Official Title: A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of Two Doses of an Ebola Sudan Chimpanzee Adenovirus Vector Vaccine, VRC-EBOADC086-00-VP (cAd3-EBO S), in Healthy Adults

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Protocol RV 508

A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of Two Doses of an Ebola Sudan Chimpanzee Adenovirus Vector Vaccine, VRC-EBOADC086-00-VP (cAd3-EBO S), in Healthy Adults

Study Product Provided By
National Institutes of Health (NIH)
National Institute of Allergy and Infectious Diseases (NIAID)
Vaccine Research Center (VRC)
Bethesda, Maryland

Study Conducted By
Makerere University-Walter Reed Project, Makerere University, Kampala, Uganda

In Consultation With
U.S. Military HIV Research Program (MHRP) Silver Spring, MD
VRC, NIAID, NIH

Study Sponsored by
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National Institute of Allergy and Infectious Diseases (NIAID)
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Bethesda, Maryland

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IND #16111 – held by VRC, NIAID, NIH

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RV 508/WRAIR #2439
Version 1.5
03 March 2020

TABLE OF CONTENTS

LIST OF TABLES

SCHEMA

Title

A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of Two Doses of an Ebola Sudan Chimpanzee Adenovirus Vector Vaccine, VRC-EBOADC086-00-VP (cAd3-EBO S), in Healthy Adults

Study Design

This is a Phase I, open-label study to examine safety, tolerability and immunogenicity of an investigational Ebola vaccine given by intramuscular (IM) injection to healthy adults. The study is a dose escalation of VRC-EBOADC086-00-VP, a chimpanzee adenovirus serotype 3 vector vaccine, which encodes wild type (WT) glycoprotein (GP) from the Sudan strain of Ebolavirus.

Table 1: RV 508 Study Design

Group	Participants	Day 0*
1	20	cAd3-EBO S at $1x10^{10}$ PU/mL
2	20	cAd3-EBO S at $1x10^{11}$ PU/mL

* All injections: administered in 1 mL volume.

It is anticipated that about 100 volunteers will be screened in order to enroll a total of 40 participants. The 40 participants will be evenly split, with 20 in each of the two dosage groups for cAd3-EBO S. The dose escalation plan includes daily review of any new safety data by a study clinician, regular review of safety data by the protocol team and a staged enrollment plan with required interim safety reviews. The study will begin with enrollment of 3 participants into Group 1 at a rate of 1 participant per day. After at least 7 days of follow-up for the first 3 vaccinated participants, an interim safety review will occur before enrollment of additional participants into the group. If no safety issues are identified, an additional 17 participants will be enrolled to complete Group 1. When there is a minimum of seven days of follow-up safety data from the last enrolled participant in Group 1, an interim safety review will occur. Once no safety issues are identified, enrollment of participants into the next dose level (Group 2) will begin with the enrollment of 3 participants at a rate of 1 participant per day. After at least 7 days of follow-up for the first 3 vaccinated participants in Group 2, an interim safety review will occur before the enrollment of additional participants into Group 2. If no safety issues are identified, an additional 17 participants will be enrolled to complete Group 2.

Product Description

VRC-EBOADC086-00-VP (cAd3-EBO S) is composed of a cAd3 vector that expresses Ebola Sudan WT GP. It is formulated at 1 x 10^{11} PU/mL.

VRC-DILADC065-00-VP (diluent) is the formulation buffer used for vaccine production and will be used when needed to prepare the 1 x 10^{10} PU/mL dose of cAd3-EBO S.

Participants

Healthy adults in the Kampala area aged 18-50 years will be enrolled.

Study Duration

Participants will be evaluated at 9 clinic visits over 48 weeks.

Study Objectives

Primary Objectives

- To evaluate the safety and tolerability of VRC-EBOADC086-00-VP when administered IM at a dose of 1 x 10^{10} particle units (PU) to healthy adults;
- To evaluate the safety and tolerability of VRC-EBOADC086-00-VP when administered IM at a dose of 1 x 10^{11} PU to healthy adults.

Secondary Objectives

- To evaluate the antibody response to the GP insert and cAd3 vector in VRC-EBOADC086-00-VP at 4 weeks after vaccination as assessed by GP ELISA and vector-specific neutralization assays, respectively.
- To evaluate the Ebola Sudan GP-specific T cell responses in VRC-EBOADC086-00-VP at 4 weeks after vaccination as assessed by Intracellular cytokine staining (ICS).

Exploratory Objectives

- To evaluate the immunogenicity of VRC-EBOADC086-00-VP by various assay methods at some or all of the research sample collection timepoints indicated in the Schedule of Evaluations (SOE); genetic factors associated with immune response may also be evaluated.
- To evaluate vaccine-induced mRNA expression profiles through Study Week 1.
- To evaluate the time course and durability of cAd3 neutralizing antibody titers, mediators of inflammation following vaccination and time course and durability of immune response by a variety of exploratory assays using samples collected throughout the study.
- To isolate Monoclonal Antibodies (MAbs) to determine epitope specificity and their functional capacity.

Study Clinical Site

Makerere University-Walter Reed Project
[redacted]
Kampala, Uganda

Study Laboratory

Makerere University – Walter Reed Project Laboratory
[redacted]
Kampala, Uganda

NIAID Vaccine Immunology Program (VIP)

[redacted]

NIAID VRC Immunology Laboratory

[redacted]

Study Data Management Center

EMMES Corporation

[redacted]

Reviewing IRBs

Makerere University School of Public Health (MUSPH) IRB
Higher Degrees, Research and Ethics Committee
(FWA00011353, IRB00005876)

[redacted]

Kampala, Uganda

Local Regulatory Authorities

Uganda National Council of Science and Technology
(FWA00001293, IORG0001117)

[redacted],

Kampala, Uganda

National Drug Authority (NDA)

[redacted]

Kampala, Uganda

LIST OF ABBREVIATIONS

Abbreviation	Term
Ad5	Human adenovirus serotype 5
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
AoU	Assessment of understanding
APA	Anti-phospholipid antibody
BDBV	Species Bundibugyo ebolavirus
BMI	Body mass index
cAd	Recombinant chimpanzee adenovirus
cAd3	Recombinant chimpanzee adenovirus serotype 3
cAd3-EBO	Recombinant chimpanzee adenovirus type 3-vectored Ebola virus vaccine
cAd63	Recombinant chimpanzee adenovirus serotype 63
CBC	Complete blood count
cGMP	Current Good Manufacturing Practices
DNA	Deoxyribonucleic acid
EBOV	Species Zaire ebolavirus
EHF	Ebola hemorrhagic fever
ELISA	Enzyme-linked immunosorbent assay
ELISPOT	Enzyme-linked immunospot
EVD	Ebola virus disease
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GP	Glycoprotein
GP (S)	Glycoprotein from *Sudan ebolavirus*
GP (Z)	Glycoprotein from *Zaire ebolavirus*
HA	Influenza hemagglutinin protein
HAE	Hereditary angioedema
HCV	Hepatitis C vaccine
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
IB	Investigator's Brochure
ICS	Intracellular cytokine staining
ICTV	International Committee on the Taxonomy of Viruses
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscular
IND	Investigational new drug
IP	Investigational product
IRB	Institutional Review Board
LIMS	Laboratory Information Management System
MAbs	Monoclonal Antibodies

MHRP	U.S. Military HIV Research Program
NHP	Non-human primate
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NP	Nucleoprotein
NSAID	Nonsteroidal anti-inflammatory drug
PBMC	Peripheral blood mononuclear cells
PFU	Particle forming units
PSRT	Protocol Safety Review Team
PT	Prothrombin time
PTT	Partial thromboplastin time
PU	Particle units
rAd	Recombinant human adenovirus
rAd5	Recombinant human adenovirus serotype 5
RESTV	Species *Reston ebolavirus*
RNA	Ribonucleic acid
RPR	Rapid plasma reagin
SAE	Serious adverse event
SAS	Statistical Analysis System
SUDV	Species *Sudan ebolavirus*
SUSAR	Suspected, unexpected and serious adverse reaction
TAFV	Species Taï *Forest ebolavirus*
ULN	Upper limit of normal
VCMP	Vaccine Clinical Materials Program
VIP	NIAID Vaccine Immunology Program
VP	Virus particle
VPP	VRC Pilot Plant
VRC	Vaccine Research Center
WBC	White blood cell
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research
WT	Wild type

1.0 INTRODUCTION

1.1 Background: Ebola Infection

In 2013, the International Committee on the Taxonomy of Viruses (ICTV) Filoviridae Study Group and other experts published an updated taxonomy for filoviruses. The genus Ebolavirus is one of three genera in the family Filoviridae, which along with the genera, Marburgvirus and Cuevavirus, are known to induce viral hemorrhagic fever. Five distinct species included in the genus Ebolavirus are Bundibugyo (BDBV), Reston (RESTV), Sudan (SUDV), Taï Forest (TAFV), and Zaire (EBOV) [1].

Ebolavirus is a large, negative-strand RNA virus composed of 7 genes encoding viral proteins, including a single glycoprotein (GP) [2-5]. The virus is responsible for causing Ebola virus disease (EVD), formerly known as Ebola hemorrhagic fever (EHF), in humans. In particular, BDBV, EBOV, and SUDV have been associated with large outbreaks of EVD in Africa and reported case fatality rates of up to 90% [6]. Transmission of Ebola virus to humans is not yet fully understood, but is likely due to incidental exposure to infected animals [7-9]. EVD spreads through human-to-human transmission, with infection resulting from direct contact with blood, secretions, organs or other bodily fluids of infected people, and indirect contact with environments contaminated by such fluids [6].

