, 2014 to discuss the Ethical considerations for use of unregistered interventions for Ebola Virus Disease, the usefulness of whole blood therapies and convalescent blood serums for Ebola virus management, and the need to evaluate the efficacy of this therapy remains a matter of urgency.

The World Health Organization had since developed a comprehensive document that provides guidelines on the recruitment of EVD survivors and blood donors, the provision of informed consent, blood grouping and screening for other transfusion-transmissible infections, bio-transportation, bio-storage and bio-

banking, the recruitment of study participants and other technical issues related to the transfusion process.

1.5. Principles of plasmapheresis and the passive transfer of immunity

Convalescent Ebola virus Plasma (CEP) from patients who have recovered from the Ebola virus (and are now theoretically virus-free) is believed to contain antibodies that are effective in controlling the infection, resulting in the survival of the patient. These Ebola Virus antibodies (EBOV) are likely to be complex and to be made of several immunoglobulin G isotypes with multiple functionalities. In principle, the plasma collected from a survivor would contain these antibodies, which may provide a similar beneficial virus-neutralizing effect in the recipient as the effect observed in the donor. The plasma can be collected in one of two ways. First, it can be collected either as a single donation of approximately 400–450 mL of whole blood from the survivor, from which approximately 200–250 mL of plasma is separated from blood cells (red and white cells, and platelets) by centrifugation. Second, it can be collected through a procedure called plasmapheresis, in which the donor is connected through intravenous access to an apheresis machine that is programmed to extract only plasma (typically 500–600 mL) without affecting the blood cell components that are returned to the donor. This plasmapheresis approach allows for a larger collection of plasma over more regular periods because it does not interfere with the oxygen-carrying capacity of the red cells, which is inevitably a limiting factor in blood component donation (Burnouf et al., 2014).

1.6. Ethical considerations in clinical trial design and implementation

The Ethics Community Engagement and Patients Advocacy Support (ECEPAS) working group, comprised of experts working in bio-banking, community engagement, research ethics, clinical trials, health systems research, social humanity and organizational administration held several discussions about the ethical issues in the design and implementation of the clinical trial for the target study. Discussions were held weekly through Skype, lead by the overall chair of the consortium with the secretary taking minutes and developing meeting reports. Minutes were circulated soon after the Skype discussions for group members to edit and comments on any issues that could have been incorrectly documented. Reports emanating from the minutes included issued raised by the members, the dynamics of the discussions that ensured, including agreements and divergent views and any resolutions reached. During the next Skype meeting, members would be taken through the previous meeting's report and allowed to correct and endorse the minutes before being adopted as the final discussion report. These discussions covered the following areas highlighted below.

Design of the clinical trials: Although there are no efficacy trials on the use of convalescent plasma for the management of Ebola virus, there have been widespread reports on its use during the current Ebola virus outbreak in West Africa despite the fact that Convalescent Ebola virus Plasma is in short supply (Kudoyarova-Zubavichene et al., 1999). Therefore, the working group discussed how to conduct clinical trials in which the experimental therapy was the limiting reagent and had also been used as salvage clinical therapy. Discussions about the research design at various levels ensued. There was a consensus that it was unethical to withhold a treatment option that had relatively strong potential for clinical utility. Given the long history of using plasma therapy for other infections with no harm, the study was seen as conforming to the principle of non-maleficence. This decision resulted in the first design to apply deferential doses to two clinical trial arms. The realization that CEP would be in short supply to support such a study led to further modifications, resulting in a study design in which patients who were infected with Ebola virus and who were willing to be transfused and monitored under experimental conditions served as the study intervention arm. The control arm would consist of patients infected with Ebola virus who did not have access to convalescent blood because of the non-availability of matched plasma. Patients in the control arm would receive standard therapy for Ebola virus infection, and those in the intervention arm would receive convalescent plasma along with standard therapy.

Inclusion of children in the trial: Initially, the exclusion of children from the trial was proposed. This is common practice for phase 1 trials because children are categorized as vulnerable, and hence, there must be a good justification for doing research on children. There have been multiple public debates about the rationale for such exclusion, especially when the outcome of the study would result in the extrapolation of data from studies conducted in adults to cater for children's needs (Kelly and Mackay-Lyons, 2010).

