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The 2014-2015 Ebolavirus Disease (EVD) Epidemic in West Africa: An opportunity to reform the Standard approach to clinical research during an outbreak response by reconciling two seemingly competing ethical obligations

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I would like to thank my mother, my father, my sisters, every friend and mentor I have encountered along the way and who all helped my build and reinforce my own moral sense: morality is not just about discerning right from wrong, it's often about being open to finding a way.

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INTRODUCTION

The 2014-15 EVD Epidemic in West Africa: Building the Context

Ebolavirus is the agent that causes Ebolavirus disease (EVD) when infected in humans and other primates. While the Ebola Virus Disease (EVD) is the result of infection with its agent, the Ebolavirus itself, is not visible to the human eye without the use of a handy electron microscope, its effects are by no means immeasurable, its pathogenic power, blaring. The biological and broader effects of EVD will be further explain in Chapter One; meanwhile it is noted that they have contributed to the 2014-onging EVD outbreak, and the extreme nature of the epidemic characterized by its magnitude and high case fatality rate (CFR). The World Health Organization (WHO) ethics advisory committee stated, in response to the EVD outbreak in West Africa, that it is *ethical* to offer investigational agents as treatment for those suffering with EVD, and that a *moral duty* exists to evaluate these interventions in the best possible clinical studies (WHO, 2014). Which clinical trial design is the most *ethical,* fulfills this *moral duty,* in the specific case of this EVD epidemic in West Africa while retaining scientific feasibility? What does this statement reveal about the apparent two simultaneous ethical responsibilities present during an epidemic: (1) providing immediate care to individuals suffering currently, and (2) upholding scientific structures and gathering data to better prepare for future outbreaks. Balancing these short and long-term ethical imperatives poses a fundamental challenge to outbreak response.

August 8th, 2014, marks the day that the WHO declared that the EVD in West Africa is a matter of Public Health Emergency and International Concern (PHEIC), but let us take a couple of steps back and understand how we arrived at this juncture. A situation in which it has been stated that scientific sta (Branswell, 2014) (Branswell, 2014)ndards (i.e. following through an entire clinical trial design) must be set aside in order to quickly develop and test not yet existing therapies/ vaccines.

The first official case of the 2014-2015 EVD outbreak occurred in March (2014) in Guinea, quickly spreading to Liberia. All of the while, the number of cases and fatalities rose rapidly across the three affected locations, particularly in Liberia. Internally, militaristic forces were called upon to ensure containment of infected individuals in hospitals; and with the alarming rise in cases and deaths, a palpable fear and unease was spreading relentlessly. In Guinea, rumors spread claiming that healthcare workers deliberately spread the virus, causing riots and threats to attack hospitals (Branswell, 2014). Not until September 2nd, 2014, did the director of the Center for Disease Control (CDC), Dr. Thomas R. Frieden, report that the outbreak was "spiraling out of control" (Botelho, 2014). A few days later, the United Nations Secretary- General Ban Ki-moon issued an "international rescue call […] (for a) massive surge in assistance" from the global community, warning that the disease is "spreading faster than the response". At this point, the total number of confirmed, and suspected cases totaled 3,988, 2,112 of which were deaths, exceeding the case numbers and fatalities of all previously recorded EVD outbreaks combined (CDC, 2015). The president of Sierra Leone clearly captured the state of crisis: "The very essence of our nation is at stake" (Nossiter, 2014). Truthfully, several cases of infection of EVD were observed as early as December 2013 in southern Guinea, but national and international authorities paid no attention until March of 2014, resulting in a response that was always playing

catch up, not only in regards to understanding the mechanisms of Ebolavirus and its' transmission, but in terms of optimal timing for containment and treatment strategies.

Even once international health authorities, such as Médecins Sans Frontières (MSF) (Doctors without Borders), the Samaritan's Purse, the CDC, the WHO, caught wind of the gravity of the outbreak their efforts were hampered by several factors. These factors included: the fragile state of governance in Liberia, Guinea, and Sierra Leone due to a recent history of coups, juntas, and civil wars; the resentment and suspicion among the local constituents of any authority, the inadequacy of the healthcare infrastructure and lack of basic healthcare services (reflected in the extremely low per capita expenditures on health); the pressing shortage of money and necessary outbreak supplies such as gloves, personal protective equipment (PPE), masks, gowns, rubber boots, bleach, plastic buckets; the porous nature of the borders between the three affected countries; and the reluctance of family and community members to trust the measure of isolation and the suspension of traditional burial practices. The 2014-2015 EVD outbreak is unprecedented in comparison with past EVD outbreaks in its duration, number of people affected, and geographic extent. Previous outbreak were restricted to rural regions, whereas the most recent outbreak infiltrated urban hubs too.

Emerging infectious diseases begin as any puzzle expedition does, with a desired endpoint and many steps and rearrangements between now and then. As research is conducted and data is accumulated connections are made between the puzzle pieces: the hazardous viral agent, its origin, its ecologic vector, transmission, replication cycle and pathology. As more and more pieces become connected, the ultimate picture is elucidated. It then becomes a matter of detailing the smaller connections, the point at which all of the remaining puzzle pieces look similar and it requires attempting to fit each in various orientations to illuminate the missing

intricacies of what began as a black box (Latour, 1987). In the case of Ebola virus disease (EVD), some but not all of the pieces are still missing, and accordingly some of the connections between them have yet to be fit: the identity of the Ebolavirus' host reservoir, the non-human animal to human transmission, and the geographic pattern/ distributions of outbreaks.

The objective of this piece of work is to grapple with the challenge of balancing two ethical obligations during an emergency outbreak: alleviating the suffering of those suffering from EVD now and efficiently gathering data that will better inform and potentially prevent any future outbreaks. The thesis will consider what factors tip and pull this balance in either direction. Most broadly, the contradiction of short and long-term care is evident in conducting concurrent clinical trials for both experimental treatments and potential vaccines. The heart of the discussion will privilege a specific locus of this imbalance in the conversation about widely accepted clinical trial design and how it might be changed to prioritize individuals' wellbeing right now as opposed to focusing on future potential cases. It appears as though the motivations behind conducting clinical trials during to this EVD epidemic diverge into either: (1) containment of the current epidemic thereby preventing its becoming endemic (or improving patient outcomes by rebuilding confidence in health care within communities); or (2) collecting robust data about efficacy and safety of experimental agents for the eventual profit of future patients. The two significant benefits of testing for an intervention (clinical trial) are not mutually exclusive, but depending on which is prioritized, a different trial *design* is ethically appropriate.

The 2014-2015 EVD outbreak is undoubtedly an issue of global public health emergency. This thesis will however, approach its study of which clinical trials are implemented from a *bioethical lens*. The international community has both humanitarian and global justice

obligations to those regions and individuals directly affected by the current EVD outbreak in West Africa (Milllum and Emanuel, 2012). While this thesis focuses on how international support, financial and manpower, invest in developing new treatments, this is not the whole story. These unproven interventions play a marginal role in the global response. Rather, the fundamental focus of this current Ebola outbreak, along with any future outbreaks, must be largely on strengthening existing (or non-existent) healthcare systems and their infrastructure. This text will also fail to account for the most time-pressing challenge confronted by international public health officials, the issue of containment. Containment of the virus and of infected individuals is encompassed by the actions of: universal infection control, contact tracing and monitoring, surveillance, and raising awareness locally within the communities as well as internationally (WHO, 2014).

Before we tackle the question at hand regarding constructing an informed and holistic outbreak response, we must first establish a better understanding of Ebolavirus, as well as the disease, framed in the context of the current epidemic. Accordingly, the first chapter will work on establishing a biological, sociological, and historical contextualization of this EVD epidemic with which to ground our understanding and subsequent discussion. Next, we must understand the motivations behind conducting clinical research, and how ethical values do and do not fit into the trial models. Chapter two therefore will explain the process of a clinical trial, and provide an ethical evaluation of its approach. In Chapter threes, we are finally ready to apply the knowledge of the current EVD outbreak and weigh our options in regards to clinical trial designs, ultimately two contrasting designs are discussed, (1) Randomized-controlled clinical trials (RCT) and (2) Adaptive Clinical Trials (ACT). Each have their own merits and priorities, and the relevance of these factors is considered along with the established ethical responsibility in the context of the

recent epidemic in the third chapter, ultimately recommending the use of one trial design over the other.

CHAPTER ONE

What is Ebola?
A Biological, Historical and Social Overview

In order to adequately understand and critique the current manner that we (the global health community) approach outbreak response, we must first attain a reasonable understanding of the virus's biological and social contexts must be realized. Gaining this working knowledge will allow for a more informative and nuanced lens through which to examine and critique ethical issues concerning how we provide care during an epidemic, specifically in the case of clinical trial design of therapies and vaccines for the current EVD epidemic as well as highlight its magnitude in size, speed, and potential damage.

Ebola virus disease (EVD), previously Ebola hemorrhagic fever after its most dramatic symptom, is the manifestation of infection with the Ebola virus. The Ebola virus is an aggressive pathogen that is lethal, with a historically observed case fatality range of 25-90% when infected in human and nonhuman primates (i.e. monkeys, gorillas, and chimpanzees) (WHO, 2015; CDC, 2015).

Cell and Molecular Biology

The Ebola virus is challenging to study (see section '(why we don't have) Treatment' due to its highly pathogenicity, but mechanisms for its function have been proposed.

1. PHYSICAL STRUCTURE OF VIRUS PARTICLE (VIRION)

Ebolavirus is a member of the *Filoviridae,* a family of viruses that contain a single, linear, negative sense single stranded (ss)-RNA genome. Structurally, the Ebola virus is unique, containing a genome that is 19kb long with seven open reading frames, coding for seven genes: NP, VP35, VP40, GP/GSP, VP30, and VP24, L. The tubular Ebolavirus virions are typically 80 nm in diameter and 800 nm in length. In the center of the virion is the viral nucleocapsid which is made up of the helical ssRNA genome, wrapped around the NP, VP35, VP30, and L proteins. The membrane is embedded with several viral proteins and glycoproteins. Viral proteins VP40 and VP24 are found between the nucleocapsid and envelope.

2. REPLICATION CYCLE:

2.1 Attachment- *the virus needs to be able to attach to its host in order to enter the 'correct' or 'target' cell. This first step is both critical and an excellent target for antiviral therapies (Shors, 2009).*

The Ebolavirus's surface proteins bind to a target cell, typically a monocyte, fibroblast, or endothelial cell, triggering a process called macropinocytosis. The host cell unknowingly invites the virus inside.

2.2 Entry-*once attached, the virus must cross the lipid bilayer plasma (or nuclear) membrane of its host cell in order to enter, typically by one of two methods: endocytosis or direct membrane fusion (Shors, 2009).*

The mechanism by which the virus attaches and enters the host cell remains poorly understood. Commonly, enveloped viruses, including Ebolavirus, rely on endocytosis in order to infect the cell. The universal mechanism of entry is to transport the virions through sequential endocytic vesicles until they reach a compartment with appropriate conditions. In the case of the Ebola virus, a low pH is

ideal (K. Schormberg, 2006) (G.J, 2009). Once the membrane fuses, the capsid moves into the cell cytoplasm where gene expression and replication proceed.