EVD has an incubation period of 2 to 21 days (7 days on average, depending on the strain) followed by a rapid onset of non-specific symptoms such as fever, extreme fatigue, gastrointestinal complaints, abdominal pain, anorexia, headache, myalgias and/or arthralgias. These initial symptoms last for about 2 to 7 days after which more severe symptoms related to hemorrhagic fever occur, including hemorrhagic rash, epistaxis, mucosal bleeding, hematuria, hemoptysis, hematemesis, melena, conjunctival hemorrhage, tachypnea, confusion, somnolence, and hearing loss. Laboratory findings include low white blood cell and platelet counts and elevated liver enzymes [6]. In general, the symptoms last for about 7 to14 days after which recovery may occur. Death can occur 6 to 16 days after the onset of symptoms [7, 10]. People are infectious as long as their blood and secretions contain the virus; the virus was isolated from semen 61 days after onset of illness in a man who was infected in a laboratory [6].

Immunoglobulin M (IgM) antibodies to the virus appear 2 to 9 days after infection whereas immunoglobulin G (IgG) antibodies appear approximately 17 to 25 days after infection, which coincides with the recovery phase. In survivors of EVD, both humoral immunity and cellular immunity are detected, however, their relative contribution to protection is unknown [11].

While prior outbreaks of EVD have been localized to regions of Africa, there is a potential threat of spread to other countries given the frequency of international travel. The 2014 outbreak in West Africa was first recognized in March 2014 and, as of June 18, 2014 the known case rate exceeded the largest prior EVD outbreak which occurred in Uganda in 2000-2001 with 425 cases and 224 deaths (case-fatality rate=53%) [12]. By March 30, 2016 the WHO declared an end to the Public Health Emergency of International Concern regarding the Ebola virus disease outbreak in West Africa, with a combined total (laboratory-confirmed, probable and suspected) 28,646 cases and 11,323 deaths reported (case fatality rate = 40%) [13]. In subsequent years, there have been multiple Ebola outbreaks with cases detected in many countries, including at least nine outbreaks in the Democratic Republic of the Congo (DRC). The outbreak that started

in 2018 in the DRC has become the second largest after the 2014 West African outbreak with a combined total (laboratory-confirmed and probable) of 1,016 cases and 634 deaths (case fatality rate = 62%) as of March 24, 2019 [14].

Viruses in the Filoviridae family are also categorized as potential threats for use as biological weapons due to ease of dissemination and transmission, and high levels of mortality. Currently, no effective therapies or FDA-licensed vaccines exist for any member of Filoviridae family of viruses.

1.2 Rationale for the Ebola Sudan Chimpanzee Adenovirus Vector Vaccine, VRC-EBOADC086-00-VP (cAd3-EBO S) and RV 508 Study Design

A vaccination strategy to achieve immediate protective immunity in most recipients with a single vaccination against Ebola would be desirable in an outbreak setting. Vaccination strategies that achieve durable protective immunity would be desirable for populations in areas of the world where outbreaks occur sporadically. Optimally, one approach would serve both needs, but a different approach may be needed for rapid immunity than is needed for durable immunity.

The VRC/NIAID/NIH and GSK have developed and evaluated a recombinant cAd3-EBO vaccine. The candidate vaccine is comprised of two vectors, each of which respectively encodes WT GP - one from the Zaire (cAd3-EBO Z) and one from the Sudan species of Ebola (cAd3-EBO S). Clinical evaluation of cAd3-EVOZ was accelerated with the occurrence of the West African Ebolavirus outbreak in 2014. Based on 1) cAd3-EBO vaccine safety, immunogenicity and protection studies in NHP, 2) experience with other viral vaccines using the cAd3 expression system, and 3) the timing of the severe Ebola outbreak in west Africa, human clinical trials evaluating the cAd3 vectors with both the WT GP of the Ebolavirus Zaire and of the Ebolavirus Sudan and the cAd3-EBO Z only vaccine began in September, 2014 (the VRC 207 study). VRC 207 and subsequent studies demonstrated both cAd3-EBO and cAd3-EBO Z were safe and immunogenic in humans at doses as high as 2x10^11 PU IM (VRC 207, RV 422) [15-19]. By the end of 2017, greater than 500 participants will have received the cAd3-EBO Z vaccine in ongoing international studies.

The cAd3 Ebolavirus Sudan vaccine, (cAd3-EBO S) VRC-EBOADV086-00-VP, which could also be used in the event of an Ebola Sudan outbreak, has not been evaluated as a stand-alone vaccine to confirm its safety and immunogenicity. RV 508 will evaluate the single vector cAd3 Ebolavirus Sudan vaccine at the same doses as were evaluated in VRC207 and RV422. Because of the small amount of existing safety data on cAd3-EBO S as a component of the cAd3-EBO vaccine, RV 508 will evaluate the two doses of cAd3-EBO S alone in an open-label, dose-escalation design to collect more data on the safety and preliminary immunogenicity that may further describe the extent of cAd3-EBO S' rapid immunity with a single injection.

1.2.1 Previous Human Experience with VRC Filovirus Vaccines

The VRC/NIAID/NIH has developed seven different investigational Ebola vaccines to date, which were previously evaluated in a series of Phase I clinical trials. The vaccine constructs were shown to be safe, well tolerated and immunogenic in human clinical trials (Table 2).

Table 2: Summary of the Studies for Evaluation of VRC Ebola and Marburg Vaccines

Study Identifier (Clinicaltrials.gov)	Study Design	Vaccine Product (s)	Dosage, route, x N administrations	Accrual Product/Placebo
VRC 204 [20] (NCT00072605)	Phase I, randomized, placebo-controlled, dose escalation	VRC-EBODNA012-00-VP (Ebola DNA, ΔTM GP)	2 mg IM x 3 doses 4 mg IM x 3 doses 8 mg IM x 3 doses	5/2 8/2 8/2
VRC 205 [21] (NCT00374309)	Phase I, randomized, placebo-controlled, dose escalation	VRC-EBOADV018-00-VP (Ebola-rAd5, PM GP)	$2x10^9$ vp† IM x 1 dose $2x10^{10}$ vp IM x 1 dose	12/4 12/4
VRC 206 [22, 23] (NCT00605514)	Phase I, open label	VRC-EBODNA023-00-VP (Ebola DNA, WT GP) VRC-MARDNA025-00-VP (Marburg DNA, WT GP)	4 mg IM x 3 or 4 doses 4 mg IM x 3 or 4 doses	10/0 10/0
RV 247 [24] (NCT00997607)	Phase Ib, randomized, placebo-controlled	VRC-EBODNA023-00-VP (Ebola DNA, WT GP) VRC-MARDNA025-00-VP (Marburg DNA, WT GP) VRC-EBODNA023-00-VP (Ebola DNA, WT GP) and VRC-MARDNA025-00-VP (Marburg DNA, WT GP)	4 mg IM x 3 doses 4 mg IM x 3 doses 4 mg IM x 3 doses; both vaccines	30/6 30/6 30/6
RV 422 (NCT02354404)	Phase Ib, randomized, open label	VRC-EBOADC069-00-VP (cAd3-EBO, WT GP) VRC-EBOADC076-00-VP (cAd3-EBO Z, WT GP) VRC-EBOMVA079-00-VP (MVA-EbolaZ)	(prime) $2x10^{10}$ PU IM x 1 dose $2x10^{11}$ PU IM x 1 dose (prime) $1x10^{10}$ PU IM x 1 dose $1x10^{11}$ PU IM x 1 dose (boost) $1x10^8$ PU IM x 1 dose	**30**/0 **30**/0 **15**/0 **15**/0 **66**/0
VRC 207 [17] (NCT02231866)	Phase I/Ib, open label	VRC-EBOADC069-00-VP (cAd3-EBO, WT GP) VRC-EBOADC076-00-VP (cAd3-EBO Z, WT GP) Further evaluate cAd3-EBO Z*	$2x10^{10}$ PU IM x 1 dose $2x10^{11}$ PU IM x 1 dose $1x10^{10}$ PU IM x 1 dose $1x10^{11}$ PU IM x 1 dose	**10**/0 **10**/0 **10**/0 **10**/0 100 (final study accrual – 143*)

Study Identifier (Clinicaltrials.gov)	Study Design	Vaccine Product (s)	Dosage, route, x N administrations	Accrual Product/Placebo
VRC 208 (NCT02408913)	Phase I/Ib, open label, dose escalation and rollover study of VRC 207	VRC-EBOMVA079-00-VP (MVA-EbolaZ)	$1x10^7$ PFU* IM x 1 dose	**5**/0
		VRC-EBOMVA079-00-VP (MVA-EbolaZ)	$1x10^8$ PFU IM x 1 dose	**5**/0
		VRC-EBOADC069-00-VP (cAd3-EBO, WT GP) + VRC-EBOMVA079-00-VP (MVA-EbolaZ)	(prime) $2x10^{11}$ PU IM x 1 dose + (boost) $1x10^8$ PFU IM x 1 dose	**13**/0
		[Received in VRC 207] [VRC-EBOADC069-00-VP] [VRC-EBOADC069-00-VP] [VRC-EBOADC076-00-VP] [VRC-EBOADC076-00-VP] + VRC-EBOMVA079-00-VP (MVA-EbolaZ)	(prime) $2x10^{10}$ PU x 1 dose $2x10^{11}$ PU x 1 dose $1x10^{10}$ PU x 1 dose $1x10^{11}$ PU x 1 dose + (boost) $1x10^8$ PFU x 1 dose	**ongoing** **(up to 140)**/0
Mali and Maryland [19] (NCT02231866; NCT02267109)	Phase I single blind, randomized; Phase Ib, open label and nested double-blind, dose escalation of MVA-BN®-Filo	VRC-EBOADC076-00-VP (cAd3-EBO Z, WT GP)	(Maryland) $1x10^{10}$ PU IM x 1 dose $1x10^{11}$ PU IM x 1 dose (Mali) $1x10^{10}$ PU x 1 dose $2.5x10^{10}$ PU x 1 dose $5x10^{10}$ PU x 1 dose $1x10^{11}$ PU x 1 dose	 **10**/0 **10**/0 **10**/0 **35**/0 **35**/0 **11**/0
		VRC-EBOADC076-00-VP (cAd3-EBO Z, WT GP) + MVA-BN®-Filo	nested study (from above) $1x10^{10}$ PU x 1 dose $2.5x10^{10}$ PU x 1 dose $5x10^{10}$ PU x 1 dose $1x10^{11}$ PU x 1 dose	 **5**/5 **7**/6 **10**/9 **5**/5
GSK monovalent ChAd3 Ebola Zaire [16] (NCT02240875)	Phase Ia, open label, long term immunology	VRC-EBOADC076-00-VP (cAd3-EBO Z, WT GP)	(prime) $1x10^{10}$ PU x 1 dose $2.5x10^{10}$ PU x 1 dose $5x10^{10}$ PU x 1 dose (prime) (reduced prime boost interval, 7 or 14 days)	 **20**/0 **20**/0 **20**/0 **8**/0 (7 days)

