Social Science & Medicine 148 (2016) 163–170

Contents lists available at ScienceDirect

Social Science & Medicine

journal homepage: www.elsevier.com/locate/socscimed

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

Francis Kombe [a, *], Morenike O. Folayan [b, c], Jennyfer Ambe [c], Adaora Igonoh [c], Akin Abayomi [c, d], GET members[c]

[a] KEMRI-Wellcome Trust Research Programme (KWTRP), P.O Box 230, Kilifi, Kenya
[b] Department of Child Dental Health, Obafemi Awolowo University, Ile-Ife, Nigeria
[c] Global Emerging Pathogens Treatment Consortium (GET), 1 Mainland Hospital Road, Yaba, Lagos, Nigeria
[d] Division of Haematology, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg Hospital, Private Bag X3, Parow Valley, 7505 Cape Town, Cape Town, South Africa

ARTICLE INFO

*Article history:*
Received 23 March 2015
Received in revised form
27 August 2015
Accepted 11 November 2015
Available online 30 November 2015

*Keywords:*
Africa
Ebola virus disease
Ethics
Emerging infectious diseases
Emergency health situation

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.


## 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

* Corresponding author. KEMRI Wellcome Trust Research Programme, P.O Box 230, Kilifi 80108, Kenya.
*E-mail address:* Fkombe@kemri-wellcome.org (F. Kombe).

http://dx.doi.org/10.1016/j.socscimed.2015.11.017
0277-9536/

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