2.3 Gene expression: *before a new virus can be assembled, the new viral genomes and other virion proteins must be produced. This process is dependent on the family and class of virus (Shors, 2009).*

Once the virus enters the host, viral RNA polymerase, encoded by the L protein, begins to read each gene as a separate transcriptional unit and transcribe them into mRNA. The genome is transcribed into seven monocistronic RNAs. Similarly to other negative sense RNA viruses, the transcription process begins when the polymerase complex binds to the specific binding site in the promoter region of the genome. The complex then runs along the RNA template, successively transcribing the individual genes in the 3' to 5' direction. NP, the first gene, is transcribed at the highest levels, while L, the last gene at the lowest (K. Schormberg, 2006).

Ebolavirus achieves immune suppression by inhibiting multiple antiviral pathways through synergistic antiviral signal blockades which will not be specifically discussed here. The result is that the virus is able to evade the host's immune response for long enough to create extreme amplification damage to the liver, spleen and lymphatic system, contributing to hemorrhage and vascular collapse, before the host even realizes it was invaded (Sullivan, Yang, and Nabel 2003).

2.4 Genome replication- *Before viruses can infect, two events must take place: production of virus structural proteins and enzyme, and replication of the viral genome (Shors, 2009).*

Replication occurs in the cytoplasm. Ebolavirus encodes two forms of the glycoprotein gene: one small (sGP) and one large (GP) (Simmons et al, 2002). sGP is

secreted into the bloodstream of the infected host. The full-length and fully functional GP inserts into the viral membrane during transcriptional editing of the glycoprotein origin of replication, and encodes a trimeric, membrane bound form. This envelope GP is expressed at the cell surface and is incorporated into the virion to drive viral attachment and membrane fusion (Yonezawa, Cavrois, & Greene, 2005). The aforementioned nucleocapsid proteins, specifically NP, VP35, L, and VP30 catalyze replication and transcription of the genome (Mühlberger et al., 1999). GP might contribute to the hemorrhagic fever symptoms by targeting endothelial cells, while sGP might alter the immune response by inhibiting neutrophil activation (Sullivan, Yang, and Nabel 2003).

2.5 **Assembly**-***an essential step in the replication cycle because it is when the immature virus particle is formed. All of the components of the virus must be assembled in order to create a stable structure. Some therapeutic agents can inhibit virus-specific reactions needed to assemble new virus particles (Shors, 2009).***

The RNA and NP (ribonucleoprotein complex) assemble with viral proteins (VP24, VP40, and GP), and the resulting virions bud from the cell surface.

2.6 Exit: ***the newly formed viruses are either released to the external environment by lysis (disintegrating as the virus escapes) or budding (through plasma membrane) (Shors, 2009).***

The VP40 matrix protein is needed for virion egress, the first step of the viral release from the infected cell.

Viral Reservoirs

Notably, the identity of Ebolavirus' natural reservoir and its mode of transmission to non-human primates and humans remains undetermined. The 2014-15 EVD epidemic expresses a particularly exaggerated version of a global phenomenon; the zoonosis of emerging infectious diseases coupled with the threat of a global pandemic. Zoonosis is a non-human animal infection

that is transmissible to human hosts, such as the Bubonic plague, all strains of influenza, SARS, West Nile, Marburg, etc. (Quammen, 2014). In fact, 60% of all infectious diseases have gone through the animal to human transmission leap[1]. Ebola is a zoonotic. Ebolavirus non-infectious sequences, have been detected in samples collected from bats in Central Africa (Leroy et al., 2005). Yet, subsequent studies have suggested that bats are at least one of the reservoir hosts of Ebolaviruses in Africa (Leroy et al., 2007).

Transmission and Pathology

The transmission pathway from bats to humans, and the potential role of the bat reservoir in initiating the 2014-2015 EVD outbreak in West Africa remain unconfirmed. The first person is likely infected through direct contact with the infected fruit bat, called a spillover event. Once a human is infected, the virus may spread through direct contact of contaminated bodily fluids through broken skin or mucous membranes (i.e. eyes, nose or mouth) with: (a) blood or bodily fluids (i.e. sweat, saliva, vomit, urine, feces, breast milk or semen) of an individual who contracted Ebola, or (b) objects that have been contaminated with the EBOV (i.e syringes, needles). *In vitro* studies have found that animals can be infected with Ebolavirus through droplet inoculations of the virus into the mouth or eyes (Jaax et al., 1996).This suggests that humans can be infected with the virus due to inadvertent transfer of the virus from contaminated hands. Healthcare providers in the care of Ebola infected patients and family members or friends in close contact are therefore at the highest risk of becoming contracting the disease themselves. This has been evidenced by the several hundred African doctors and nurses that have become

[1] 'Animal' for all intents and purposes will refer to all non-human animals in this context

infected while caring for patients during the early phases of the 2014-1025 EVD outbreak. Ebola is *not* spread through air, water, or generally food (CDC, 2014).

Due to the difficulty of performing clinical research under outbreak conditions (see section '(why we don't have) Treatment' below), the overwhelming majority of data on the pathogenesis of EVD come from laboratory experiments of non-human animal host. Case reports and observational studies of the current outbreak will provide the urgently needed data about human pathogenesis of EVD (Chertow et al., 2014).

Signs and Symptoms

The incubation time, or the time period between infection with the virus and onset of symptoms, is 2 to 21 days. When humans are infected with Ebola virus they are not contagious until they develop symptoms (WHO). The first symptoms are fever, severe headache, fatigue, muscle pain, and sore throat. Next, a patient may experience weakness, diarrhea, vomiting, abdominal (stomach) pain, rash, impaired kidney or liver function, unexplained hemorrhage (bleeding or bruising). Tests performed in a laboratory might indicate a low white blood cell and platelet count and a heightened liver enzymes, which is an indication of liver damage (WHO, 2015). In the terminal stages of EVD, an infected individual may experience diffuse bleeding and hypotensive shock, resulting in death (Colebunders and Borchert**,** 2000).

Fatal cases of EVD are characterized by early onset of severe symptoms and progression to multi-organ failure and septic shock. Death, in fatal cases, typically transpires between days 6 and 16 after the onset of symptoms. In non-fatal cases, patients typically begin to show signs of improvements between day 6 and 11.

Diagnosis of viral infection with EVD is dependent on a correlation between symptoms and risk factors. High risk exposure is characterized by percutaneous, mucus membrane, or

exposure to blood or bodily fluids of an infected individual without the use of personal protective equipment (PPE) and direct contact with a dead body of a person known to be infected with EVD. Low-risk exposure refers to house-hold and close contact (in health care or community settings) with an infected individual (Bishop, 2014).

Historic context of EVD

Up to date there are five acknowledged species of the virus's genus, all within the family of *Filoviridae,* genus *Ebolavirus. Marburg virus* is an additional member of the *Filovirus* family (but a different genus); both are pleomorphic, negative-sense RNA viruses (Sullivan, Yang, and Nabel, 2003).The five known Ebolavirus species are: (1) Ebola virus/ *Zaire ebolavrius (EBOV-Z);* (2) *Sudan virus (EBOV-S);* (3) *Tai Forest virus,* also *Côte d'Ivoire ebolavirus (EBOV-IC*); (4) Bundibugyo virus*;* (5) *Reston virus (EBOV-R).* All first four species are classified as disease-causing in humans and nonhuman primates; while the fifth, Reston virus, has only caused disease in nonhuman primates. Each species is named after the location in which its outbreak was discovered. The Zaire species has historically exhibited the highest rate of lethal infections (Sullivan, Yang, and Nabel, 2003).

A brief historical overview is tasked with placing the 2014 West Africa outbreak within a broader context of past EVD outbreaks and their subsequent responses. Ebolavirus emerged in 1976 and has been confirmed in 10 African countries, never before had it reached West Africa.

What follows is a brief chronological outline of Ebola virus outcomes:

Table 1. Historic timeline detailing previous outbreaks

Year	Location	Number of Cases	Case Fatality Rate (CFR) (%)

1976	Zaire	318	88
1976 (2)	Sudan	284; 34	53; 65
1994	Gabon	52	60
1995	Congo	315	81
1996	Gabon	37	57
1996-1997	Gabon	60	74
2000-2001	Uganda	224	53
2001-2002 (2)	Gabon, Congo	65; 57	82; 75
2002-2003	Congo	143	89
2003	Congo	35	83
2004	Sudan	17	41
2007	Congo	264	71
2007-2008	Uganda	149	25
2008-2009	Congo	32	47
2012 (2)	Uganda; Congo	11; 36	36; 36
2014-present	West Africa	23218	53-64

[2]

Given this data (including the smaller outbreaks not mentioned), CFR of EVD for the *Zaire ebolavirus* is about 50%, ranging from 25% to 90%. While the current outbreak's CFR is lower than that of many previous outbreaks, the total number of cases far exceeds the number of all previous EVD infections since 1976. The countries with the highest number of outbreaks are, in descending order, The Republic of Congo (11); Uganda (5); Gabon (4); and Sudan (3). It ought to be noted that the first EVD outbreaks were localized in remote villages in Central

[2] These numbers are taken from the WHO website, most recently updated on January 28, 2015. The case fatality rates (CFRs) are estimated, hence the range.

Africa, while the most recent outbreak has infected both major urban hubs as well as rural areas in West Africa (CDC, 2014b).

Previous and recurring social attitudes

Studying the above timeline of previous outbreak is helpful, but the numbers alone do not convey the entire context, particularly the social reaction (or lack thereof) to these events. Previous epidemics, such as HIV/AIDS, SARS and the Influenza, serve as a stark reminder of the power of infectious disease to cause continued upheaval in individuals' lives, politically, economically, culturally, socially, and racially.

Ebolavirus outbreaks, similarly to other virulent outbreaks, hold not only the risk of immense infection within surrounding communities, but the capacity for outbreaks to become global pandemics with unprecedented speed. The awesome power of epidemics evokes and reinforces an unshakable fear and distrust. The fear is of a faceless, insidious enemy and the potential travesty of infection; a fear of non-knowledge and lack of control.

Ebolavirus has been popularized by the media as a ferocious beast emerging from the tropics of Africa and threatening to infiltrate ad devastate global populations, particularly in the mid-late 1990s. Films and books, including *The Hot Zone* by Richard Preston (1994), *The Coming Plague* by Laurie Garrett (1994), and the movie *Outbreak* starting the likable Dustin Hoffman (1998), all synthesized and spread a fear about EVD (then Ebola hemorrhagic fever) in the Western world.These portrayed the Ebolavirus as an active agent going around and attacking people, infecting them through the air or by touching them, and they are left to suffer until a man in a white lab coat discovers a vaccine or some other cure—otherwise everyone dies. These stories uphold a clear cut scientific heroism saving a panicked, violent, and competitive group of

people from the disease. What is also notable, is the urgency to intervene in any way seems highly dependent on the possibility of the virus to the rest of the world, or the Western world.

Despite the 'success' of industrialized nations, the global load of infectious disease remains substantial, accounting for approximately one-quarter of annual global deaths (WHO, 2005b). A disproportionate amount of this burden lies on the shoulders of the poorest individuals and poorest countries. This is not a shocking finding, since conditions characterized by poverty, including a lack of sanitation, overcrowding, and forced migration are conditions that encourage the transmission and persistence of infectious disease. Nearly all of the EVD outbreaks, and the 2014-15 West Africa outbreak is no exception to this pattern, have emerged out of various regions of Africa that are also struck with widespread poverty and a poorly supported healthcare infrastructure (from a Western standard).