Study Identifier (Clinicaltrials.gov)	Study Design	Vaccine Product (s)	Dosage, route, x N administrations	Accrual Product/Placebo
			$2.5x10^{10}$ PU x 1 dose	**8**/0 (14 days)
			(boost)	
		MVA-BN®-Filo	$1.5x10^{8}$ PU x 1 dose	**34**/0
			$3x10^{8}$ PU x 1 dose	**12**/0
GSK monovalent ChAd3 Ebola Zaire [25] (NCT02289027)	Phase I/IIa, double-blind, placebo controlled, dose finding	VRC-EBOADC076-00-VP (cAd3-EBO Z, WT GP)	(potentially deployed)	
			$2.5x10^{10}$ PU x 1 dose	**9**/0
			$5x10^{10}$ PU x 1 dose	**9**/0
			(non-deployed)	
			$2.5x10^{10}$ PU x 1 dose	**42**/**42**/2
			$5x10^{10}$ PU x 1 dose	

† viral particles
^ particle units
* plaque forming units
# MVA-BN®-Filo is an MVA vaccine expressing Ebola-Zaire GP, -Sudan GP, Marburg GP, and Tai-Forest Ebola nucleoprotein

Each clinical trial has contributed to product development and a better understanding of human immune responses to filovirus antigens. The first investigational vaccine study, VRC 204, was initiated in 2003. This was a 3-plasmid recombinant DNA vaccine, VRC-EBODNA012-00-VP, that encoded for nucleoprotein (NP) from the Zaire strain of Ebola and for transmembrane deleted (ΔTM) Ebola GP sequences from both Zaire and Sudan strains. At that time, deletion of the TM region of the GP was included in the vaccine construct design to address theoretical concerns related to cellular toxicity that had been observed during in vitro experiments when plasmids expressing full length, WT GP proteins were transfected into cell culture [26].

The second investigational vaccine study, VRC 205, evaluated a replication-defective, recombinant adenovirus serotype 5 vaccine, VRC-EBOADV018-00-VP (Ebola-rAd5). The constructs in this vaccine encoded GP genes with a point-mutation [aspartic acid substituted for glutamic acid at position 71 (E71D)], which had been found to be safe and immunogenic in animal studies. The vaccine induced humoral and T cell responses to the point mutant GP inserts with a single vaccination, but pre-existing immunity to the Ad5 virus partially blunted antibody responses to the rAd5-expressed antigen [21]. Because complete protection in macaques vaccinated with this Ebola-rAd vaccine encoding for E71D GP (Z) combined with E71D GP (S) was demonstrated, the vaccine was further evaluated in people (VRC 205) [27].

Non-human primate (NHP) studies, ongoing in parallel with the conduct of these human clinical trials, demonstrated that ΔTM GP- and PM GP-expressed antigens were partially protective against Ebola virus infection, but WT GP constructs provided the highest level of protection [27]. Therefore, the WT GP antigen became the focus of Ebola vaccine research and development at VRC/NIAID.

The third investigational Ebola vaccine to undergo NHP evaluation, VRC-EBODNA023-00-VP (Ebola DNA WT), was a recombinant DNA vaccine composed of 2 plasmids, each encoding for the wild type (WT) GP of the Zaire or Sudan strain of Ebolavirus. At the same time, a DNA

vaccine encoding for GP of the Angola strain of Marburgvirus, VRC-MARDNA025-00-VP (Marburg DNA), was evaluated. The plasmid DNA vaccines encoding for Ebola WT GP and Marburg WT GP evaluated in both the VRC 206 and RV 247 studies were safe and immunogenic but repetitive DNA-GP vaccinations with 3 or 4 doses were needed to achieve high response rates to some of the antigens. Importantly, the evaluation of WT GP constructs has not been associated with coagulopathy or serious adverse events [22-24].

As noted above, emergence of the 2014 Ebola epidemic rapidly advanced the next Ebolavirus candidate vaccines into trial. The vaccine antigens were chosen based on the above DNA data of the WT GP antigens from the Zaire and Sudan strains of Ebola. The chimpanzee Ad3 vector (cAd3) was selected because 1) it has little to no pre-existing immunity in human populations, 2) its superior immunogenicity in humans (as rAd5 vectors were no longer being pursued by VRC) relative to DNA vaccines for other viral diseases, and 3) its performance in NHP Ebolavirus challenge studies.

To further build on the immunogenicity of the cAd3-EBO GP candidate vaccine, a Modified Vaccinia Ankara (MVA) Ebola vaccine has also been developed. VRC-EBOMVA079-00-VP (MVA-EbolaZ) is also undergoing staged clinical evaluation both as a single IM injection at doses of $1x10^7$ PFU and $1x10^8$ PFU and as a boost to study participants who previously received cAd3-EBO (a combination of cAd3-EBO Z and EBO S) and cAd3-EBO Z (n=30, ongoing) in VRC 208 as well as in international studies being conducted by others. To date, cAd3-EBO, cAd3-EBO Z, and MVA-EbolaZ have been well tolerated and appear safe for further evaluation in humans.

1.2.2 Previous Human Experience with Chimpanzee Adenovirus Vector Serotype 3 (cAd3)

Recombinant chimpanzee adenovirus serotype 3 (cAd3 or ChAd3) is a subgroup C adenovirus with properties similar to those of human adenovirus serotype 5 (Ad5). Both cAd3 and cAd63 vectors were initially considered for development of a new Ebolavirus vaccine based on their immunological properties and because the vectors had already advanced into Phase I human clinical trials. Both the cAd3 and cAd63 were shown to be safe and immunogenic in human studies evaluating candidate vaccines for hepatitis C virus (HCV) [28] and malaria [29], respectively. After initial consideration of these adenoviral vectors, the cAd3 vector was chosen for further development as a candidate vaccine because it appeared more protective against Ebola infection in the NHP model.

Serological studies showed a low seroprevalence in human sera for antibodies to cAd3 [30] [and unpublished VRC data], and when present, antibody titers are low. Ad5 pre-existing immunity did not appear to cross-react with cAd3 in mice [31, 32] [and unpublished VRC data]. The cAd3-based vaccines were capable of inducing an immune response comparable to human Ad5 vectored vaccines [31, 32]. VRC investigators showed that cAd3 vectors had similar levels of potency as rAd5 with various antigens including influenza HA and HIV Env [unpublished VRC data].

In a Phase I study, Barnes et al. tested two rare serotype adenovirus vectors, cAd3 and human adenovirus serotype 6, each expressing HCV antigens. A total of 41 participants were vaccinated by intramuscular (IM) injection with dosages up to $7.5x10^{10}$ viral particles (vp) per injection.

Several prime-boost schedules were evaluated with 4-6 participants per treatment group. Overall, these vaccines were assessed as safe and well tolerated. Mostly mild, self-limited local and systemic reactogenicity was observed which was dose-dependent but did not differ significantly between priming and boosting. The vaccinations induced HCV-specific immunity with broad specificity that was sustained for at least 1 year after the boost with heterologous adenoviral vector [28]. Chimpanzee adenoviral vector type 3 vaccines have been safe in healthy adults at dosages up to 2 x 10^{11} PU per injection in completed and ongoing clinical trials [28, 29].

Published data supporting evaluation of the cAd3-EBO S comes from the Phase I, dose-escalation, open-label trial of cAd3-EBO (cAd3-EBO Z and –EBO S) performed by Ledgerwood, *et. al.* [17] Twenty healthy adults, sequentially enrolled in two groups of 10, received IM doses of 2×10^{10} particle units or 2×10^{11} particle units. No safety concerns were identified, although transient fever developed within 1 day after vaccination in two participants in the high dose group. Glycoprotein-specific antibodies were induced in all 20 participants, however the high dose group developed antibodies of higher magnitude and more frequent CD4 and CD8 T cell responses to vaccine antigen. The antibody levels of the high dose group were in the range associated with vaccine-induced protective immunity in NHP challenge studies, and the antibody responses were sustained to week 48. Other studies of cAd3-EBO and cAd3-EBO Z in U.S., Swiss and Malian adults showed the vaccines to be safe and immunogenic [16, 17, 19, 25]. Equivalent cAd3 Ebola Sudan WT GP doses will be tested in this slowly enrolling, staged, dose-escalation study.

It has been noted the $2x10^{11}$ PU dose of cAd3-EBO vaccine was associated with more reactogenicity than the $2x10^{10}$ PU dose, and the pattern is similar to other adenoviral vector vaccines. The first sets of clinical data suggest that about 70% of participants will have at least one systemic reactogenicity symptom. Reactogenicity typically occurs on the day of or day after vaccination and may include headache, malaise, myalgia, with a smaller percentage also experiencing fever or chills. When present, fever onset was within one day of vaccination and resolved within 24 hours of onset. A pattern of fever, occurring later than one day after vaccination or lasting longer than a day, may require evaluation for additional etiology [33].