The working group considered the counter-argument that children have been reported to bear the highest burden from the Ebola virus in the current epidemic (Walker, 2014). Although a few studies have shown that the Ebola virus prognosis in children and adolescents is better than that of adults, current clinical practices using CEP have not excluded children and adolescents. Their exclusion from this study was therefore unjustified; as such exclusion would enhance their vulnerability given the high mortality rate of EVD. The continued request for data on children for various drug therapies by the Food and Drug Administration in the United States before drug licensure is another reason why it was important that this study generate information on the use of CEP in children.

However, counter-arguments were raised, based on the inability of children to give informed consent. The working group did conclude that consent could be given by the parents of the children, and viable assent from children who are old enough to give assent as determined by the Ethics Review Committee should suffice to address this concern.

Non-exclusion of pregnant women from the trial: Very often, women who are or anticipate getting pregnant during the trial are excluded from participating in therapeutic research. Pregnant women are excluded because of concerns about the unproven teratogenic nature of experimental products and their impacts on the fetus (Hall, 2000; Opinion Ac, 1999). For these reasons, pregnant women were excluded from the initial protocol. However, members of the ECEPAS argued against this exclusion based on the principle of justice; first, pregnant women were affected by the Ebola virus epidemic. Therefore, learning about the use of a potentially effective therapy for their management was important. Second, pregnant women are not generally excluded from being recipients of plasma transfusions. Their exclusion in this case therefore had no scientific rationale. Third, exclusion of pregnant women from this study meant that individuals would be unfairly excluded from an action with potential benefits. For these reasons, a case was made for the non-exclusion of pregnant women from the research.

Compensation of donors of convalescent plasma: One of the most extensively discussed issues was the compensation package for EVD survivors who were blood donors. The possibility of providing food packages rather than payment for donated plasma was explored, not only as part of the survivor support initiative but also with the knowledge that balanced nutritional support would improve their blood parameters and general well-being and increase their likelihood of qualifying as plasma donors. There were

arguments against the provision of food packages to EVD survivors because this action could possibly be seen as coercion. This decision was made in view of the current food crisis in many parts of the countries affected by Ebola virus and the associated food shortages (Centre UNN, 2014), the challenges EVD survivors face in getting access to income that results from stigma and discrimination (Davtyan et al., 2014; Tambo et al., 2014), and the challenges that result from the extensive loss of personal property that is destroyed following a diagnosis of Ebola virus.

It was argued that first, providing food packages as an essential support to EVD survivors was a moral good and was justifiable on moral grounds. However, providing food packages for EVD survivors who are critical for the success of the study would make them face an increased pressure to give plasma in exchange for food, owing to widespread food shortages facing the affected countries. Second, providing food only to EVD survivors without due consideration for their families and other community members who are facing similar challenges and do not have options would further deepen the stigma and discrimination against EVD survivors in their communities. EVD survivors have had to deal with stigma because of their history of infection with EVD (Davtyan et al., 2014).

Cash for participating in plasma donation research: The ECEPAS working group had to deliberate on the question of whether survivors should be compensated for plasma donations. Monetary compensation for plasma is common worldwide, including West African countries. However, in the context of research, the transactional exchange of blood or plasma would create the potential for undue inducement and influence, which is the same concern as in exchanging plasma for food packages. It was therefore necessary to explore a reasonable and acceptable mechanism, without deviating too much from the norm. One alternative was to come up with a reasonable compensation for plasma donation because many EVD survivors were already selling their plasma to generate income in places such as Liberia (Folayan et al., 2014b). Although the Consortium does not promote plasma donation for monetary gain, it was believed that compensation of this nature would have limited negative social impacts on the EVD survivors as well as give them the opportunity to use their compensation to access other basic needs. Several arguments were leveled against providing monetary compensation for plasma donation. First, given the current poor financial status of a large number of EVD survivors, any form of monetary compensation had the potential to cause undue inducement. This compensation may also increase the risk of trial disruption because donors can organize, form cartels and then negotiate for increases in the financial incentive for plasma donation. The complex nature of this issue indicated that it was essential to strike a reasonable balance that would ensure survivors were adequately compensated yet not unduly induced to compromise their decision-making autonomy. Similar delicate balances have also been discussed by Njue et al. (2014), Njue et al. (2015).