The disinterest that America, as well as other Western countries, exhibited in its extremely slow response to the 2014-15 EVD outbreak in West Africa unfortunately echoes past (lack of) interactions with EVD outbreaks. There are two ways to interpret this display of non-action: one is racism—the constructed sentiment that the people who are suffering and dying from Ebolavirus infections are so "different" from "us" that they (Westerns) cannot possibly empathize and do not want to sympathize with them, the second is unwarranted compassion fatigue—*isn't there always some awful disease plaguing Africa, Africans?* Many of the news articles about the EVD outbreak written in English characterize "ignorant" and "superstitious" Africans who prefer to practice witchcraft to the wonders of modern medicine For example:

> "The key to halting Ebola is isolating the sick, but fear and panic have sent some patients into hiding, complicating efforts to stop its spread […] Preachers are calling for divine intervention, and panicked residents in remote areas have

> on multiple occasions attacked the very (white) health workers sent to help them. In one town in Sierra Leone, residents partially burned down a treatment centre over fears that drugs given to victim were actually causing the disease" (CBC, 2014)

This analysis was repeated throughout several major news outlets, pointing to exact xenophobic Western mindset that those suffering from EVD (in West Africa) distrust, and hints at the rationale behind the Western disinterest in the current outbreak. The doubt with which many individuals in Liberia, Guinea, and Sierra Leone considered modern medical interventions is historically, rather than superstitiously justified. The history being one of the exportation of medical experimentation to countries that are poor. Moreover, International relief organizations in these countries set up emergency treatment that will be taken down when the immediate threat is over. But the community remains. Therefore opposing suggested public health measures such as isolation of symptomatic people can be a pragmatic and sensible choice to rely on the kinship and community networks that have kept people alive in the past.

(Why we don't have) Treatment

"There is intense public interest in, and demand for, anything that offers hope of definitive treatment (for EVD). A range of unproven interventions-blood products, immune therapies, drugs and vaccines are under different stages of development but none have yet been licensed for standard use," according to the WHO (2015).

Nearly two dozen outbreaks of EVD have been recorded since 1976, "yet the world was woefully unprepared for the current tragedy, with no licensed vaccines or treatments".[1] How did we arrive at this juncture, faced with yet another outbreak, no—an enormous epidemic, and still no preventative or curative treatment so to speak of?

While the structural components of the Ebolavirus are known, the exact mechanisms by which it causes disease (EVD) in humans are not completely understood. This poses a major challenge for treatment development and to date prevention is the best mode of action to avoid an Ebola outbreak. Or, basic interventions are used to ameliorate specific symptoms and maintain stable cardiovascular function while the immune system mobilizes an adaptive response to fight the viral infection. The most important aspect of supportive care is the use of intravenous therapy (IV) to prevent intravascular volume depletion and repair electrolyte abnormalities in order to avoid shock. Additional supportive measures include symptomatic management of fever, pain, nausea, vomiting and diarrhea. Renal replacement therapy may be needed to combat acute kidney injury during shock (Fowler et al, 2014). Currently treating EVD patients therefore necessitates a multidisciplinary approach.

In part, the lack of any vaccine or therapy to combat EVD reflects the arduous process of therapeutic medications and vaccine development. Yet, advancements to this process could have certainly been made in the past four decades, and therefore it must be concluded that there are additional forces at play.

There forces ought to be reviewed. Ebola virus infection, similarly to the case with Severe Acute Respiratory Syndrome (SARS) caused by the SARS coronavirus (SARS-CoV), vaccine development is restrained due to the disease not being endemic, meaning the disease has been is not found only in a certain area or in a certain group of people. This makes it difficult to

identify at- risk populations as target sites to test potential vaccines. The current outbreak is taking place more than 2,000 miles away from previous Ebola Zaire virus outbreaks, which complicates our assumptions and understanding of the ecological basis for viral transmission (CDC, 2015).

The virulence and extremely high CFR with infection (as high as 90 percent) of Ebolavirus is another cofounding factor in difficulties developing therapeutic drugs/ vaccines, since it restricts researches working with the virus to special approved facilities and high-level protective resources and biohazard containment.[3] Moreover, there was a difficulty in collecting samples and studying the course of the disease due to its past occurrences in relatively remote areas.

EVD is caused by a virus, rather than bacteria, and researchers have struggled to a greater extent with developing treatments for viral diseases; "Antiviral therapy has lagged behind antibacterial therapy for decades" Dr. Derek Gatherer (bioinformatics researcher studying virus genetics and evolution, Lancaster University, UK) explains. The reason for the lag time is that viruses are and only produce a few proteins, resulting in fewer targets for treatment when compared to more complex bacteria.

Another obstacle in the avenue to develop treatments and vaccines for Ebola virus is market-based capitalist economies that dominate the countries in which research is being pursued. That is, until now, the monetary (and temporal) investment has not made economic sense for the pharmaceutical companies or their governments because the disease only affected a relatively small number of people in poor countries. The lack of sufficient economic incentive is

[3] Experiments with Ebolavirus are required to be conducted in 'biosafety 4' laboratories, the highest (and most expensive) level of protection.

evident in several examples of the FDA halting safety trials on experimental EVD treatments in recent years due to lost funding (McGrath, 2012).

The FDA, finally, following a statement with by the WHO ethics advisory panel in August (2014) gave the green light for accelerating EVD potential therapeutic/ vaccine clinical trials, meaning proceeding with only minimal preliminary data (and little to no phase II) (WHO, 2015).

Experimental Therapies (drugs)

In addressing the question of how do we care for those immediately affected by a devastating disease such as EVD while concurrently developing preventative measures to avoid future outbreaks, a discussion of the development of therapies and vaccines is crucial.

Most obviously, the purpose of a therapeutic drug is distinct from that vaccine. A therapy aims to attack the virus at some point, depending on the particular drug and its mechanism, but always after the virus has entered the host cell signalling the beginning of its replication cycle. A vaccine aims to trigger an immune response prompting our bodies to create antibodies to fight the virus, essentially simulating the viral infection without actually infecting the individual with the disease. Vaccines are preventative; therapies (antibody, antiviral, or convalescent transfusions) are corrective. Vaccines operate in the long-term; therapies in the near-term. Notably, trials conducted on both therapeutic drugs and vaccines run into short *and* long-term considerations.

Only a select few therapeutic treatments or vaccines have recently been approved for use to treat EVD (to date). These are categorized as follows: (1) monoclonal antibodies; (2) plasma

transfusions from convalescent (recovering) patients; (3) antiviral agents; (4) vaccines. The focus of the subsequent chapters, is in the context of the ethical complications embedded in conducting clinical trials for first three categories, also called therapies. A brief summary of these treatments follows. The FDA had approved the use of two experimental drug treatments, ZMapp and TKM-Ebola on Americans who became infected with EVD. These treatments are now undergoing clinical trials. This paper does not focus on the real-time course of these ongoing clinical, but instead on how we set these trials up.

(1) Antibody therapy

***ZMapp.** A passive immunotherapy that combines three humanized monoclonal antibodies produced in *Nicotinia* (tobacco) plants. It is in early stages of development, but it being used in emergency situations, such as the current one (Pollack, 2014). To simplify, the antibodies in ZMapp are directed against the aforementioned viral glycoproteins, and ideally the body's immune system will vigilantly fight off the virus with these antibodies. A recent trial found that when administered five days following inoculating macaque monkeys with the virulent EVD strain, they were able to prevent mortality from the disease showing promise for ZMapp. Since, at least six (western) healthcare workers, have been treated with slightly varying doses of ZMapp with a high rate of recovery, but the results remain statistically insignificant due to the small sample size. Therefore, due to ZMapp being in its early development stages, sufficient safety and efficacy data are lacking. It is important to note that available supplies of ZMapp are largely exhausted due to the low amount of initial supplies and the difficulty of expanding production.

(2) Transfusion therapy

The WHO has announced that blood or plasma transfusions from convalescent patients may be used to treat individuals infected with EVD (Gullard, 2014). In a previously conducted study in the Democratic Republic of Congo, eight infected EVD patients were treated with blood transfusions from five recovering patients. The blood transfusions were positive for the Ebola immunoglobulin G (IgG) EVD antibodies, but negative for Ebola virus antigen. [4] Of the eight patients, seven survived, an optimistic outcome given the case fatality rate associated with EVD. Why then, are blood transfusions not being widely applied to treat EVD currently? The reason for their limited use is because the current epidemic is taking place in West Africa, there have been deemed to be insufficient infrastructure and resources for safely collecting and screening blood from convalescent patients (Burnouf T, Emmanuel J, Mbanya D, et al., 2014) Blood transfusions are further restricted by the requirement of matching the blood type between donor and recipient.

(3) Antiviral therapy

Possible antiviral therapies include: Brinicidofovir (CMX-001). Favipiravir (T-705), AVI-7537, and BCX-443. It remains outside the scope of this thesis to explore the detailed mechanisms or consequent of these treatments.

***TKM-Ebola** is comprised of short interfering RNA (siRNA) molecules bind to specific sequences in the viral messenger RNA and can effectively block Ebolavirus infection *(in vitro)*. The therapy that has been FDA approved for emergency use and phase I trial of TKM-Ebola began in January 2014.

[4] IgG is the most abundant antibody in our body

Given that these antivirals are small molecules, increasing their production to a larger scale ought to be easier than it would with the monoclonal antibodies (ZMapp).

(4) Vaccines

To date (April 30, 2015), two vaccine candidates for preventing EVD infection are entering efficacy trials in humans: chAd3-ZEBOV (developed by GalxoSmithKline and the US National Institute of Allergy and Infectious Disease (NIAID) and rVSV-ZEBOV (NewLink Genetics and Merck Vaccines (US) with the Public Health Agency of Canada). Both have demonstrated safety and have been well tolerated in human subjects in Phase I of clinical trials. A two-dose vaccination approach is being developed (by Johnson & Johnson and Babvarian Nordic) that uses two different vaccines for the first and second doses, called a heterologous prime-boost). The vaccine candidates are: Ad26-EBOV and MVA-EBOV. A recombinant protein vaccine for EVD (by Novavax) targeting the 2014 Guinea Ebolavirus strain is entering Phase I clinical trials in Australia. Several other alternative vaccine candidates are being tried, including a recombinant influenza vaccine (Russian Federal Ministry of Health), an oral adenovirus platform (Vaxart), an alternative vesicular stomatitis virus vaccine (Profectus Biosciences), an alternative recombinant protein (Protein Sciences), a DNA vaccine (Inovia) and a recombinant rabies vaccine (Jefferson University).

CHAPTER TWO

How is Clinical Research Conducted during an Outbreak Response? Considering standard and alternative approaches

Prior to beginning to consider whether a more holistic approach to outbreak response, one that incorporates both short-term therapeutic interventions in addition to gathering data for long-term application and prevention of potential outbreaks, we must understand the current response system in place. Specifically, this work will consider the way in which clinical research (on therapeutic drugs / vaccines) is designed and where it fits into this question of providing immediate treatment and future outbreak prevention.

A background understanding of the history and mechanism of clinical trials along with the bioethics they imbed must be conquered before delving into analyzing which clinical trial design is best suited, taking into account current and future ethical responsibilities, for use in the ongoing EVD epidemic. Whereas ethics is defined as the exploration aimed at addressing philosophical questions about morality, bioethics is the philosophical study of ethical controversies emerging from advances in biology, medicine, and technology. Bioethics emerged as a recognized discipline in the 1960s.