1.3 Preclinical Studies Supporting the Safety of VRC-EBOADC086-00-VP (cAd3-EBO S)

Prior to evaluation as an Ebola antigen vector, cAd3 underwent nonclinical toxicology evaluations as both an investigational HCV vaccine product, AdCh3-HCV (BB-IND 14818, Okairos, Inc.) and an investigational HIV vaccine product, VRC-HIVADC064-00-VP. In addition, DNA plasmid vaccines expressing the Ebolavirus Zaire or the Sudan DNA WT GP antigens have been evaluated in both a GLP toxicity study and two Phase I clinical trials (BB-IND 13609, RCHSPB). The March 2014 Ebola outbreak in West Africa [34] prompted the VRC/NIAID to accelerate evaluation of VRC-cAd3-EBO [EBOADC069-00-VP – a mix of two vectors - one expressing the WT GP Zaire and one expressing the WT GP Sudan]; and the VRC/NIAID proposed to the FDA that the prior, related nonclinical and clinical studies (AdCH3-HCV, cAd3-HIV, Ebola DNA WT GP) supported evaluation of the cAd3-EBO vaccine through a staged, dose escalation Phase I study design without the conduct of a GLP toxicity study. The FDA concurred and no preclinical GLP toxicology study was performed prior to phase I initiation. The VRC/NIAID with its collaborating researchers then sought and received approval to evaluate the cAd3 EBO WT GP Zaire vaccine alone as a vaccine under the same

IND. This was designated VRC-EBOADC076-00-VP (cAd3-EBO Z). The current proposal is now to re-evaluate the other component of cAd3-EBO, cAd3-EBO S as a separate vaccine with the same staged, dose escalation Phase I study design.

1.4 Nonclinical Immunogenicity and Protection Studies of cAd3 Constructs

Several non-GLP studies were performed in cynomolgus macaques to select the cAd3-based EBO constructs for further development and to provide animal proof-of-concept data before the Phase I clinical studies. Research-grade materials, made with the same constructs as clinical material, of 1) cAd3 EBO Z (containing GP from Ebolavirus Zaire), 2) cAd3 EBO S (containing WT GP from Ebolavirus Sudan), 3) cAd3-EBO (composed of a 1:1 ratio of cAd3 EBO Z and cAd3 EBO S) [18] were used in all respective viral challenge studies summarized below in Table 3.

Table 3. Preclinical Proof-of-Concept Studies in Cynomolgus Macaques

Study Purpose	Study Outcome
Demonstrate protection against lethal challenge with Ebolavirus Zaire in cynomolgus macaques after single IM dose of cAd3-EBO Z	100% protection after a single IM dose of cAd3-EBO Z at 10^{10} and 10^{11} VP
Demonstrate protection against lethal challenge with Ebolavirus Zaire in cynomolgus macaques after single IM dose of cAd3-EBO	100% protection after a single IM dose of cAd3-EBO at $2x10^{10}$ VP 50% protection after cAd3-EBO at $2x10^{9}$ VP
Demonstrate protection against lethal challenge with Ebolavirus Sudan in cynomolgus macaques after single IM dose of cAd3-EBO	100% protection against Ebolavirus Sudan after a single IM dose of cAd3-EBO at $2x10^{10}$ VP
Demonstrate generation of humoral and cellular immune responses after single IM dose of cAd3-EBO at $2x10^{9}$ or $2x10^{10}$ VP	Single IM dose of cAd3-EBO at $2x10^{9}$ VP or $2x10^{10}$ VP elicited antibody and antigen-specific CD4+ and CD8+ T cell responses. The lower cellular immune responses correlated with the lower level of protection (50%) observed after the $2x10^{9}$ VP dose.
Demonstrate durability of the immune responses after single IM dose of cAd3-EBO Z at 10^{11} VP or cAd3-EBO at $2x10^{10}$ VP administered 10 months before the lethal challenge with Ebolavirus Zaire.	Protective immune responses measured during the acute phase of infection declined over time. When challenged 10 months after vaccination, 2/4 macaques were protected after a single IM dose of cAd3-EBO Z at 10^{11}VP while 0/4 were protected after a single IM dose of cAd3-EBO at $2x10^{10}$ VP.

Demonstrate protection against lethal challenge with Ebolavirus Zaire in cynomolgus macaques after prime with single IM dose of cAd3-EBO and week 8 boost with single IM dose of MVA (expressing GPs from EBOV and SUDV)	100% protection after a prime with a single IM dose of cAd3-EBO at 10^{10} VP and week 8 boost with a single IM dose of MVA (expressing GPs from EBOV and SUDV) at 10^{8} PFU**
Demonstrate immunogenicity and protection against lethal IM or aerosol challenge with Ebolavirus Sudan in cynomolgus macaques after single IM dose of cAd3-EBO S	100% protection against IM challenge with Ebolavirus Sudan after a single IM dose of cAd3-EBO S at 10^{10} VP; 4 of 5 animals survived aerosol challenge after a single IM dose of cAd3-EBO S at 10^{10}VP. Pre-challenge plasma anti-GP titers were comparable in both groups of animals.
*VP – Viral Particles **PFU – Plaque forming units = A measure of the quantity of individual infectious particles (e.g. virus particles) based on the number of plaque formed per unit volume.	

1.5 Dose Justification for cAd3-EBO S

Quantification of the vaccine is based on cAd3 particle units (PU). The cAd3-EBO S vaccine will be evaluated in humans at $1x10^{10}$ PU and $1x10^{11}$ PU doses. These doses were selected based on a good safety profile, ease of administration, and reliable immunogenicity from data collected in non-human primate studies. In addition, the doses were shown to provide partial to full protection in the accepted challenge model. Doses between $1x10^{10}$ PU and $1x10^{11}$ PU demonstrated Ebola-Sudan GP-elicited immunogenicity was also comparable to that seen to the Ebola-Zaire and Marburg GP antigens when expressed by the same cAd3 vector. The doses of cAd3 vector proposed for this study, when expressing a variety of viral inserts, have also been demonstrated to be safe in humans. Please refer to the IB for additional details.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

- To evaluate the safety and tolerability of VRC-EBOADC086-00-VP when administered IM at a dose of 1 x 10^{10} particle units (PU) to healthy adults;
- To evaluate the safety and tolerability of VRC-EBOADC086-00-VP when administered IM at a dose of 1 x 10^{11} PU to healthy adults.

2.2 Secondary Objectives

- To evaluate the antibody response to the GP insert and the cAd3 vector in VRC-EBOADC086-00-VP at 4 weeks after vaccination as assessed by GP ELISA and vector-specific neutralization assays, respectively.
- To evaluate the Ebola Sudan GP-specific T cell responses in VRC-EBOADC086-00-VP at 4 weeks after vaccination as assessed by ICS.

2.3 Exploratory Objectives

- To evaluate the immunogenicity of VRC-EBOADC086-00-VP by various assay methods at some or all of the research sample collection time points indicated in the SOE; genetic factors associated with immune response may also be evaluated.
- To evaluate vaccine-induced mRNA expression profiles through Study Week 1.
- To evaluate the time course and durability of cAd3 neutralizing antibody titers, mediators of inflammation following vaccination and time course and durability of immune response by a variety of exploratory assays using samples collected throughout the study.
- To isolate MAbs to determine epitope specificity and their functional capacity.

3.0 ENDPOINTS

3.1 Primary Endpoints: Safety

Assessment of product safety will include clinical observation and monitoring of clinical chemistry and hematology parameters. Safety will be closely monitored after injection and evaluated through 48 weeks after the study injection. The following parameters will be assessed:

- Occurrence of solicited local reactogenicity signs and symptoms for 7 days following the vaccination
- Occurrence of solicited systemic reactogenicity signs and symptoms for 7 days following the vaccination
- Change from baseline for safety laboratory measures
- Occurrence of adverse events of all severities through 28 days after the study injection
- Occurrence of serious adverse events and new chronic medical conditions through the last study visit

3.2 Secondary Endpoints: Immunogenicity

Antibody titers, response rates and magnitudes will be the immunogenicity endpoints for the following assays where relevant: ELISA and neutralization antigen-specific assays for antibody responses and ICS assays for T cell responses. The principal time point for assessing antibody and T cell responses is Week 4 after vaccination.

3.3 Exploratory Endpoints

ELISpot assays to assess T and B cell responses will be performed with research samples collected at study timepoints shown in the SOE (Appendix 1), as well as evaluation of genetic factors associated with immune responses and time courses of immune responses (i.e. AUC evaluation) may be completed as exploratory evaluations. MAbs may be isolated from cryopreserved peripheral blood mononuclear cells (PBMC) and evaluated to determine among other characteristics, epitope specificity, and functional capacity. Vaccine-induced mRNA expression profiles through 1 week after vaccination may also be performed as an exploratory evaluation. Plasmablasts will be isolated from whole blood at day 7 to evaluate immediate development of antibodies to Ebola GP.

4.0 STUDY DESIGN AND POPULATION

This is a Phase I open-label, dose-escalation clinical trial to evaluate the safety, tolerability and immunogenicity of a recombinant vector for the Sudan strain of the Ebola virus. This study will be conducted at the MUWRP in Kampala, Uganda.

A total of 40 healthy adults, 20 in each dosage group, will receive a single vaccine injection of cAd3-EBO S at 1 x 10^{11} PU/mL or 1 x 10^{10} PU/mL. The study will begin with enrollment of 3 participants into Group 1. After at least 7 days of follow-up for the first 3 vaccinated participants, an interim safety review will occur before enrollment of additional participants into the group. If no safety issues are identified, an additional 17 participants will be enrolled to complete Group 1. When there is a minimum of seven days of follow-up safety data from the last enrolled participant in Group 1, an interim safety review will occur. Once no safety issues are identified, enrollment of participants into the next dose level will begin with the enrollment of 3 participants. After at least 7 days of follow-up for the first 3 vaccinated participants in Group 2, an interim safety review will occur before enrollment of additional participants into Group 2. If no safety issues are identified, an additional 17 participants will be enrolled to complete Group 2. For the first 3 participants in each group, only one participant per day will be enrolled. The study groups and vaccination schema is shown in Table 1.