Members of the ECEPAS Working Group considered the plasma donors and associated loss of resources resulting from participation in the research, that is, their time, travel costs, loss of income during the time scheduled for blood donation, and possible discriminatory practices/stigmatization that would occur because of their engagement with the research. The group argued that it would be appropriate to offer participants breakfast and/or lunch because it would take several hours from the time the plasma donors registered to the end of the actual plasma collection. Group members emphasized that this form of compensation is an entitlement of the participants and should not be promoted as a benefit of trial participation. Monetary reimbursement for transport and lost wages was appropriate. However, the appropriate value of the monetary compensation should be concluded in consultation with the Ethics Review Committee and other community engagement approaches that account for community views, as well as the prevailing governance structures. Such kind of community consultations have been seen to offer an important alternative to identifying and integrating community views in institutional policies and guidelines and community wide research interventions. (Molyneux et al., 2012; Marsh et al., 2013).

Provision of ancillary care for the EVD survivors who were recruited for trials: Reports from the study sites show that EVD survivors face three major challenges post recovery, namely (i) stigma (ii) food/non-food supplies shortage (iii) and post-Ebola virus disease clinical syndrome, including post-traumatic stress disorders. The group explored the feasibility of supporting the establishment of support groups for EVD survivors around the country to facilitate access to peer counseling. The network would also facilitate individual access to Ebola virus crisis response teams through access to established support groups. Relief agencies working in the affected region find this approach to be a very useful and viable option for supplying essential goods. The recognition of EVD survivors as a vulnerable population would also promote the prioritization of their networks for access to essential commodities.

However, ECEPAS members argued against the direct engagement of the target study team in setting up EVD survivor networks as part of the clinical trial implementation plan because this engagement could be considered as a conflict of interest; setting up networks would directly benefit the research team because the network would serve as a route for easy access to EVD survivors for plasma collection. Additionally, the EVD survivors in the networks may feel obliged to donate plasma in return for the favors and support they received from the research team.

The Working Group proposed that the target study team should hold dialogues and discussions with representatives of EVD survivor networks at the study site about appropriate compensation packages, including appropriate transport reimbursement. This discussion would help the researchers reach decisions that would be acceptable to both the target study team and EVD survivors. Such an inclusive process had the potential to prevent trial disruptions, and facilitate community input into the study design. The possibility of free plasma donations should also be explored.

The investigators should also collect details on the mental health status of EVD survivors during the registration process. Where there is evidence suggesting post-traumatic stress disorder (PTSD), the EVD survivor should be referred for psychotherapy in institutions with the capacity to provide such support. However, the investigators need to develop a Memorandum of Understanding (MOU) with institutions to which clients would be referred, thereby ensuring that priority attention is given to patients on referral. This practice is selected to recognize that access to ancillary care is considered an ethical imperative for study participants in resource-limited settings (Haire and Ogundokun, 2014).

Similar considerations were also given to discussions on the management of HIV and hepatitis B or C for EVD survivors and plasma donors if these infections were identified after blood screening. Folayan et al. (Folayan et al., 2014b) highlighted the potential for these co-infections to occur in the affected region. Although it was agreed that it was not within the scope of the trial to manage these chronic infections, it was appropriate for infected individuals to be referred to established HIV and hepatitis treatment programs in-country. This approach will also require that the investigators draw up MOUs with hospitals to which patients would be referred for management to ensure prompt patient access to this management. Potential participants who become ineligible after screening for medical reasons such as testing HIV- or Blood-Borne Virus (BBV)-positive should be referred to their nearest health facility.

Counseling EVD survivors post recovery: The World Health Organization recommends that male EVD survivors should abstain from sex or use condoms for seven weeks following their recovery from EVD (WHO 2015). Following recovery, the Ebola virus is still detectable in vaginal, rectal, and conjunctival swabs and the seminal fluid of EVD patients according to RT-PCR (Rodriguez et al., 1999). However, except for semen, these other body fluids were negative following viral culture and viral antigen assays (Rowe et al., 1999). The Ebola virus was not detected in urine and saliva by RT-PCR post-recovery (Rodriguez et al., 1999).

On the strength of the existing evidence and based on the World Health Organization's recommendation, the working group concluded that all EVD survivors recruited for the trials should be educated on post-survivor safety practices including the need for male EVD survivors to avoid sex or use condoms for safe sex over the next 7 weeks post-recovery. The sexual transmission of EVD had not been reported at the time of this deliberation though a recent case of EVD transmission through sexual intercourse has recently been reported. However, with the evidence of sexual transmission of the Marburg virus, a filovirus closely related to the Ebola virus that also causes viral hemorrhagic fever (Martini and Schmidt, 1968), the working group felt very strongly that counseling EVD survivors on the prevention of sexual EVD transmission was crucial for patient management, and the current study should also try to assess the possibility of the sexual transmission of EVD during follow-ups on the EVD survivors who were managed as participants of the clinical trial.