Framing the Issue

Let us break down the specific needs and limitations that characterize an outbreak response for the 2014-15 EVD Outbreak in West Africa. Extreme emergency, scarcity of

resources, lack of approved therapies or treatments, poverty, insufficient healthcare infrastructure, and rapid spreading of infection all converge to represent the complex state of this epidemic. In a state of irrefutable emergency such as the current EVD outbreak, readjustment, flexibility, and creativity are welcome and needed approaches to be applied to the current structure of outbreak response, for example with clinical research. Scarcity of resources in this case refers not only to a lack of sufficiently-stoked hospitals and clinics, but a very limited amount of some of the experimental therapies and vaccines being tested. The way in which we may ethically and inventively think about distribution of these resources will be discussed in this chapter (see 'Ethical Allocation of Scarce Resources'). Evidently, all of the aforementioned characteristics of the current EVD epidemic in West Africa are well positioned to help us question the way in which we approach outbreak responses and the possibility of incorporating short and long-term, curative and preventative treatment.

Clinical research is often boldly distinguished from therapeutic medicine. Clinical research with humans aims at gaining a better scientific understanding of human health and illness using a systematic approach, ultimately hoping to find a *safer* and more *effective* way to prevent, diagnose, and treat human diseases. Therapeutic medicine is concerned with bettering the situation of the person who is ill right now by providing whatever treatment, resources, and support are available. This distinction is evident in the language we use to refer to the implicated individuals. They are "patients" when they seek care from a physician in a therapeutic setting, but 'participants' when they enroll in a clinical trial conducted by a researcher investigator; the term 'patient' connotes a relationship that is based in compassion, while using the word 'participant' creates an intentional distance and anonymity.

The same distinction, when considered from an ethical standpoint, is only accepted by some (Difference Position), while many others reject the distinction between clinical research and clinical medicine (Similarity Position). The Similarity position believes that the ethics of clinical research ought to be based on the norms expected of therapeutic medicine; while the Difference position insists that the two activities are fundamentally different and as such require different ethical approaches (Miller and Brody, 2003). Dismissal of the distinction (Similarity Position) between therapeutic medicine and non-therapeutic research produces an increase in both conceptual clarity and concern for the potential exploitation of participants. Clinical research, therefore ought to be concerned with and accountable for the participant's health concurrent to its objective of producing data in order to develop new clinical interventions. Therefore, the next two chapters will aim to support the Similarity Position (or question the distinction between therapeutic care and clinical research) and illustrate how the scope of clinical research can be broadened to include improving patient conditions in the present and generating a database that will help benefit future patients.

Clinical research refers chiefly to clinical trials. The goal of clinical research is to gain a better understanding of human health and illness by finding safer and more effective ways to prevent, diagnose, and treat human disease. It must be noted that these intentions refer to a desire to improve prevention, diagnosis and treatment without a specification on when, or for whom. They do not necessarily connote a sense of urgency, or if they do, the urgency does not translate into benefit for any individual right now. Rather, the chief motivation for clinical trials is to test for *safety* and *efficacy* of a given experimental intervention in human participants. Clinical trials are further subdivided into: (a) treatment trials, exploring experimental treatments or

combinations of drugs, and (b) prevention trials, i.e. testing vaccines. Clinical trials are laden with ethical concerns, the most obvious one arising from the inherent risk (burden) that participants are expected to accept in order to promote scientific research to benefit for society. As it stands, the overwhelming majority of clinical research is principally utilitarian, rather than individual (Freedman, 1987). Can we conceive of an alternative structure for conducting clinical research that incorporates consideration of the very imminent needs of individuals suffering in the present?

Ethical Allocation of Scarce Resources

The question of how we distribute a limited supply of IVs or of an experimental intervention begs us to think about those who are sick with EVD right now. While perhaps the intention and typical protocol with new drugs or vaccines forces us to tip the balance in the direction of long-term provision, this thesis urges us to resist privileging either short or long-term reduction of suffering.

Allocations of scarce medical resources/ interventions is no new ethical challenge, including the scarcity of beds in intensive care units, organs, and vaccines during pandemic influenza (Troug, Brock, Cook, et al, 2006). In some cases of intervention, demand simply exceeds supply. When there is only a limited supply of a therapeutic treatment, as is the case with ZMapp for EVD, considering the challenge of balancing data generation concurrent with patient treatment is less ambiguous since it is not feasible to conduct a clinical trial large enough to yield sufficient/ statistically significant data anyway. Therefore, the question becomes how we distribute the limited existing treatments rather than should we, tipping the balance towards ameliorating some current suffering.

Distribution of scarcely available interventions can be dissected into eight relevant ethically-motivated principles. These principles are grouped into four categories: (a) treating people equally; (b) favoring the worst-off; (c) maximizing total benefits; and (d) promoting/ rewarding social usefulness (Persad, Werthemier, and Emanuel, 2009). The principles will here be evaluated as either sufficient, or insufficient, from an ethical standpoint. Since no principle on its own is able to account for all of these moral considerations, it has been proposed to integrate a combination of principles into an appropriate allocation strategy. One example of an integrated system is the complete lives system, suggested by (Persad, Werhemier, and Emanuel, 2009).

Many medical resources are indivisible, such as organ transplants, and so ensuring equal treatment of individuals' means providing an equal opportunity at receiving the intervention, instead of considering amounts. There are two allocation principles that attempt to meet this objective. First, allocation based on *lottery* attempts to prevent small differences from having large ramifications on eligibility. In addition to valuing all lives equally, a lotter can be conducted quickly and requires little information about participants. The disadvantage to the lottery principle is that its blindness leads to neglect of many relevant factors, such as age, rendering it ultimately insufficient (on its own) despite its simplicity. The second principle is *First-come, first-served,* commonly accepted, for example, as a solution for scarce bed allocation in intensive care units or of organs for transplant. Some have referred to this principle as a natural, egalitarian lottery. It promotes fair equality of opportunity. Similarly to the lottery, it ignores differences between people. Moreover, though, it fails to treat people equally, as individuals who are well off, well-informed, and have access to travel (lack concerns about childcare, employment) will benefit most. It therefore allows morally irrelevant factors, wealth, power, connections, to dictate distribution of treatment, rendering it insufficient.

Favoring the worst off is also characterized as prioritarianism. Franklin Roosevelt eloquently stated that: “to test our progress is not whether we add more to the abundance of those who have much, it is whether we provide enough for those who have too little”. The question of how do we define “worst-off” is an important one. Two principles take into account this value, sickest first, and youngest first. The sickest-first principle, is beneficial to those who are suffering right now, appealing to the “rule of rescue”, and accordingly is most appropriate when there is temporary scarcity. It is criticized however for failing to meet the needs of those who will become sick in the future, and encourages waiting until a prognosis is very poor to treat. This is in fact where one of the chief controversies about distributing experimental intervention during EBV. It is obvious who is benefited by the second principle. This principle can be criticized for being ageist, and neglecting to place an appropriate amount of significance on care for the elderly. This is particularly interesting/ problematic in our western society that places an exaggerated emphasis on privileging end-of-life care.

The category of maximizing total benefits is rooted in utilitarian reasoning, the difference between principles becomes which benefit is maximized. For example one principle prioritizes saving the most lives, assuming an equivalence between individual lives, ultimately claiming it is always best to save five lives over one. Is anything ever equal though? Some lives have been shorter than others, and some lives can be extended longer than others, but whether and how to consider these factors against saving more lives is unclear, therefore saving more lives is an insufficient principle on its own. The second principle is about prognosis, or in other words, privileging saving the most life-years, by essentially rejecting individuals with poor prognoses in the inclusion criteria. This principle has been applied in penicillin allocation, as well as in disaster triage. There is an intuitive sympathy towards this argument that claims since living

more years is valuable, saving more years must be too. The principle fails however, to account for distribution and quantity. For example, what is the justification for giving an older person an extra year over a younger person? Or, how is it just to make a well-off person slightly better off than marginally improving a worse-off person's life? Lastly, how do we distinguish between giving a few life-years too many differs from giving many life-years to a few? Therefore, the prognosis principle is similarly insufficient on its own.

The final category deals with promoting and rewarding social usefulness (d). This idea is rooted in social value, unlike all of the previous ones, and as such acts as in indirect allocation, by promoting an individual who then promotes values that are deemed important by people in power. Social allocation must not represent socially conventional, mainstream values, as these already have a voice. This approach is of course insufficient, because its appeal is because of its promotion of other values, for example saving lives. Healthcare workers are 'worth more' because prioritizing them allows them to benefit others. Instrumental value allocation recognizes the moral importance of each person. This principle has been shown to yield abuse of the system. Moreover, what constitutes as usefulness? Only when a person is genuinely indispensable in assuring morally relevant principles does instrumental value hold. The second principle is reciprocity, named for its retroactive nature, as it rewards past usefulness or sacrifice. For example, reciprocity may consider preferential distribution of vaccines in a clinical trial to past organ donors, or prioritizing care for military veterans. Reciprocity is the flip side of instrumental value allocation, as it looks back instead of into the future in regards to health promotion. Reciprocity is variable depending again on what actions or what work is deemed valuable.

The complete lives system (Persad, Wertheimer, and Emaneul, 2009) is an alternate example of an aggregate of five principles, in attempt to meet all of the ethical requirements of resource allocation and achieve equal outcomes, or 'complete lives'. The five principles are: (1) youngest-first, (2) prognosis, (3) save the most lives, (4) lottery, and (5) instrumental value. The complete lives system has been accepted by many as the most appropriate embodiment of distributive justice, since it places emphasis on individual human lives, rather than individual human experiences. Defining the youngest, in the youngest-first principle is a matter of debate, and some have recommended that adolescents ought to be prioritized over infants because more has been invested in them and they are capable of forming and valuing long-term plans for which a full life is required (Dworkin, 2009). Prognosis is a principle that also values the ability to live a complete live as a factor for allocation. The issue that arises is once again that an uneven amount of resources will be directed for young people with poor prognoses. Saving the most lives is an important principle, since facilitating more complete lives is preferable to fewer. A lottery might be an appropriate strategy when faced with deciding between mostly similar individuals, and to avoid stigmatizing exclusions of anyone being deemed as past-the-point of help. When applied to a sample population, the complete lives system will create an age-based priority curve that identifies those in the age bracket of 15-40 as the best candidates for allocation. The complete lives system is not particularly vulnerable to corruption, and is driven by the incentive of preserving and improving lives. More than just satisfying the required ethical principles, an allocation system must be legitimate, as is decided by public understanding, accessibility, and power to voice questions and concerns. During an emergency situation, such as the 2014-15 EVD epidemic, the complete lives system also recommends allocation of scarce

resources to people who are instrumental in realizing the four principles (i.e. healthcare workers on the frontlines of care provision).

Thus, taking into account the scarcity of (some) of the novel treatments and vaccines being evaluated in the current EVD epidemic, tips the scale slightly in the direction of favoring treating those who are critically suffering right now, as there may not even be enough supply to justify conducting a traditional (randomized) clinical trial.

Clinical Trials: How they work

Clinical research is most simply understood as a series of steps following the trajectory of the intended goal, to develop and test the safety and efficacy of experimental or preventative interventions. Clinical trials are divided into preclinical research and clinical testing. Preclinical research is further characterized into laboratory (*in vitro)* and animal studies *(in vivo). In vitro* studies precede *in vivo* and aim at identifying promising human interventions. In order to arrive at the few potential treatments, hundreds of thousands of molecules are tested in lab. Next, the target compounds are evaluated for their desired therapeutic effect and safety in animal models[5]. It must be noted, and it will be analyzed with further detail in the context of EVD later, that the way a potential treatment functions in the given animal model may vary from the way it will function in humans.