Study agent administration will be on Day 0. The study includes daily review of any new safety data by a study clinician and weekly review of safety data by the Protocol Safety Review Team (PSRT). The staged enrollment plan and plan for interim safety reviews (Section 7.3) applies to both Group 1 and Group 2. The interim safety reviews will be conducted by the PSRT.

4.1 Eligibility

Screening for eligible volunteers will be performed within 8 weeks before the first administration of study vaccine at Week 0. Study participants must be healthy (on the basis of medical history, physical examination, vital signs measurement, and laboratory assessments), adult men and women, aged 18 to 50 years.

4.1.1 Inclusion Criteria

A volunteer must meet all of the following criteria:

1. 18 to 50 years old.

2. Available for clinical follow-up through Week 48 after enrollment.

3. Able to provide proof of identity to the satisfaction of the study clinician completing the enrollment process.

4. Able and willing to provide fingerprints and have their photographs taken including injection site photographs.

5. Must allow home visits

6. Must complete an Assessment of Understanding (AoU) prior to enrollment by answering 9 out of 10 questions at least once in 3 attempts.

7. Able to read (English or Luganda) and willing to complete the informed consent process.

8. In good general health without clinically significant medical history.

9. Physical examination and laboratory results without clinically significant findings and a body mass index (BMI) ≤ 40 within the 56 days prior to enrollment.

Laboratory Criteria within 56 days prior to enrollment:

10. Hemoglobin ≥ 11.0 g/dL for women; ≥12.5 g/dL for men.

11. White blood cells (WBC) = 2,500-12,000 cells/mm^3.

12. Total lymphocyte count ≥ 800 cells/mm^3.

13. Platelets = 125,000 – 400,000/mm^3.

14. Alanine aminotransferase (ALT) ≤ 1.25 x upper limit of normal.

15. Serum creatinine ≤ 1 x upper limit of normal.

16. HIV-uninfected as evidenced by a negative HIV diagnostic test.

Female-Specific Criteria:

17. Negative β-HCG (human chorionic gonadotropin) pregnancy test; serum β-HCG at screening and urine β-HCG at enrollment if woman is of reproductive potential.

18. Agrees to use an effective means of birth control from at least 21 days prior to enrollment through 24 weeks after study vaccination if assessed to be of reproductive potential.

4.1.2 Exclusion Criteria

A volunteer will be excluded if one or more of the following conditions apply:

Volunteer has received any of the following substances:

1. Investigational Ebola or Marburg vaccine in a prior clinical trial or prior receipt of a cAd3 adenoviral vectored investigational vaccine.

2. Chronic use of immunomodulators and systemic glucocorticoids in daily doses of glucocorticoid equivalence > 20 mg of prednisolone, for periods exceeding 10 days. Non-steroidal anti-inflammatory drugs [NSAIDS] are permitted. Participants that have used less than the stated glucocorticoid dose may still be excluded at the Investigator's discretion.

3. Blood products within 112 days (16 weeks) prior to enrollment.

4. Investigational research agents within 28 days (4 weeks) prior to enrollment.

5. Live attenuated vaccines within 28 days (4 weeks) prior to enrollment.

6. Subunit or killed vaccines within 14 days (2 weeks) prior to enrollment.

7. Current anti-tuberculosis prophylaxis or therapy.

Female-specific criteria:

8. Woman who is pregnant, breast-feeding or planning to become pregnant during the first 24 weeks after study vaccine administration.

Volunteer has a history of any of the following clinically significant conditions:

9. Serious adverse reactions to vaccines such as anaphylaxis, urticaria (hives), respiratory difficulty, angioedema, or abdominal pain.

10. Allergic reaction to excipients in the study vaccine including gentamycin, neomycin or streptomycin.

11. Clinically significant autoimmune disease or immunodeficiency.

12. Asthma that is not well controlled.

13. Positive result on an RPR test.

14. Diabetes mellitus (type I or II).

15. Thyroid disease that is not well controlled.

16. A history of hereditary angioedema (HAE), acquired angioedema (AAE), or idiopathic forms of angioedema.

17. Idiopathic urticaria within the last 1 year.

18. Hypertension that is not well controlled.

19. Bleeding disorder diagnosed by a doctor (e.g. factor deficiency, coagulopathy, or platelet disorder requiring special precautions) or significant bruising or bleeding difficulties with IM injections or blood draws.

20. A malignancy that is active, currently being treated, or not surgically cured.

21. Seizure in the past 3 years or treatment for seizure disorder in the past 3 years.

22. Asplenia or functional asplenia.

23. Psychiatric condition that precludes compliance with the protocol; past or present psychoses; or within five years prior to enrollment, history of a suicide plan or attempt.

24. Any medical, psychiatric, social condition, occupational reason or other responsibility that, in the judgment of the investigator, is a contraindication to protocol participation or impairs a volunteer's ability to give informed consent.

5.0 STUDY PROCEDURES

5.1 Schedule of Evaluations

Evaluation of the safety of this vaccine will include laboratory studies, medical history, physical assessment by clinicians, and participant self-assessment recorded on a 7-day diary card. The schedule of evaluation is located in Appendix 1. Total blood volume drawn from each participant will not exceed 450 mL in any 3-month period.

5.2 Recruitment, Consent, Screening and Enrollment

Participants will be recruited through IRB-approved recruitment materials (to include flyers, posters, newspaper ads and radio scripts). Volunteers interested in the study will be invited and scheduled to a briefing session at their convenience. Briefing sessions will be conducted by the Principal Investigator (PI) or designee at the MUWRP facility at regular intervals throughout the recruitment phase. The briefing session will be followed by an opportunity for questions from the volunteers. All volunteers interested in this study will subsequently, individually be administered informed consent.

5.2.1 Consent Procedures and Screening

The PI or their designee will review the consent form in detail with potential participants and answer any questions. Written informed consent will be obtained from each participant before any study procedures are performed. All informed consent forms will be administered individually, in a private setting, with strict respect of confidentiality. Participants will be given ample time and opportunity to inquire about details of the study, discuss with close family members or friends and ask any questions before dating and signing the consent forms. A copy of the signed informed consent form will be given to the participant along with a copy of the volunteer event schedule (Appendix 3). The consenting process will be documented in the case report forms (CRFs).

After providing signed informed consent the volunteer will complete an Assessment of Understanding (AoU). Volunteers are allowed to take the AOU three times, but must have a passing score of 90% or greater by the third attempt to participate in the study. If after 3 attempts to pass the AOU the volunteer is unable to do so, the volunteer will become ineligible for study participation.

Volunteers who have passed the AoU and have given written informed consent will undergo a complete medical history, physical examination, and screening laboratory assessments to determine eligibility for trial participation. The following screening assessments will be completed after the informed consent process has been completed:

- Medical history
- Physical exam
- Vital signs and weight
- Serum pregnancy test for all females
- CBC with total lymphocyte count
- Creatinine
- ALT

- HIV testing (including pre/post-test counseling), and referral as appropriate
- Syphilis serology testing
- Pre-existing vector immunity testing
- Peripheral blood mononuclear cells (PBMC) and plasma for storage

Screening evaluations for specific eligibility criteria must be completed within the screening visit window specified (Appendix 1) prior to enrollment, but may be repeated one time within the screening visit window, if the initial laboratory result is not deemed medically significant in the clinical judgment of the investigator, in order to confirm eligibility. Counseling on the potential risks of becoming pregnant during this trial will be provided. Pre-HIV test counseling and post-HIV test counseling will be provided during the screening process.

Study volunteers may be scheduled for a second Screening Visit to evaluate laboratory and test results if an abnormality or illness had been identified at the first screening. This approach will allow study staff to evaluate the recovery from any illness identified at the first screening as well as to repeat screening laboratory tests that were abnormal at the first screen due to transient illness.

The PI or Investigator at the site may discover an illness or condition, which requires treatment for the volunteer. The site will provide basic care and treatment as per National guidelines and refer these subjects to an appropriate healthcare facility for further evaluation and treatment.

Eligible and willing volunteers will be scheduled for an appointment for enrollment and the initial vaccination visit within 56 days of having satisfied eligibility requirements.

5.2.2 Day 0 Through Week 48

Day 0 is defined as the day of enrollment and study injection. Study eligibility criteria are reviewed on Day 0 as part of the enrollment process. If clinical assessment on Day 0 suggests significant changes may have occurred since the screening visit, then the physical examination, hematology tests, and blood chemistries done at screening must be repeated, as appropriate, before the participant can receive a study vaccination. Pregnancy test results for women of childbearing potential must be obtained prior to the study injection. Day 0 evaluations immediately prior to the first injection are the baseline for subsequent safety assessments.

Refer to the table in Appendix 1 for details on the Schedule of Evaluations and the window(s) permitted. After Day 0, deviations from the visit windows in completing study visits are discouraged and will be recorded as protocol deviations, but are permitted, at the discretion of the PI (or designee), in consultation with the sponsor, in the interest of obtaining participant safety and immunogenicity evaluations following exposure to the investigational vaccine.