Safety of participants: One critical consideration in the study was the need to ensure that the transfusion transmission of infections (TTI) was eliminated. These concerns include the prevention of Ebola virus, HIV, hepatitis, malaria, and syphilis transmission, among others. Thus, standard guidelines for screening donated blood and plasma should be strictly adhered to while collecting and storing plasma.

In addition to the prevention of TTI, considerations for the management of transfusion-related reactions, including rare reactions such as transfusion-related acute lung injury and the prevention of graft-versus-host-disease, were considered critical and essential. It was emphasized that all health care workers who engaged with the trial for clinical, laboratory and data management would have to be trained and retrained on the prevention, recognition and management of these transfusion reactions. Patients would also have to be monitored during the follow-up period for delayed transfusion-related infections including the possibility of late neurological complications observed after Argentine hemorrhagic fever (Maiztegui et al., 1979). The treatment of Argentine hemorrhagic fever with convalescent plasma led to increased survival though associated with late complications, perhaps resulting from the dysregulation of the normal immune response to infection (Maiztegui et al., 1979). The continued monitoring of the cohort of EVD survivors who were managed with CEP for many years post-therapy was therefore considered very important and ethically appropriate for this study.

Privacy and confidentiality: The challenge of maintaining study participant privacy was identified. Although privacy is germane to ethical practices, the management of patients with EVD infections is conducted in open wards at Ebola virus treatment centers. Although privacy could not be guaranteed in this respect, the confidentiality of information generated through interviews and laboratory investigations would need to be ensured, unless breaching their confidentiality would be of direct benefit to the participant.

Safety of healthcare workers: The safety of the health care workers who would be engaged with the trial is also essential. The use of personal protection equipment (PPE), the weekly training and retraining of staff on infection control, and the need to keep the care burden of the staff engaged in the trial very low to prevent patient management error and errors in their adherence to safety precautions were emphasized. The risk of EVD transmission by fomites in a clinical setting in which decontamination is performed frequently is unlikely (Bausch et al., 2007). Priority access to treatment by trial staff workers who acquire EVD was also discussed. One option was the possibility of enrolling them immediately in the target study as study participants. To promote early infection detection, the body temperature of staff workers who had direct contact with study participants should be monitored on a daily basis.

Community engagement: The initial protocol did not contain a community engagement and communication plan at the time of review. ECEPAS members underscored the importance of having a community engagement plan for the trial. The plan should describe how key stakeholders would be engaged. Dialogue with stakeholders should include discussions about the experimental nature of CEP administration and the potential to record morbidity and mortality during the trials. The need for therapy for the management of EVD, the history of CEP use for Ebola virus therapy and the limited understanding of the efficacy of CEP in EVD management were identified as issues that had to be addressed during community dialogues. The high potential for therapeutic misconception and the low research literacy level of the trial host communities were the reasons for holding community dialogues. It was important that research team members should not unduly raise hope and optimism about the efficacy of CEP for EVD management, and they should continue to reinforce information on the experimental nature of the trial during public discussion and communication to prevent therapeutic misconceptions. Community engagement should also continue after the conclusion of the study because recipients of CEP should be followed for several years after the conclusion of the CEP efficacy trials, irrespective of whether the use of CEP for EVD management is found to be efficacious or not.

The dissemination of the outcomes of the study should also be conducted immediately after the study results are out, irrespective of the study findings. The trial results should be disseminated to all stakeholders who were engaged during the study design and implementation.

2. Discussion

The ethical discussion of the design and implementation of the target study draws extensively from existing ethical discussions on the management of infectious diseases, standards of care for patients engaged in clinical trials, guidelines on blood donation, existing literature and the management of specimen repositories. One of the peculiarities of the target study is the need to manage two populations ethically, that is, the population that provides the intervention therapy (CEP) and the population that receives the intervention therapy (study participants). There are multiple ethical guidelines about human study participation in trials, and thus, handling the ethical discussions on study participants for the target study was not as tricky as handling the ethical discussion on EVD survivors as blood donors for the trial. We did not come across ethical guidelines on dealing with humans who provide study intervention products. However, we considered potential convalescent plasma donors as having the same vulnerability as EVD research participants as they also may have to deal with the issue of potential exploitation, coercion and/or undue influence.