The clinical trial portion of clinical research is designed to collect data about the target therapeutic intervention. The central questions being examined are whether the experimental treatment is safe and effective; what dosage is best; what the side effects are; and whether the

[5] From an ethical standpoint, animal testing in and of itself raises controversy, unfortunately this issue is not within the scope of the present argument, as the focus will remain on clinical research with human participants.

treatment is as or more effective than other available treatments. It is further portioned into four distinct phases (see chart), typically resulting in a randomized control trial (RCT). RCTs have long been, and still remain considered by some (in the scientific community) the gold standard for clinical research in humans. RCTs are the reason clinical research is characterized as distinctly non-therapeutic, as the RCT model values producing the best data at the expense of participant care.

Table 2. Phases of traditional clinical trial deign (for experimental therapies):

Phase	Purpose	Participants	Distinct Features
Phase 1	Asses safety (including safe dosage), identify side effects, and pharmacokinetics*	N=20-80 (Small; typically healthy volunteers, sometimes advanced diagnoses	Typically first human trial
Phase 2	Further evaluate safety and observe expected effect in humans	N=hundreds (participants with target condition)	May be RCT
Phase 3	Further assess/ confirm effectiveness of treatment vs. BASC**	N=even larger than Phase 2 (participants with target condition)	Typically RCT
Phase 4 (post marketing)	Collect additional info once approved about risks, benefits, and use in alternate populations/ long term	N=various size and population	

*Pharmacokinetics= the movement of drugs move within the body

**BASC- Basic Available Supportive Care

(Grady, 2012)

Experimental vaccines undergo an overall similar phased clinical trial design, with some notable exceptions. They too are divided into preclinical and clinical trials. Where preclinical trials are conducted *in vitro* and *in vivo* and aim to: (1) determine whether a vaccine works as

intended and (2) to identify any harmful effects. The clinical trials are divided into four phases, as follows:

Table 3.Phases of clinical trial deign (Vaccines):

Phase	Purpose	Participants	Distinct Features
Phase 1	Asses safety and immune response; identify adverse reactions	N=20-few hundred (only healthy volunteers)	Typically first human trial
Phase 2	Determine optimal vaccine composition for achieving protection with safety	N=hundreds to thousands (healthy)	May be RCT
Phase 3	Ability to prevent target disease as intended; further safety	N=thousands to tens of thousands (healthy)	Typically RCT
Phase 4 (post licensing)	Identify less common adverse effects, long-term effects or effects to specific subset of target population	N=target population	Surveillance occurs through spontaneous reporting systems to health authorities

(WHO, Ebola Vaccines, Therapies and Diagnostics; March 17, 2015)

Players

There are four players involved in the development side of clinical trials, the drug regulatory authority (i.e. Food and Drug Administration (FDA) in U.S.); the trial sponsor (i.e. either individual biotechnology or pharmaceutical companies or institutions); the researcher or investigator (i.e. a team comprised of researchers, PhD/ graduate students, etc.); and the Ethics Committee (i.e Institutional Review Board (IRB), also called Research Ethics Committee). The drug regulatory authority is responsible for reviewing and approving the clinical trial protocols, as well as ensuring the clinical trial complies with national and international regulations. The trial sponsor oversees the initiation, management, and financing the trial. The clinical research

team acts as the bridge between the participants and the FDA for example. The Ethics Committee is primarily charged with protecting the patients' rights, safety, and wellbeing.

The process of passing the review of a preclinical followed by a clinical trial process is long and arduous, and will not be fully detailed at this point. In an emergency situation such as the current EVD epidemic in West Africa, there simply is not enough time to adhere to the expected lengthy FDA process. In order to qualify for expedited drug development, such as fast-tracking, information must be able to demonstrate the potential of the drug to address unmet medical needs based on the given drug's development stage. In order to fast track human trials, the design must assess the potential for the experimental treatment to address unsatisfied medical need based on the preclinical animal and pharmacological data.

Clinical trial design structures

There are essentially only two different clinical trial designs that are implemented: Randomized control trials (RCTs) and more recently, Adaptive clinical trials (ACTs).

(1) Randomized control trial (RCT): participants are assigned at random and without knowledge to either a treatment or a control (typically placebo) study arm.

(2) Adaptive clinical trial (ACT): There is no one uniform structure (as indicated by its name), but generally the design includes a prospectively planned opportunity for modifying one or more specific aspects of the study design (i.e. dosage) based on analysis of data from enrolled participants.

Clinical Trials & Global Health

Clinical trials are well-situated to significantly benefit the world's poorest regions that are also most affected by disease and suffer a resulting extremely high number of deaths.

Inexcusably, these clinical research is underrepresented in these communities, particularly, exposure to ACTs. In fact, ACTs have remained underrepresented in the larger realm of Global Health, despite their success for pharmaceutical industries in countries in the western world (i.e. United Kingdom, United States). (Nelson, 2010). The ACT design might be an especially good fit for disease management studies, particularly because it condenses the standard four phase model into a single study that adapts flexibly to acquired knowledge in real time. A single protocol can advance the trials safely from the learning to the confirmatory phase of testing, saving time, money, and speedy evidence when compared to the standard placebo-controlled RCT design currently being used. Moreover, the ACT directly challenges the current outbreak response (i.e. using RCTs) that lacks a dual ethical consideration: for the people sick and dying right now, and the potential benefit of those who may contract the disease in the future.

There are two main limiting factors in applying ACT design to Global Health issues, such as disease management, or in the case of EVD, disease management and prevention. The first concern in the use of technology, and the second is the capacity for strong statistical support; both infrastructures are often lacking in resource-limited settings that are restricted by finances and capacity. Neither of these are deemed to be substantial enough obstacles, especially when weighed out against the aforementioned potential benefits. The use of technology is extremely pertinent as it applies to optimizing time during the trial, that is, the ability to collect data, enter it into the software, have it reviewed and implement new suggestions in as close to real time as possible is vital.

Clinical trials are needed in order to realize developments in global public health, through the testing of new drugs and vaccines, and by improving our understanding of managing disease. Since developing countries carry the largest burden of disease, they stand the benefit the most

from clinical trials, yet these populations remain underrepresented compared to populations in wealthier countries. There are still too few trials, and an insufficient number of people with the skills to run the clinical trial, and they are mostly from affluent, Western countries (23). ACT designs can make trials more cost-effective while minimizing patient exposure to harmful or less effective interventions. All of the advantages that have been noted for ACTs in other settings ought to be at least as beneficial in developing countries.

Ethically Evaluating Clinical Trial Design

Clinical research has a long prevailing history in biomedicine resulting in substantial societal benefits by furthering scientific understanding, prevention, and treatment of disease and illness. Still, many ethical concerns arise about clinical trials specifically, as they ultimately use human participants as a means to generate knowledge that will benefit society, privileging the long-term societal benefits over the current suffering of people. While participants *may* benefit from the acquired knowledge, they do not necessarily benefit, and in fact are exposed to serious risk from the research process. Notably therefore, the participants' benefit is not the goal of clinical trials. "Of course nobody wants the placebo," Nir Eyal (Bioethicist of the Harvard School of Public Health) says, "But the point of medical trials is not to provide the intervention that's medically best for the research subject. It's to establish something that's important—and this point is crucial—for a far larger population and to prevent human catastrophe." ( ). Therefore, the very nature of clinical research, according to Eyal, and many other proponents that herald the RCT as the gold and only standard for clinical trials, inherently tips the scale in the direction of favoring robust data collection as opposed to treatment.

Ethical analysis and resulting guidelines help create confines within which clinical research, particularly with human subjects, must operate. Several internationally recognized research guidelines exist, often termed ethics codes. These codes include The Nuremberg Code, the Declaration of Helsinki, International Conference on Harmonization of Technical Registration of Pharmaceuticals (ICH) Good Clinical Practice (GCP), the Belmont Report, and the U.S. Code of Federal Regulations (45 CFR 46 AND 21, CFR 50, 56, etc.), and they act as guidance for researchers. The purpose of outlining these existing ethical codes and protocols is to clearly understand our assumed drive behind clinical research and the scope that they are/ are not able to account for currently, before we can offer an alternative method. Many of the aforementioned codes and regulations were written in response to examples of decided abuse of power such as the Public Health Service Tuskegee syphilis study or Nazi doctor experimentation during World War II. A summary of these codes/ regulations was synthesized by bioethicists Ezekiel Emanuel, David Wendler, and Christine Grady into seven principles or criteria for ethical clinical research:

(1) Value: Ethical research should aim to answer a clinically, scientifically, or socially valuable question that will contribute to generalizable knowledge about health or be useful to improving health

(2) Validity: Ethical research should use an appropriate, rigorous, and feasible design, methods and implementation plans that ensure valid and interpretable data

(3) Fair subject selection: the process should be fair and based on scientific appropriateness, minimizing risk and vulnerability, and maximizing benefits

(4) Favorable risk-benefit ratio: research risks should be minimized and justified by potential benefits to participants and/or to society

(5) Independent review: independent review should evaluate adherence to ethical guidelines in the design, conduct, and analysis of research

(6) Informed Consent: research should include clear processes for providing adequate information to and promoting the voluntary enrollment of research participants

(7) Respect for enrolled participants: both during and at the conclusion of the research, actions should demonstrate respect for the rights and welfare of participants (Emmanuel, 2000).

These principles frame the ethical obligation to the assurance of upholding scientific rigor and to treat participants with respect rather than prioritizing provide them with much needed treatment. Reviewing these seven ethical criteria therefore reinforces the inherent separation between clinical research and therapeutic treatment by demonstrating that the distinction is not only built into the trial design, but also holds true throughout the popular ethical analysis of clinical research. This is the divide that needs to be rejected and instead worked to be creatively unified, by considering other clinical trial designs and involving the affected community

Randomized Controlled Trials (RCTs)

Looking back: RCTs During the Polio Vaccine

While the scientific challenges of developing an EVD vaccine pose different challenges from those experienced in developing the poliomyelitis vaccine, reflecting back on these

previously conducted trials can illuminate lessons that might prove useful to the acceleration of the development of an EVD vaccine.

In 1954, a whole-virus vaccine against poliomyelitis (polio) was tested in what remains the largest public health experiment ever conducted (Oshinski, 2005). Jonas Salk developed the formalin-inactivated formula which brought forth a significant amount of controversy in regards to its safety and efficacy. The trial was completed in less than 12 months, 623 972 school-aged children in the U.S. were injected with wither the vaccine or a placebo, and more than a million others participated as 'observed' controls (Francis et al., 1955) The vaccine reported 80-90% efficacy against the paralytic poliomyelitis virus. In 1955 it was licensed and deemed fit for immediate distribution. A parallel exists between the polio and EVD vaccine in regards to the number of cases trending downward prior to the introduction of the vaccines, or during clinical trials (Mensi and Pregliasco, 1988).

The example of the polio vaccine is relevant to the discussion the current EVD epidemic because it echoes the particular nuances and issues with developing a vaccine and conducting clinical trials during the height of public fear and amidst the epidemic. Both epidemics were going through clinical trials while being declared International Public Health Emergencies by the World Health Organization (WHO 2014a, 2014b). The polio vaccine was created in 1955, during the time where polio disease had the most devastating effects on the United States, an average of 20,000 cases identified per year (CDC, 2007). The statistical design implemented in this vast experiment was singular, using the textbook model: a randomized, blinded, placebo-controlled trial (RCT) design in 11 states; while 127 test areas in 33 states used an 'observed control design': all children participating received injections of the vaccine, no placebos issued.