Study visit procedures and tests through Week 48 include the following as indicated in the SOE (Appendix 1):

1. Signature of study participation informed consent form
2. AOU (prior to enrollment)
3. Clinical evaluations: vital signs; targeted physical examination on any visit if indicated by interim complaints or laboratory findings
4. Interim medical history, including any new medications taken

5. Counseling on avoidance of pregnancy
6. Post-injection vital signs and assessment of injection site at 30 to 60 minutes post-injection (with target of 30 to 45 minutes, when possible)
7. Diary Card: In the evening on the day of injection; 7-days for self-assessment by participant
8. Urine pregnancy test for females of reproductive potential
9. CBC, total lymphocyte count, platelet counts
10. Blood creatinine and ALT
11. HLA Type
12. Serum, PBMCs, and plasma for protocol assessments, including intracellular RNA and archiving

Stored samples with consent for genetic testing may be used to elucidate genetic factors associated with immune response to a vaccine and to further evaluate responses to the vaccine. Results from genetic testing will not be provided to participants as the results are not validated for clinical use. Any remaining cells, serum, or plasma will be stored at the NIAID Vaccine Immunology Program (VIP) for future exploratory virological and immunological assays as per individual participant's consent for future use.

5.3 Administration of the Study Injection and On-Study Assessments

Injections will be administered IM in a 1 mL volume by needle and syringe. It is recommended, but not required, that the injection be administered into the non-dominant arm. When choosing an arm for the injection, clinicians should consider whether there is an arm injury, local skin problem or significant tattoo that precludes administering the injection or will interfere with evaluating the arm after injection.

Following the study injection, participants will be observed for a minimum of 30 minutes. Vital signs (temperature, blood pressure, and pulse) will be taken 30 to 60 minutes post-injection (target of 30 to 45 minutes). The injection site will be inspected for evidence of local reaction during this period. In keeping with good medical practice, acute medical care will be provided to participants for any immediate allergic reactions or other injury resulting from participation in this research study.

5.3.1 7-Day Solicited Reactogenicity

Temperature and solicited local and systemic signs/symptoms will be recorded in the clinic prior to vaccination and at a minimum of 30 minutes post injection and then daily by the participant for 7 days.

Participants will be given a "Diary Card", a thermometer, and a ruler. The diary card will be used as a memory aid, on which the participant will record temperature, local and systemic symptoms and concomitant medications daily for 7 days after the injection. Participants will be trained to complete the paper diary card, how to use the thermometer, and how to measure injection site swelling and redness using the ruler. Completion of the diary card training will be noted in source documents. The written (paper) diary card will be transcribed into the study database and will be stored in the participant file for monitoring purposes.

The solicited signs and symptoms on the diary card (among others) will include: joint pain, malaise (feeling unwell), myalgias (muscles aches other than at injection site), headache, chills, nausea, and pain at injection site. Where multiple assessments are taken on the same day, participants will be requested to record the day's highest measured temperature and measurement of largest diameter for redness and swelling at the injection site. The completed diary cards are collected at the first visit following completion of the 7-day diary card (about 2 weeks after the injection).

Follow-up on participant well-being will be performed by telephone or clinic visit on the day following vaccination and by clinic visit on Day 3 following the injection to assess their clinical status. Participants may call or come to the clinic at any time-point for evaluation, if they experience unusual, moderate or severe signs and symptoms. Diary cards will be reviewed with the clinician at any visit from day of vaccination through the first study visit following completion of the diary card. If upon reviewing the clinician finds that general symptom or injection site symptom information (except swelling or redness measurements) is missing from the diary cards, the participant will be asked to provide the missing information to the best of their recollection.

At every visit through study day 28, all participants will be asked about other interim adverse experiences, which will be recorded in source documents and entered into the study database within 3 business days. After study day 28, only serious adverse events and new chronic medical conditions that require ongoing medical management will be recorded in source documents and entered into the database, through the last study visit. All other adverse events will be recorded on source documents only. The PI or designee will assess the relationship of the study product to the events.

5.3.2 Management of Reactogenicity Adverse Events Following Study Vaccinations

Participants will be informed that a fever of 38.5˚C (Grade 2) or higher lasting greater than 24 hours, rash, urticaria, or significant impairment in the activities of daily living (ADL) should prompt a visit to the clinic. Fever less than 38.5˚C or lasting less than 24 hours may prompt a clinic visit at the discretion of the study clinicians. Any condition which in the judgment of the clinician should be evaluated clinically or by laboratory testing would require a clinical visit. Participants are permitted to initiate an unscheduled clinic visit at their discretion but these visits will be compensated as per Section 10.5.

5.3.3 Management of Laboratory Abnormalities After Vaccination

If any lab result is a Grade 3 or Grade 4, then repeat testing of the abnormal test will be performed within 48 hours. The specific timing of repeat testing for a Grade 2 laboratory test change will be determined by the study clinicians as medically appropriate.

5.4 Concomitant Medications

Current concomitant medications are recorded in the study database at enrollment and for 7 days post-vaccination. Subsequently, concomitant medications will be updated in the study database if there is an occurrence of an adverse event that is considered related to the IP or that requires expedited reporting or development of a new chronic medical condition that requires ongoing medical management.

Clinicians should discuss with study participants with regard to the timing of FDA or locally-approved vaccines. Receipt of a licensed vaccine during study participation will be recorded in the study database. Otherwise, a record of other concomitant medication changes throughout the study will not be recorded in the study database.

5.5 Study Discontinuation

The study may be stopped or cancelled at any time by decision of the PI, Walter Reed Army Institute of Research (WRAIR) IRB, the United States Army Medical Research and Development Command's (USAMRDC) Office of Research Protections (ORP), Human Research Protection Office (HRPO), NIAID, the U.S. FDA, U.S. DoD, the Office for Human Research Protection (OHRP), Uganda National Drug Authority (NDA), Uganda National Council of Science and Technology (UNCST), or the Makerere University School of Public Health (MUSPH) IRB. The PI will notify the IRB in writing of any stoppage or cancellation of the study.

5.5.1 Early Discontinuation or Withdrawal of Study Participants

A participant will be taken out of the study entirely under the following circumstances:

- Repeated failure to comply with protocol requirements
- Participant requests withdrawal
- Participant develops a medical condition that is a contraindication to continuing study participation
- The PI assesses that it is not in the best interest of the participant to continue participation in the study

Each participant has the right to withdraw from the study at any time for any reason without affecting the right to treatment by the investigator. The investigator should make an attempt to contact participants who did not return for scheduled visits or follow-up. Although the participant is not obliged to give reason(s) for withdrawing prematurely, the investigator should make a reasonable effort to ascertain the reason(s) while fully respecting the participant's rights.

Any participant who withdraws consent will not have any further data collected after consent has been withdrawn. However, samples and data that were collected prior to a participant's withdrawal of consent will be used/included in sample and data analysis.

If a participant withdraws from the study prior to receiving the study injection, the next available participant will be placed in the vacated slot. Participants who withdraw prior to receiving the study injection will not count toward the total participants enrolled in the study. Replacements for participants who withdraw from the study after receiving the study injection are not permitted.

5.6 Management of Participants Who Become Pregnant

Pregnant women and women who plan to become pregnant during the first 24 weeks after study vaccine administration are excluded from enrollment. If a participant becomes pregnant during

the course of the study, they will continue to be followed for the remainder of the study period per protocol SOE; however, for all subsequent study visits, blood draws will be limited to safety tests only (samples for research immunology will not be drawn). Full blood draws can resume post-pregnancy or post-abortion only if deemed safe for the participant, per the clinical judgment of the PI in consultation with the IND Medical Officer. The PI or designated AI will be responsible for reporting any pregnancy. New pregnancies will be reviewed weekly in aggregate with other safety data and forwarded as necessary to IRBs and study sponsors.

If a participant becomes pregnant within 24 weeks after the study vaccination, every effort will be made to remain in contact with the pregnant participant to record the outcome of pregnancy for the study database. Pregnancy outcomes will be recorded via a standardized pregnancy CRF. Information documented on this form will include date of last menstrual period, date pregnancy confirmed, history of complications during prior pregnancies (such as congenital abnormalities or spontaneous abortions). A separate pregnancy outcome CRF will be completed for the outcome of the pregnancy including date of termination or delivery, any complications of pregnancy, the gender, weight, presence of any congenital abnormalities, APGAR score, other complications of delivery and the status of the child.

Reporting outcomes of pregnancies that begin later than 24 weeks is not required by the IND Sponsor, nor is there an IND Sponsor requirement for annual evaluation requirement for children born to vaccine recipients. However, all children conceived within 24 weeks post-vaccination and born to vaccine recipients will be annually evaluated for a minimum of 2 years to meet requirements set by regulatory authorities in Uganda. After termination of the study, the site will be solely responsible for maintaining and reporting applicable data obtained in this long-term follow-up.

5.7 Management of Participants Who Become Incarcerated

Participation of prisoners is not planned and any participant will be suspended from study visits while incarcerated, except visits or telephone contact for the purpose of ensuring participant safety. The IRB will be notified of the period of incarceration and safety assessments to be conducted. Data and samples that were collected before the period of incarceration may still be stored and used for analyses. After release from incarceration, the participant may either return to participation in study visits according to the SOE or study participation may be terminated at the discretion of the PI.

Participants who have returned to the clinic after a period of incarceration of more than 12 months will review pertinent sections of the consent form with a study staff. A note to the effect that the review was done will be written in the progress notes in the participant's binder.

5.8 Management and Counseling of Participants with Positive HIV or Syphilis Test

Participants found to be infected with HIV or syphilis at screening will be counseled appropriately by a study physician/nurse and referred to a local healthcare facility for care or treatment.

6.0 PHARMACY AND VACCINE ADMINISTRATION PROCEDURES

Study treatment is defined as VRC-EBOADC086-00-VP (cAd3-EBO S). Refer to the Investigator's Brochure for further information about the study agent.

6.1 Regimens

Forty healthy adult volunteers in the Kampala area, ages 18-50 years, will be enrolled into one of two groups of 20 participants each as shown in Table 1. Participants in Group 1 will receive a single injection IM of cAd3-EBO S at $1x10^{10}$ PU and participants in Group 2 will receive a single injection of cAd3-EBO S at $1x10^{11}$ PU.