Two critical ethical considerations that evolved from this discussion were as follows: first, the reflection of the study design considered knowledge of existing clinical practice on the use of convalescent plasma for managing Ebola virus despite the

unestablished efficacy of the therapy. Although the working group identified the need for rigorous evaluation of the efficacy of convalescent plasma for managing Ebola virus infections, the study design also accommodated the continued use of convalescent plasma for clinical therapy. The flexibility of the study design therefore addressed the concerns of ethicists and scientists who were divided over the compassionate use of therapy for patients while promoting the rigorous evaluation of these therapies. Lessons from the design of the study on the efficacy of convalescent plasma could also help to inform ongoing debates about design studies that rigorously evaluate the efficacy of therapies without preventing the compassionate use of such therapies. Notably, the issues raised by members of the ECEPAS working group mirrored those raised during a meeting that was organized by the African Vaccine Regulatory Forum in South Africa in November, 2014, which identified some important ethical aspects about EDV clinical trials, such as how to motivate donors without undue inducement, how to use the precautionary principle to recruit participants and how to address vulnerable groups such as pregnant women, the elderly, and children. Importantly, we noted the need to strike a balance between research participation and causing social harm by ensuring that plasma donation volunteers do not suffer any forms of social harm that may in turn discourage them from participating in the study.

The second consideration had to do with addressing the standard of care and access to ancillary care. The ethical debate that ensued during the design of this study highlights some of the contentions between science, ethics and social responsibilities. Many studies that are conducted in resource-limited settings must often address the expenditure of research funds to address healthcare and social needs beyond the immediate trials. Researchers often have to decide which forms of care access are statutorily expected of their research which are good practices and morally praiseworthy (Folayan et al., 2011). There are currently no international or regional guidelines on the standard of care for biomedical research that can help with the decision making on this issue. This ethical debate highlighted the need to avoid conflicts of interest while providing access to ancillary care programs and conducting clinical trials. Community dialogues and debates can help research teams reach a consensus on appropriate compensation. For the target study, although the Consortium would like to promote the social care of EVD survivors, we felt it was essential to consider issues bordering on conflicts of interest. Therefore, to avoid coercion, the investigators could not be directly engaged in providing life-saving social services for the same group of persons who would need to supply study intervention products.

Although the ethical discussion by the ECEPAS working group helped resolve many issues, a few gaps in knowledge were identified, thereby limiting efforts at reaching evidence-based decisions. First, there was sparse evidence in the literature on the sexual (vaginal, anal and oral) transmission of Ebola virus infections and the risk of EVD transmission through vaginal, anal and oral sexual intercourse at the time of the debate. Second, there is little known about the transmission of Ebola virus infections through breast milk. Third, there is little known about EVD transmission from mother to child during pregnancy and/or the impact of EVD infections in pregnant women on the health of the fetus and the life-course of the child. These gaps in knowledge limited the quality of information that was proposed to be provided to EVD survivors following recovery. These limitations highlight the need for long term follow-up studies of EVD survivors to generate evidence to address the knowledge gaps.

3. Conclusions

Disease outbreaks often catch many countries unprepared. The clinical history, pathogenesis and prognosis of a disease such as EVD have challenged the viability of routine research procedures for assessing the efficacy and effectiveness of investigational therapeutics during an epidemic in a place with weak public health systems and infrastructures, as witnessed with the current EVD outbreak in West Africa. This scientific dilemma also comes with ethical dilemmas. Extensive consultation and dialogue can help resolve these ethical dilemmas, and existing experiences from multiple fields in public health can be of assistance. For the EVD outbreak, lessons garnered from experiences with the management of HIV, other neglected tropical diseases such as polio and malaria and other hemorrhagic diseases, and the management of infectious disease outbreaks such as influenza have helped to shape this ethical discussion. We have also come to learn that although we pursue knowledge generated from scientific endeavors, the social context of the lives of people engaged in this research would and should shape the way the research is conducted. Bioethical discussions help us to ensure that scientific endeavors are sensitive to the social and cultural contexts of the lives of those affected by the infections we investigate. This ethical discussion on experimentation with CEP for EVD management during an outbreak is one attempt at making science socially responsive.

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