In addition to being the largest clinical trial to date, the polio vaccine field trials were hugely publicized and are revered as a historic landmark of medical advancement. The vaccine is referred to as the ultimate example of a triumphant vaccine that easily eradicated a terrible disease that is no longer with us, but this is certainly a generous account. The implementation of the polio vaccine trials were controversial because they faced huge unknowns regarding the short and long-term risks of the vaccine due to the urgency needed. Similarly to the case with experimental vaccines (and therapies) for the 2014-15 EVD epidemic, the overwhelming sentiment was that although there were risks associated with taking the vaccine, the potential benefits were far greater. Extreme urgency stemmed directly from experiencing and seeing the devastating effects of polio on those who did contract it, and serves to reinforce the lengths to which individuals amidst an epidemic, either dying themselves or watching loved ones pass away uncomfortably around them, are willing to go to seek treatment or prevention ( ). Once again the significance of providing immediate and widespread care is highlighted not only for the polio vaccine, but for current experimental interventions for EVD.

As aforementioned, RCTs are highly regarded scientifically because they generate useful data for calculating safety and efficacy, and for this reason clinical research is situated distinctly outside of clinical therapy. However, prior to excavating and dissecting the ethical complications embedded in RCTs, under the analytical microscope, we will explain the purpose of RCTs and establish a case for them. The overall goal of RCTs is to enforce scientific rigor in order to attain its clear desired results. To do so, a RCT has several distinctive features, including: randomization, control, blinding/masking, and statistical evidence. Randomization means that neither participants nor investigators have choice in whether they are assigned (randomized) into

the “experimental” or the “control” groups; the experimental group being the one that receives the designated experimental treatment, while the control will receive either a placebo, or the basic alternative standard care (BASC). The goal of randomization is to obtain similarity in the groups in the uncontrolled variables. Blinding, or masking, refers to the non-knowledge of participant (single blind) nor the researcher (double blind) of which group the participant receives. A predetermined statistical algorithm that indicates with statistical significance whether the experimental intervention is better than, equal to, or worse off than the control treatment. The commonly accepted statistical significance is $p \leq 0.05$.

RCTs are performed to gather data about the safety and efficacy of the given therapeutic agent, with the goal of bettering healthcare provision for future patients. The measures an RCT takes (randomization, placebo, control, blinding) pose a tension between acquiring the necessary knowledge to improve future needs and supporting the welfare of human subjects. This is where the ethical justification of RCTs, or clinical equipoise enters the picture. Clinical equipoise refers to an uncertainty within the expert medical community about the preferred treatment, in terms of therapeutic efficacy, safety, or clinical usefulness (Freedman, 1987). The lack of evidence in favor of one of these treatments over the next morally justifies randomizing enrolled participants to either study arm (Fried, 1974). Clinical equipoise therefore relies on the duty of therapeutic beneficence (a physician’s obligation to help their patients), a pillar of therapeutic medicine, to justify randomization in clinical trials, implying the Similarity Position Still, the RCT design is not built to directly provide therapeutic benefit to its participants, but is instead concerned with the data that will be obtained from the current participants’ trial experiences and will serve to benefit the outcomes of future patients. Can a clinical trial embody both providing therapeutic

care and generating useful data regarding the experimental intervention? An RCT cannot, but perhaps there is an alternate approach.

Considering Alternatives: Adaptive Trial Designs (ACTs)

An ACT design allows for modifications to the trial and/or statistical procedures of the trial after it begins without undermining its validity and integrity. The goal is to make clinical trials more flexible, efficient, and fast. ACTs have largely been used for drug and vaccine development. The FDA (2010) released industry guidelines that explain how adaptive designs are prospective (Dragalin V, 2006).

There are a number of different types of ACTs, the following are only three (of many) examples: (1) Dose finding; (2) Response finding; and (3) Amending sample size:

Table 4. Understanding ACT designs

Adaptive Trial Design	Objective	Description	Drawbacks
Dose finding	To avoid giving therapeutic doses, or overdosing	Data reported and collected as close to in real-time as possible, then reviewed and applied in making decisions about lowering/ raising doses	Requires the manpower and technology to generate and record
Response adapting (Outcome Adaptive)	To reduce exposure to an ineffective trial arm or adverse side affects	Gather safety/ efficacy data as accurately as possible. Next participants are randomized to according to the outcome ('play the winner')	"
Amending sample size	To allow the trial to run until the question has been answered and avoid exposure to an experimental therapy unnecessarily	As the trial begins to inform the assumed sample size, the power calculation can be amended accordingly	Requires time and attention

The very fact that the RCT is dubbed the gold standard, and for a long time, the only accepted structure for clinical research indicates a general tendency to tip the balance in the direction of upholding scientific integrity and gathering data (the goal of an RCT) rather than the treatment of trial participants.

An adaptive trial design differs from a traditional trial design (RCT) because it relies on results accumulated during the trial to alter the remainder of the trial approach. The adaptations most commonly applied, roughly in order of prevalence include: terminating the trial early or extending trial, dose manipulation, responder population finding, and varying the accrual rate.

One common type of ACT is the Outcome Adaptive Randomization, and was first introduced 1993 by Thompson (who?). The concept was later translated into calculating the Bayesian probability than one arm of the clinical trial is a superior treatment than the other, and assigning the subsequent participant to the former treatment. [6] This design circumvents the dominant design of randomization and its ethical shortcomings, particular its insistence on maintaining a distance between clinical research and therapeutic care. The first study to report using this trial design was Giles et al (2003) in a two-arm trial design. The premise has since been extrapolated to three or more arm trial that are able to drop trial arms when their assignment probabilities became too low. Therefore, adaptive randomization can actually be viewed as an intermediate step between dropping arms and fixed randomization, as it gradually identifies responding subpopulations by dropping arms along the way. It may end up similar in structure to a two-armed fixed randomization trial design.

[6] Bayseian probability is

ACTs provide information about which drugs benefit which patients. Experimental drugs that test positively move quickly through the trial, thereby shortening the drug development process and preventing the unnecessary waste of resources, resulting in better treatment. No RCT design can achieve this because one cannot discern which arm is more efficacious before the trial, due to clinical equipoise. One of the most appealing traits of the ACT is its ability to tackle several questions simultaneously, such as: variations in experimental drugs, doses, regiments, or combination therapies.

The advantages to using this ACT model is it can concomitantly inform the efficacy (and safety) of a given treatment(s) and rule out experimental drugs that do not exhibit sufficient efficacy. The ACT design is beneficial to participants, as no individual is left untreated entirely, being for the duration of the trial. Adaptive trails start with equal randomization, and sometimes the response difference between arms is not obvious for some time, leaving randomization balanced for a while. Therefore, participants that enroll in an ACT later will benefit significantly more from its adaptive trait. The ACT is accordingly an example of the ability to simultaneously treat individuals with EVD right now and gather the most clinically useful data to prepare for any future EVD outbreaks.

For example, Adaptive trial designs have been proposed for HIV vaccine trials (HAVEN'T BEEN INTRODUCED YET) as a means to maximize the value gained from the efficacy trials, by evaluating possible efficacy very early on and allowing the parallel evaluation of multiple regimens. Particularly given the limited resources and expanding types of vaccines being tried, the increased efficiency of ACT design is appealing in the climate of HIV and EVD vaccine development.

ACT: Disadvantages and risks

There are important disadvantages and risks to ACT designs that ought to be reviewed. Much of the criticism against ACT design are constructed at the two-arm setting, not its ideal structure (Korn and Friedlin). One of the concerns regards security and confidentiality. The adaptations implemented during the trial might be outside of the scope of confidentiality presented by the Data and Safety Monitoring Board (DSMB) and can have ramification for added participants. There is a heightened chance of information leakage in comparison with blinded trials.

Moreover, the increased complexity of the ACT is made possible by more demanding logistics and planning than most RCTs. In order to keep track of outcomes of all experimental arms throughout the trial and as participants accrued, a centralized database is needed that is likely connected to the software that assigns the treatments. This intricate high-tech set up creates ample room for error. Additionally, the mere setting up process of an ACT requires an additional amount of work, for example selecting the power x in an outcome-adaptive design.

Moreover, securing sponsorship from industry may prove challenging because a company will unlikely willingly fund a trial in which there is a chance that only a small percentage of the participants are actually assigned to the company's drug treatment.

From an ethical standpoint, adaptive clinical trial (ACT) designs are desirable in certain cases. The rationale behind ACTs is favoring the "most effective treatment" given the current available information (Lecoutre and Elqasyr,). Participants arrive sequentially and are assigned to a treatment, but the treatment may be updated as more data is gathered. Therefore, ACTs present the most potential advantages in complicated settings where little is known about any treatments in the field, such as the current EVD epidemic in West Africa.

One example of an ACT design is the *play-the-winner* distribution rule that involves an all-or-nothing framework. It was organically designed for a treatment with a dichotomous outcome measured by either success or failure, where subsequent participants are assigned to the successful, or the 'non-failure' treatment. Another way to think about this design is if the treatments are represented by balls, where red balls represent the experimental arm and black balls represent the control (or a different) treatment) arm. At the beginning, there is an equal amount of red and black balls (initial randomization). When the first participant is randomized, a ball is randomly drawn, and if treatment was successful, then the ball of the drawn color is added to a bag. Eventually, later enrolled participants are skewed to the more successful treatment (GO OVER THIS) The design was later extrapolated to be made applicable for three of more treatments, as well as taking into account slower appearing outcomes; these designs are often referred to as *randomized play-the-winner* rule. The method of these modified versions of the original rule follow a linear adaptive model. While the rule may appear to be deterministic, it is in fact based on the probabilities of the given treatment's success.

Table 3. ?RCTs vs. ACTs: Relative merits and ethical considerations of each trial design

Trial Design	Principal Advantages	Principal Disadvantages	Who is most benefitted?	Who is most burdened?	Additional ethical considerations
RCT	- Aims to control for confounding factors and ensure systematic equivalence - Regulators familiar/ comfortable with design -'gold standard' - Deductive→ leading to high internal validity - Effectively blinds investigators and controls for selection bias	- limited scope of inference affects external validity - Confounding effects may challenge the ability to make valid inferences from trial populations to target populations - feasibility in health care systems that are non-existent or breaking down - largely ignores immediate responses	- Individuals affected by target disease following the trial (including in future epidemics), if therapy is found to be efficacious -Manufacturers of the therapeutic agent, as RCTs provide perhaps the best pathway for drug development and licensure	- If investigational therapeutic agent is efficacious, those randomized to control group - If investigational therapeutic agent is harmful, those randomized to experimental group	- Only ethical when there is equipoise, which can break down when BASC offers little benefit for diseases with high CFR - Scientific validity may be distorted if participants fabricate inclusion criteria due to desperation
ACT	-Aims to balance the scientific validity with alleviation of suffering -Can limit participant exposure to unnecessary/ ineffective treatments - More appropriate in desperate, life-threatening situations where the risk to the individual patient is greatest -Flexibility in modifying study parameters during the study -Able to incorporate new interventions as they become available, and drop ineffective ones -External information can be incorporated into the study while in progress	- Regulators not as familiar with design because not accepted by scientific community - Claims of safety and efficacy may carry less weight -Potential for insufficient top- down financial support from R&D - additional time for planning - Lack of blinding may increase response bias and data can be leaked jeopardizing study's credibility - Lack of a concurrent control group may confound efforts to reach valid inferences about the investigational agent's safety and efficacy	-Trial participants, who are treated as effectively as possible given current and emergent evidence -Affected communities, since rapid identification and deployment of beneficial therapeutic agents could in turn curb the spread and impact of disease	-Trial participants enrolled earlier in the study, due to adaptive nature -Manufacturers of therapeutic agent, insofar as additional trials may be required following ACTs in order to develop and license agent for broader use	-ACTs provide a compromise between data generation on safety and efficacy that is used to inform future decisions, and utilizing accumulated data to alleviate suffering for current patients - Criteria ought to be developed to guide the level and scope of design adaptation

CHAPTER THREE

Evaluating Potential Clinical Trial Designs and Resource Allocation for EVD

The current EVD that is aggressively sweeping across West Africa is unique in two ways. First, with the current number of cases reaching 25831 it has long ago earned the title of the most severe and largest documented Ebola outbreak. The outbreak is taking place in some of the world's poorest countries (UNDP. Human Development Report, 2014), furthering its complexity and lack of healthcare resources and workers. Secondly, experimental interventions that are only in their preclinical phase and are limited in supply, not yet tested on humans, have been first administered to healthcare workers coming from wealthy countries, centering the discussion around potential therapeutic and vaccine interventions in a controversial place (SEE Arie, 2014; Gostin, Lucey, and Phelan, 2014). All of these unique factors pointing to the extreme emergency of the current EVD outbreak in West Africa contribute to the importance of the challenge being posed of reframing the standard approach of outbreak response to include increased attention to providing immediate care to those suffering while conducting research for the benefit of any future outbreak.