6.2 Study Product Formulation, Preparation, and Storage

6.2.1 Formulation

The drug substance was manufactured by Advent S.r.l. (Pomezia, Italy, a subsidiary of Okarios, Inc.) and the vaccine, VRC-EBOADC086-00-VP (cAd3-EBO S) and diluent were manufactured at the VRC Pilot Plant (VPP) operated by the Vaccine Clinical Materials Program (VCMP), Leidos Biomedical Research Inc., Frederick, MD (formerly SAIC-Frederick, MD), according to cGMP regulations. The drug product is a sterile, aqueous, buffered solution composed of cAd3-EBO S drug substance filled into single dose vials at 1×10^{11} PU/mL. Vials are aseptically filled under cGMP to a nominal fill volume of 1.2 mL ± 0.1 mL to allow withdrawal of 1.0 mL for IM administration. Vials are intended for single use only and thus do not contain a preservative. Additional details on VRC-EBOADC086-00-VP (cAd3-EBO S) composition and manufacturing can be found in the Investigator Brochure.

The diluent, VRC-DILADC065-00-VP, was manufactured at the VPP. It is comprised of the formulation buffer and will be used to dilute the cAd3-EBO S vaccine to prepare the 1×10^{10} PU/mL dosage to be administered in this study. The formulation buffer is pH 7.4 and consists of 10 mM Tris, 10 mM Histidine, 5% Sucrose (w/v), 75 mM Sodium Chloride, 1 mM Magnesium Chloride, 0.02% Polysorbate 80 (PS-80) (w/v), 0.1 mM EDTA, and 0.5% (v/v) Ethanol. The diluent is supplied in glass vials at a nominal fill volume of 1.2 mL ± 0.1 mL to allow withdrawal of 1.0 mL. Vaccine dose levels are achieved by administering the appropriate volume directly from the vial or dilution to the appropriate dosage. Additional diluent VRC-DILADC065-00-VP composition and manufacturing information can be found in the Investigator Brochure.

6.2.2 Study Product Labels

The labels for VRC-EBOADC086-00-VP (cAd3-EBO S) and VRC-DILADC065-00-VP, diluent, will have specific product information (e.g., part number, lot number, fill volume, storage temperature) included on the product vial labels. The vaccine label will contain an Investigational Use Statement ("Caution: Limited by Federal Law to Investigational Use"), and manufacturer information.

6.2.3 Study Product Storage

VRC-EBOADC086-00-VP (cAd3-EBO S) will be stored at ≤-60°C, and VRC-DILADC065-00-VP (diluent) will be stored at -45°C to -10°C, each in a qualified, continuously monitored, temperature-controlled freezer.

If deviations in storage temperature occur from the normal allowance for the pharmacy freezer, the site pharmacist must report the storage temperature excursion promptly to the PI and the IND sponsor. The excursion must be evaluated and investigated and action must be taken to restore and maintain the desired temperature limits. Following the outcome of the investigation, the IND sponsor will notify the pharmacist if continued clinical use of the product is acceptable.

6.2.4 Preparation of Study Product for Injection

To prepare the vaccine for injection, the vial containing cAd3-EBO S and/or diluent will be thawed at ambient temperature (15-25ºC).

Preparation will be done in a clean preparation biosafety hood with limited access. Only the required vials will be present in the preparation unit during dilution, and medication labels should be strictly segregated to avoid mix-ups. All injections will be administered IM into the deltoid muscle by needle and syringe and must be administered within 4 hours after removing the vaccine vial from the freezer.

Product dilutions will be prepared in a Class II biosafety cabinet.

Preparation of VRC-EBOADC086-00-VP (cAd3-EBO S) at 1 x 10^{10} PU Dose
Preparation of the 1 x 10^{10} PU dosage of cAd3-EBO S requires one serial dilution. Remove one vial of cAd3-EBO S vaccine and two vials of diluent from the freezer and allow them to equilibrate to room temperature. Using sterile syringes, draw up 1.0 mL of diluent from one diluent vial and 0.35 mL from the other diluent vial and inject these volumes into a sterile vial. Then, using a sterile syringe draw up 0.15 mL of the 1 x 10^{11} PU/mL vaccine and inject this into the vial with the diluent to achieve a total volume of 1.5 mL. Vortex the vial at half speed for 3-5 seconds. This vial now contains 1.5 x 10^{10} PU cAd3-EBO S in 1.5 mL and has a concentration of 1 x 10^{10} PU/mL. One 1 mL injection of this preparation will be administered for each dose. Discard remnant vaccine in vial in a biohazard container for incineration.

Preparation of VRC-EBOADC086-00-VP (cAd3-EBO S) at 1 x 10^{11} PU Dose
No dilution is needed for preparation of the 1 x 10^{11} PU dosage of cAd3-EBO S vaccine. Remove one vial of vaccine from the freezer and allow it to equilibrate to room temperature in a biosafety hood. Using a sterile syringe, withdraw 1.0 mL from the vial. One 1 mL injection of the preparation will be administered. Discard remnant vaccine in a vial in a biohazard container for incineration.

6.3 Pharmacy: Product Supply, Distribution, and Accountability

6.3.1 Study Product Acquisition/Distribution

The study product(s) for this protocol are supplied by the Vaccine Research Center, NIH and should be obtained by following the instructions in the Manual of Procedures.

6.3.2 Study Product Accountability

The study pharmacist will be responsible for maintaining an accurate record of the codes, inventory, and an accountability record of vaccine supplies for this study. Electronic documentation as well as paper copies may be used.

The VRC will receive copies of pharmacy records at the end of the study.

6.3.3 Disposal of Clinical Supplies

The empty vials and the unused portion of the vial should be discarded in a biohazard containment bag and incinerated. Any unopened vials (past the re-test date or otherwise) that remain will be destroyed at the discretion of the sponsor in accordance with policies that apply to investigational agents in Uganda. Partially used vials or expired prepared doses will not be administered to other participants or used for *in vitro* experimental studies. They will be disposed of in accordance with institutional pharmacy policy. Retest dates shall be updated as per analytical analyses of the IP. No IP shall be administered to a participant beyond the current retest date.

7.0 PHARMACOVIGILENCE, SAFETY, AND ADVERSE EVENT REPORTING

7.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product and does not necessarily have a causal relationship with this product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (International Conference on Harmonization (ICH) E6) (Synonym: Adverse Experience).

A serious adverse event (SAE): An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

“Life-threatening” refers to an adverse event that at occurrence represents an immediate risk of death to the participant. An event that may cause death if it occurs in a more severe form is not considered life-threatening. Similarly, a hospital admission for an elective procedure is not considered an SAE.

All AEs will have their possible relationship to study vaccine assessed and will be graded according to the table for grading severity of adverse events (see Appendix 6). Arthralgia (joint pain) and arthritis AEs will be graded in accordance with the criteria in Appendix 7.

7.2 Adverse Event Grading and Recording

Recording of all AEs will occur during the period from study agent administration through 28 days after study agent administration. Solicited AEs will be recorded in the study database for 7 days after injection without the collection of attribute assessments. All unsolicited AEs and SAEs that occur during the period from study agent administration through 28 days after study agent administration will be recorded in the study database. After study day 28, only SAEs and new chronic medical conditions that require ongoing medical management will be recorded as AEs in the study database. Because this is an Ebola vaccine study, in the unlikely circumstance of Ebola virus disease (EVD) diagnosis in a study participant at any time throughout the study, this will be recorded on an “EVD CRF”, rather than an AE form, without requiring an investigator attribution (“relatedness to study agent”) or severity grade.

The FDA Guidance for Industry (September 2007): “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials” was adapted for the

severity grading of adverse events in this protocol. The FDA Guidance of Industry on toxicity grading scale is modified for criteria on absolute neutrophil counts and other parameters as described in Appendix 6, which also includes the definitions for severity grading parameters that do not have specific guidelines in the table. Due to the absence of specific grading criteria for arthralgias on the FDA toxicity grading scale, the "DAIDS AE Grading Table Corrected" (Version 2.1-July 2017) (Appendix 7) will be used to grade arthralgia AEs.

The clinical investigators will monitor and analyze study data including all AE and lab data as they become available and will make determinations regarding the severity of the adverse experiences and their relation to study product. AE CRFs will be completed by the research staff on a daily basis as the data become available from the clinic or laboratory. AEs are also subjected to analysis to identify those that may invoke study pause rules. To ensure that all AEs are captured in a timely manner, AE CRFs will be entered into the database within 24 hours. All other CRFs will be entered into the database within 3 business days. All CRFs will be subjected to analysis to identify AEs that may invoke study pause rules.

Although post injection reactogenicity (PIR)/Solicited AEs are documented separately from unsolicited AEs, they will be reported if they meet SAE or study pause rule definitions as noted below. Therefore the PI or designee must review both PIR and AE CRFs to ensure prompt and complete identification of all events that require expedited reporting as SAEs, study pause rules or other serious and unexpected events.

AEs will be followed by the clinical research team until resolved, and stability or chronicity has been established and documented.

7.2.1 Grading and Recording Tachypnea

The Uganda Ministry of Health (MoH) has put forth guidelines for practitioners that indicate a respiratory rate of 20 or more breaths per minute as abnormal, however respiratory rates in Kampala (at an altitude of 3900 feet), while not well defined, have been commonly observed at a rate of 20 breaths per minute (or above) without any underlying or acute illness. Given the higher respiratory rate noted in guidelines and observations, any instances of a respiratory rate that meets the grade 1 criteria in Appendix 6 will not be recorded as an AE unless it is an increase from the participant's baseline respiratory rate and all instances of gradable respiratory rate will be considered unrelated to the IP in the absence of any evidence of pathology that may indicate otherwise.