Evaluating Clinical Trial Design for (EVD)

The EVD outbreak presents a combination of acute and novel challenges for global public health and clinical research. The outbreak is a case of unprecedented emergency for EVD. While some experimental interventions have passed preclinical trials in animal vectors, at this point in time, no treatment has yet been determined to be efficacious and safe in humans. The expected primary goal of clinical trials conducted during this EVD epidemic is to develop therapies that pass our clinical standard for safety and effectiveness. However, this thesis aims to expand the goal of clinical research in the context of the 2014-15 EVD epidemic in West Africa to include alleviating the suffering of those currently infected with EVD as well as gathering data to inform treatment and vaccine development. Determining the ideal trial design to realize this extended goal requires an open-minded approach that considers issues at the intersection of scientific, practical, and ethical factors. Unsurprisingly, there is a divergence of opinions regarding which trial design will most successfully bring about the desired outcomes; the two major camps can be divided into RCT advocates and ACT advocates. This disagreement is influenced by a differential understanding of the goal of clinical research and whether, during a distinct emergency such as the current EVD epidemic, it includes the responsibility to care for individuals who are suffering and adequate therapeutic treatment is not available.

In order to determine how to best reach the aforementioned goal of 'therapeutic clinical research', three ethical questions must be addressed in the context of the 2014-15 EVD epidemic in West Africa: (1) is there room for *compassionate use* (extended access) of therapies in absence of human safety, efficacy or dosing data? (2) Considering the severe scarcity of experimental interventions (see 'Ethical Allocation of Scarce Resources, Chapter #2), which patients ought to be granted first access? (3) Ultimately, having taken the two previous ethical quandaries into consideration, what is the most appropriate clinical trial design? These questions

are all framed under the broader ethical question guiding this research, how to simultaneously maintain the responsibilities to alleviate current suffering of individuals in West Africa and to uphold scientific rigor and develop vaccines and therapies in case of future epidemics.

Compassionate use refers to the use of an unapproved intervention, outside of the context of a clinical trial and with the intention of helping participants with severe, life-threatening infections or conditions that have no comparable or satisfactory alternative treatment options (FDA,). The current EVD is therefore an ideal application of this principle, with its insurmountably high CRF and lack of FDA approved treatments. The WHO ethics advisory committee's statement in August, authorizing the use of not yet approved therapies, seems to be calling for compassionate use, with the added stipulation of an obligation to collect and share any relevant acquired date in hopes to quantify some safety and efficacy (WHO Advisory Panel, 2014). Advocates for RCTs would likely not approve of the privileging of immediate treatment at the cost of gathering scientifically and statistically sound data that is ultimately needed to best understand and treat this, and future epidemics. Further, during the first-in-human setting, a compassionate use-based trial may not even succeed in preventing more deaths, due to the lack of proven efficacy in humans. The ethical reasoning for compassionate use however, is the obligation to offer a treatment option to informed and consenting participants in the current blreak case of an utter lack of treatment. The current state of highly limited supply of experimental interventions to treat EVD certainly muddies the application of compassionate use as necessarily ethical.

Instead, compassionate use must be coupled with an ethical approach to allocating scarce resources (see 'Allocation of Scarce resources, Chapter #2). Faced with the dilemma of the number of individuals in need of treatment for EVD far exceeding the foreseeable availability of

experimental interventions, should decisions about eligibility criteria for participants in clinical trials be informed by: (a) which participants will receive most benefit from treatment; or (b) which participants are most likely to generate relevant scientific data? Are clinical trials even a viable option given the severe scarcity of some experimental interventions, such as ZMapp?

Considering the 2014-15 EVD outbreak in West Africa, how do we think about the just distribution of an inadequate amount of experimental therapeutic drugs or vaccines? The case of the limited supply of ZMapp, a monoclonal antibody, is a relevant example. Out of the tens of thousands of those infected with EVD, mostly in West Africa, how does the company decide which six or seven patients are given the experimental ZMapp treatment?[7] The first lucky recipients were two America healthcare workers, Kent Brantly and Nancy Whitebol who travelled to Liberia to assist in the outbreak response and were airlifted back to the U.S. where they were treated with ZMapp. Since ZMapp had not yet undergone any clinical trials, FDA's compassionate use regulation allowed the two Americans to access the drug. Why was compassionate use extended only to these American healthcare workers? What about West African healthcare workers? What about the tens of thousands of others suffering in West Africa? In trying to implement the complete lives system to this case, treating these two individuals might be partly justified as they are instrumental in their role of healthcare work to care for others. Still, it seems that West African community health workers and healthcare providers occupy an even more instrumental value since they have more knowledge and experience in their affected communities and will remain there long after international support flees and will likely be exposed to subsequent cases. At any rate this rationale falls further apart

[7] Mapp Biopharmaceutical, Inc. only produced 6-7 doses of ZMapp in the first batch

when we are presented with the third individual to receive ZMapp, Miguel Pajares, a 75-year-old Spanish priest. Pajares also defies the youngest-first ethical principle.

The language of compassionate use was implemented to justify the early distribution of ZMapp in lieu of invoking ethical criteria, protocol or reasoning. In doing so, ethics of allocation of the scarce resource were brushed under table. Further, there was no mention of a standardized data set, or even standardized dosing, with which to evaluate the impact of the untested treatment, thereby similarly undermining the goals of science, much to the dismay of RCT advocates. This is an example at the extreme of forgoing any systematic or long-term consideration in favor of nursing (certain) individuals back to health. Unfortunately the same luxury of urgency and resources was not granted across the board, or to those outside of the Western world. The language of compassionate use therefore seems insufficient in the context of using unregistered interventions in the current EVD outbreak, unless it is paired with an ethical approach to distributing a limited supply of resources, such as the complete lives system.

Having established the place of compassionate use and the way in which is interacts with the allocation of scarce resources, we are now equipped to ethically evaluate which clinical trial design integrates the dual responsibility of ameliorating current suffering and deploying for reactive use in future or in a prophylactic vaccination campaign.

Given the several exacerbating factors that converge to make the 2014-15 EVD epidemic in West Africa a unique case of emergency, the aforementioned seven ethical principles (see ‘Ethical Evaluation of Clinical Trials, Chapter #2) have been modified and expanded upon to contextualize them in this EVD epidemic.

First, in terms of (1) collaborative partnerships, clinical trials of experimental therapies or vaccines must involve the affected communities and stakeholders in the planning, conducting,

and overseeing of the trial. Moreover, a sustainable benefit must be ensured as a result of these clinical trials, such as working to strengthen healthcare systems and ensuring availability to eventual drug and vaccines. This principle highlights the important role of community members and healthcare workers in the quest to incorporate both short and long-term treatment and prevention of EVD infections in West Africa. The WHO ethics advisory committee for the current EVD epidemic incorporated no representation from the affected countries. In regards to (2) social value, it must be ensured that the data collected is valid and roust in order to inform decisions about the need for further research, marketing, approval or withdrawal. This data must then be disseminated and made readily available to anyone, fulfilling the demand of the WHO ethics committee. Ensuring (3) scientific validity of the trial includes reviewing all relevant existing data for feasibility and ensuring the scientific objectives are realized (i.e. adequate infrastructure for data collection/ analysis). In order to account for (4) fair selection of study participants, the trial design must be transparent about the inclusion criteria and adhere to it strictly. Prioritizing individuals for non-ethical (See 'Ethical Allocation of Scarce Resources', Chapter #2) or medical reasons (i.e. wealth, race, nationality etc.) is not appropriate. A (5) favorable risk-benefit ratio is achieved by evaluating the risks and potential benefits to participants based on relevant data, and minimizing risks to patients by providing supportive treatment, monitoring for side-affects, and establishing data regarding safety. (6) Independent review of the trial enforces public accountability through ethical review and oversight, as well as through transparency and outside review if necessary. The issue of (7) informed consent can be regulated by disclosing information and obtaining voluntary and informed consent in a manner that is culturally and linguistically respectful, with the guidance of community members. When necessary, a supplementary community or familial consent procedure can be set up. The freedom

to refuse or withdraw from the trial must be clearly stated and upheld throughout. Lastly, it is of utmost importance to ensure (8) a respect for the recruited participants and communities implicated in the clinical trial by monitoring for and treating any medical disorders or discomfort, protecting the confidentiality of participants, keeping participants informed throughout the course of the study of relevant information, and sharing the results of the study with participants and their communities (Emmanuel, 2000).

Evidently, the application of these principles reflects a consideration of both the welfare of the study participants and the generation of scientific knowledge from which therapeutic drugs and vaccines can be developed to protect society from any future EVD outbreaks. However, there is a much greater weight given to the latter, and there seems to be a lack of urgency that overlooks the widespread material suffering in West Africa. A hopefully more balanced approach to clinical trial design will be advocated for in the form of the ACT, but first, the case for the implementation of RCTs and its subsequent inadequacies for the current EVD epidemic must be exposed.

Case for RCTs in 2014-15 EVD Epidemic:

In the context of the 2014-15 EVD epidemic, an RCT would likely include randomly distributing trial participants to either an experimental arm that offers an investigational therapeutic intervention, or a control arm that BASC and a placebo.

Within the RCT advocate camp, there exists a general consensus on conducting a trial with a concurrent control group, as this measure ensures the most reliable way to obtain safety and efficacy measures. Promoters of RCT design for EVD intervention development include the NIH, FDA, Biomedical Advanced Research and Development Authority, the Department of

Defense (DOD), and pharmaceutical industry. If preclinical data suggests that the experimental agent has either a low chance of effectiveness, or potential for substantial toxicity, the BASC control group in an RCT is the most efficient way to conclusively identify the harm or benefit. Considering the accelerated nature of the drug development process for the current EVD epidemic, as dictated by the WHO, the use of RCTs might be deemed acceptable, but it is by no means known for its speed.[8] When Cox, Borio, and Temple (2014) build the case for the use of RCTs in the EVD treatment, they later include that ongoing monitoring of results, shift of treatment, and other adaptive elements to reduce time ought to all be incorporated into trial design, straying away from a traditional RCT and essentially advocating for a design that more resembles an ACT.

The advantages to using a placebo-RCT for this EVD epidemic are the following. The randomization in the trial aims to control for cofounding factors and ensure no selection bias in the participants assigned to the control versus the experimental treatment arm. It does so by blinding investigators and participants. RCTs follow deductive reasoning from a narrow hypothesis, indicating high internal validity of the results. Regulators are most familiar and comfortable with the RCT as a design trial. Manufactures of the therapy are benefited with the choice of an RCT design since it assures the development and licensing of the intended intervention, since the trial must be seen to completion. Those who will benefit most from the implementation of RCTs in the current EVD epidemic are individuals who become infected with the virus *after* the clinical trial is completed, and live in a region that will grant them access to the agent, given the intervention is found to be efficacious. The chief argument in favor of conducting an RCT in the context of this EVD epidemic is that one ought to gather the best

[8] i.e. proceeding with only data from limited phase 1 data, and potentially including no traditional phase 2 data

possible evidence during this outbreak in order to develop the safest and most effective intervention, and a placebo-controlled RCT is the most appropriate method to achieve this goal (Pullman and Wang, 2001)..

Meanwhile, the drawbacks of implementing an RCT in the context of the current EVD epidemic are summarized. Randomization of participants to different trial arms may not be feasible in the absence of an adequate healthcare infrastructure that has only been further degraded during the course of the epidemic. Randomization sacrifices mounting immediate treatment in order to obtaining data quickly for the sake of gathering well-controlled, statistically significant evidence. Scientific validity, the cornerstone of RCTs, may be distorted if potential participants fabricate inclusion criteria in desperate attempts to receive any medical intervention during the emergency situation of this epidemic coupled with the absence of any reliable treatment *and* the limited supply of experimental treatments.

Practical objections to the use of RCTs in the EVD epidemic relate to the state of existing health care systems and the fragile social order (as a result of the outbreak) in West Africa (Liberia, New Guinea, and Sierra Leone). Individuals may resist the offer of informed consent to be randomized into a placebo-controlled clinical trial due to the immense fear of the lack of trust in international healthcare workers as well as public authorities. Enforcing RCTs therefore might further worsen the state of fear and distrust by adding a weariness of the treatment centers.

A faction of individuals in the public health community push against RCTs as they are slow and too rigid. Their rejection of the control group is motivated by the moral obligation to provide therapeutic interventions as widely as possible. Instead, in attempts to circumvent the use of a control arm and to avoid the charge of denying treatment to any participants, an

amendment to the RCT is proposed, to compare real-time recovery rates to the recovery rates during previous outbreaks (since we know there was no treatment).This approach would be particularly problematic in the case of the 2014-15 EVD outbreak as the historic recovery rates of EVD are highly variable and dependent on different supportive treatments as well as other cofounding factors (i.e. location, age, multiple diagnoses, etc.). Given the limited supply of some experimental interventions, if a historic control cannot be constructed, then there is no ethical reason to favor an RCT to allocating via lottery (see 'Allocation of scarce resources' section, Chapter #2). Moreover, as Cox et al. (2014) point out, "the historical case fatality rates are irrelevant if the current study patients receive better supportive care". The use of RCTs is neither practically nor ethically adequate for the current EVD epidemic in West Africa as the primary aim must be to generate data about safety and efficacy in *the least amount of time*.

Ethically, and significantly for the purpose of this thesis, a RCT design fails when it makes a clear judgment in favor of prevention/treatment of potential future infections over valuing the lives of the many individuals suffering presently in West Africa, rather than attempting to address both.Therefore, while RCT design irrefutably remains the most scientifically definitive trial design, we must ask ourselves at what cost do we privilege scientific advancement over ameliorating current suffering? Or, in other words, is it morally permissible to sacrifice the lives of some currently infected individuals (by failing to provide them access to intervention agents) for the sake of future epidemic prevention?

Case for ACT in 2014-15 EVD Epidemic

Alternate (adaptive) trial designs can achieve this rapidly and in a more ethical manner.

There are many types of ACT design options. In the context of the 2014-15 EVD epidemic, an ACT model would involve assigning each new participant a 'new' treatment based on the best information accumulated up until that point, with the intent of treating participants in the most effective manner based on the most relevant evidence. Another possibility might be too simultaneously offer different treatments at different sites and observe the patient outcomes closely, transferring patients to the more successful or efficacious intervention. The measured effects on participants will dictate the resulting action: I. If a significant benefit is observed then the study will be rolled out; II. If there is no effect, the intervention is discarded; and III. If the treatment is characterized as showing promise, then a follow-up study of the RCT nature may be appropriate, where patients are randomized to an efficacious treatment.

ACTs have been around for less time than RCTs and as such remain less common and widely accepted (Pullman and Wang, 2001). For this reason, results from ACT designed trials may be less accepted by public health authorities meaning the experimental interventions may be less recognized too.

The following are the assumed benefits of using an ACT design during this current EVD outbreak. First, it aims to balance the production of scientifically acceptable data with the alleviation of individual suffering, meeting the criterion put forth by the WHO and by this thesis. An ACT can limit the exposure of participants to unnecessary or ineffective treatments or harmful ones.. The ACT allows for the flexibility in the study parameters necessary in an extreme situation such as this based on the evolution of the epidemic. Then, as new interventions become available, additional trial arms can be added, and ineffective ones can be dropped without the need to start an entirely new trial. Moreover, external information and findings can be incorporated into the design. Accordingly, an ACT is the most appropriate design in a

desperate (time-wise and resource-wise), life-threatening situation and such as the one at hand, since the risk to individual participants is very high. Trial participants, at the present, are most benefited by the ACT deign because their most effective and up-to-date treatment is the chief priority. This value extends to affected communities, since the rapid identification and distribution of beneficial therapeutics might curb the spread and impact of the disease.

The principal argument in favor of using an ACT trial design in the context of this EVD epidemic is that given the debilitating nature of the viral infection and the high CFR when treated with BASC alone, the health of affected individuals ought to be the main priority of clinical research. Therefore, the urgency of the situation, coupled with the shortage in supply of experimental interventions highlights the need for increased flexibility of structure as well as more ethical consideration in the methods of clinical trial testing. The ACT is the only design that offers these attributes. The unprecedented EVD outbreak, necessitates a similarly unprecedented response effort (public-private). If "the FDA has one of the most flexible regulatory frameworks in the world", according to Dr. Luciana Borio, the FDA assistant commissioner for counterterrorism and policy as well as acting deputy chief scientist, then the use of ACT based trials should be readily supported for this EVD epidemic.

The negative ramifications of using an ACT as a trial design are the following. Due to its relative newness, the ACT is not yet well understood or accepted within the scientific community, meaning obtaining approval from regulatory authorities such as the FDA and NIH, and funding from pharmaceutical companies, all diehard RCT fans, may be pose an obstacle. Claims regarding the efficacy and safety of the intervention may not carry enough traction due to the lack of established legitimacy. The ACT requires a longer amount of planning. The lack of blinding may increase response or selection bias and allows for a potential leaking of

information, while a lack of a concurrent control group may confound the efforts to reach validated conclusions about the intervention's safety and efficacy. Lastly, the design's adaptive nature may make its statistical analysis more difficult than conventional methods. Participants enrolled early on in the trial are most burdened by its adaptive nature, since they are denied access to knowledge gained, and subsequent chance in treatment, later in the study. Pharmaceutical companies (manufacturers) of the experimental agents are burdened as well, since ACTs may be inconclusive, and may even drop developed treatments along the way.

Therefore, ACTs are able to provide the sought after collaboration of data generation regarding safety and efficacy of the experimental intervention for the benefit of future contracted infections with EVD, as well as using accumulated data to diminish the suffering of current infected individuals in West Africa.

CONCLUSION

Calling for Reform of Clinical Research Approach during Outbreak Response

An epidemic is in and of itself a widespread occurrence of trauma that necessitates a unique and comprehensive response. The ongoing 2014-15 EVD epidemic in West Africa is unprecedented in a due to its magnitude, duration, geographic extent, ad extremely high CFR rate. The subsequent global response to the EVD epidemic must be of matching enormity, but even more importantly of creative, multifaceted and open-minded energy. Every epidemic is a state of emergency with its own particular needs. The needs that converge to make this epidemic a terrifying emergency are: insufficient healthcare infrastructure resulting in a lack of adequate resources, the global health response was far too slow and places a further urgency on an already total state of emergency, an extremely virulent disease that has spread rapidly, no approved interventions (therapies or vaccines) exist to date, and to further exacerbate, even the experimental interventions being accelerated through clinical trials are in scarce supply.

The human instinct to feel for human suffering and act to provide care seems intuitive, but applying it to an epidemic of such proportion requires a thoughtful and open-minded approach. This thesis began the process of doing some of the needed work to navigate these delicate ethical moments. The work is located in bringing attention to and understanding how to realize the coexistence of two overarching ethical obligations during an emergency outbreak:

alleviating the material suffering of those suffering from EVD in West Africa now and efficiently gathering data that will better inform and potentially prevent any future outbreaks. What are the gaps or oversights in our current global outbreak response preventing the dual ethical consciousness and how can we reform the approach to center it? Clinical research is considered as a place where these two duties converge and accordingly this thesis urges a rethinking and broadening of the way in which we approach and conduct clinical research during emergency epidemics.

Before carefully critiquing and suggesting an alternative method, the current structure and rhetoric of clinical research was thoroughly outlined in *Chapter two: How is clinical research conducted in outbreak response? Considering standard and alternative approaches*. In critiquing the standard clinical trial approach (a placebo-controlled RCT), the distinction between therapeutic medicine and clinical research must rejected. Instead ACTs work to incorporate and account both for the immediate needs of individuals currently suffering from EVD and the needs of potential future cases. Thus, the two main avenues to achieving the ethical consideration of both individual's suffering with EVD currently and developing vaccines and therapies to prevent and treat future EVD infections are through adjusting clinical trial design by promoting ACTs coupled with the ethical allocation of scarce resources predicated on the seven principles outlined in the chapter. This reform in the approach to outbreak response, particularly through clinical research was studied in the context of the 2014-15 EVD epidemic in West Africa, but aimed to make a case for an reconsideration in the approach that can be applied to any widespread infectious outbreak, wherever it may be.

The moral permissibility of implementing any research design should be informed by the context in which the research is conducted. It is concluded that in strenuous circumstances of the

2014-15 EVD epidemic in West Africa, if one of the two guiding ethical duties must be slightly prioritized, it is the treating of and caring for those who are amidst suffering inflicted by EVD currently. The clinical trial design that upholds the current reduction of suffering is the ACT.

Finally, this discussion should not preclude involving the voices of local, affected communities in trial planning, design, and oversight. Engaging local communities in trial design, planning, and oversight may foster trust in the trial and epidemic response, and better ensure that local values and customs are both respected and represented. As such, the input of those affected by EVD and who may be impacted by any trials conducted ought to be considered of the utmost importance in responding to the question of which trial design to implement.

A possible network through which reforming the approach to clinical research may be implemented is the Community Health Workers (CHWs) local to the affected communities in West Adfrica. CHWs embody the two ethical duties, as they are critical in the immediate response of containing the outbreak and caring for those infections, and will be likely the first to encounter any future EVD cases that may arise. They are also best equipped to ensure that the communities' voices are heard and taken into consideration, in terms of trial design and implementation, since they are a part of the community at stake. Further research into the how to center Community Health Workers in the current EVD outbreak response in West Africa, as well as a model for future epidemics of EVD or another virulent pathogen, wherever it may be, is highly recommended.