7.3 Protocol Safety Review Team

The PSRT will review all AEs (including reportable AEs) on a regular and expedited basis as needed. In addition, the PSRT will review aggregate safety data reports on a weekly basis until 4 weeks after all participants have completed the vaccination, then the safety reviews will occur monthly. The PSRT will review SAEs that potentially meet study pause criteria on an expedited basis and will decide if the study should be paused for participant safety purposes. This team includes the following: PI or designee, Associate Investigators, Protocol Consultants, DoD Research Monitor, sponsor IND Medical Officer or designee, and other VRC Representatives. Additional participants could include study personnel and senior clinical research nursing staff. A quorum is established with the PI or designee, one AI or designee, one MHRP protocol consultant or their designee, and IND Medical Officer or their designee. If the DoD Research

Monitor is not available for the PSRT call, they must provide input by email and then be immediately emailed the outcome of the PSRT discussion.

In addition to the regular and expedited meetings, the PSRT will conduct the following three interim safety data reviews to assess whether or not the safety data meet criteria for moving on to the next stage of the study.

Review for Continuation of 1 x 10^{10} PU Dose of VRC-EBOAD086-00-VP: No more than 1 participant per day will be enrolled into the group for the first 3 participants. When the first 3 participants who have received the 1 x 10^{10} PU dose have completed post vaccination follow up through at least the "Study Day 7" visit, an interim safety data review will be conducted by the PSRT. Enrollment of the remaining 17 participants in the group may proceed if the PSRT assesses the data as safe to continue.

Review for Dose Escalation to 1 x 10^{11} PU Dose of VRC-EBOAD086-00-VP: When the last participant who has received the 1 x 10^{10} PU dose has completed post vaccination follow up through at least the "Study Day 7" visit, an interim safety data review will be conducted by the PSRT. If the safety data support proceeding to the 1 x 10^{11} dose, then enrollment of Group 2 will begin.

Review for Continuation of 1 x 10^{11} PU Dose of VRC-EBOAD08600-VP: No more than 1 participant per day will be enrolled into the group for the first 3 participants. When the first 3 participants who have received the 1 x 10^{11} PU dose have completed post vaccination follow up through at least the "Study Day 7" visit, an interim safety data review will be conducted by the PSRT. Enrollment of the remaining 17 participants in the group may proceed if the PSRT assesses the data as safe to continue.

After each of these interim safety reviews, the IRB, NDA and VRC will be provided with documentation of the safety review and notification of the plan.

7.4 Safety Monitoring Committee (SMC) Reviews

The SMC for this study will be comprised of an independent group of experts who review safety data during the clinical trial. The SMC will meet as needed to deliberate upon the disposition of study pauses and/or to provide other recommendations regarding the safe conduct of the study as requested by the PI and study team. Otherwise the SMC will review study data, at a minimum annually from the time the study opened. The SMC Executive Secretary will provide the PI and study team with SMC recommendations, and the PI and MHRP Consultants will inform IRBs and regulatory authorities as appropriate. The VRC will notify the FDA of the SMC recommendation as needed.

7.5 Criteria for Study Pause or Termination

The PI will closely monitor and analyze study data as they become available and will make determinations regarding the presence and severity of adverse events. The administration of study injections and new enrollments will be paused and the IND Sponsor will be promptly notified according to the following criteria:

- **One** (or more) participant experiences a **SAE** that is assessed as possibly, probably or definitely related to study agent, or

- **Two** (or more) participants experience the same **Grade 3 or 4** adverse event assessed as possibly, probably or definitely related to study agent.

Plan for Review of Pauses and Resuming Rules:
The study injections and enrollments would resume only if review of the adverse events that caused the pause resulted in a recommendation to permit further study injections and study enrollments. The reviews to make this decision will occur as follows:

Pauses for SAEs: The IND Sponsor and PSRT will consult with the SMC to conduct the review and make the decision to resume, amend or close the study for any SAEs that meet the criteria for pausing the study. The FDA will be notified of any SAE pause review.

Pauses for Grade 3 or 4 AEs: The IND Sponsor and PSRT will conduct the review and make the decision to consult the SMC, resume, amend or close the study for the Grade 3 or 4 events that meet the criteria for pausing the study. As part of the pause review, the reviewers will also advise on whether the study needs to be paused again for any subsequent Grade 3 or 4 event of the same type. The FDA will be notified of all Grade 3 or 4 pause reviews.

When indicated, safety data reports and changes in study status (study pauses) will be submitted to the IRB in accordance with institutional policy.

7.6 Reporting Serious and Unexpected Adverse Events

7.6.1 Study Reporting Period for SAEs

The protocol-defined expedited event reporting period is 48 weeks after study agent administration (study completion) or discontinuation of the participant from study participation for any reason. After the end of the protocol-defined SAE Reporting Period stated above, sites must report suspected unexpected serious adverse reactions (SUSARs) if the study site staff becomes aware of the event from a participant on a passive basis (i.e., from publicly available information).

7.6.2 Adverse Event Reporting to the IND Sponsor

All SAEs must be reported and submitted by the clinical site on an expedited basis to the IND sponsor, VRC/NIAID/NIH, according to sponsor guidelines as follows:

- results in death
- is life threatening
- results in persistent or significant disability/incapacity
- requires unplanned inpatient hospitalization or prolongation of existing hospitalization
- is a congenital anomaly/birth defect in the offspring of a study participant
- is an important medical event that may jeopardize the participant or may require intervention to prevent one of the other outcomes listed above

In addition, any event, regardless of severity, which in the judgment of an investigator represents a serious adverse event, may be reported on an expedited basis.

An investigator will communicate the initial SAE report within 24 hours of site awareness of occurrence to the IND sponsor throughout the study reporting time period. Notification of SAEs will be sent via email to the PSRT, which includes the IND Medical Officer.

A written report by investigator should be submitted to the IND Sponsor within 3 working days. In order for the IND Sponsor to comply with regulations mandating sponsor notification of specified SAEs to the FDA within 7 calendar days, the investigator must submit additional information as soon as it is available.

7.6.3 IND Sponsor Reporting to the FDA

The IND Sponsor is responsible for making the determination of which SAEs are SUSARs that meet criteria for expedited reporting as defined in 21 CFR 312.32.

- *Suspected adverse reaction* means any adverse event for which there is a reasonable possibility that the drug caused the adverse event.
- *Unexpected Adverse Event* means an AE that is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed.

The IND Sponsor will submit written IND Safety Reports to the FDA in accordance with 21 CFR 312.32 as soon as possible and, in no event, later than 15 calendar days after determining that the information qualifies for reporting.

The IND Sponsor is responsible for providing copies of IND Safety Reports for submission to the MUSPH IRB, UNCST and NDA as applicable.

7.6.4 Reporting Serious and Unexpected Adverse Events to the Local Regulatory Bodies & Institutional Review Boards

All SAEs regardless of relationship to the intervention and all unexpected events (whose nature, severity or frequency had not been identified in the Investigator's Brochure or the protocol) of greater than moderate severity regardless of relationship to the intervention, to include SUSAR, must be reported to the MUSPH IRB and the NDA as soon as possible and in any case no later than 7 calendar days of becoming aware of the event. Thereafter, a detailed report of the SAE should be submitted within 7 days.

All other reportable adverse events should be reported to the IRB as soon as possible and in any case no later than 14 calendar days. These include:

a. All events associated with protocol violations regardless of severity and relationship to the intervention;
b. When the criteria for stopping or pausing a study as stipulated in the protocol is met;
c. Any event mandated by regulatory authorities;
d. Any event stipulated in the protocol as reportable to the regulatory bodies.

Follow up reports will be submitted as additional information becomes available. A summary of the non-serious adverse events and SAEs (both related and unrelated) that occurred during the reporting period will be included in the continuing review report (CRR) to the MUSPH IRB.

7.6.5 Reporting Serious and Unexpected Adverse Events to WRAIR and HRPO

All SAEs that are considered related or possibly related, and all deaths, will be promptly (within 48 hours) reported to the WRAIR HSPB. Written reports will be submitted within 10 working days to the WRAIR HSPB. The WRAIR HSPB will report SAEs to USAMRDC ORP HRPO as per SOP UWZ-C-636. Follow up reports will be submitted as additional information becomes available.

The WRAIR HSPB will be immediately notified if any study pause criteria are met. WRAIR HSPB will forward to USAMRDC ORP HRPO as per SOP UWZ-C-636.

7.7 Unanticipated Problems Reporting

All non-serious unanticipated problems (events not involving risk to participants or others) will be reported in the continuing review report to the MUSPH IRB.

All serious unanticipated problems involving risk to subjects or others (UPIRTSOs) (including but not limited to disclosure of personal health information, breach of confidentiality, destruction or loss of study records, unaccounted for study drug, etc.) should be promptly (within 48 hours) reported to the WRAIR HSPB and the IND sponsor via email. The PI will then forward a written report within 10 working days to the WRAIR HSPB.

All unanticipated events of greater than moderate severity, regardless of relationship to the intervention, will be reported to the MUSPH IRB as soon as possible and in any case no later than 7 calendar days of becoming aware of the event. A detailed report of the unanticipated event should be submitted within 7 calendar days from the date it is reported to the MUSPH IRB.

Follow up reports should be submitted as soon as additional information becomes available. A summary of the serious unanticipated problems will also be included in the continuing review report submitted to the MUSPH IRB and NDA.

Unanticipated problems related to the investigational product, such as problems with the actual product itself (e.g. visible discoloration or particulate matter not consistent with product description), will be promptly reported to the study sponsor (for reporting to the US FDA), MUSPH IRB and NDA by the PI.

The DoD medical monitor should also review all unanticipated events involving risk to participants or others and provide an independent assessment for submission to VRC/NIAID, WRAIR HSPB, MUSPH IRB, and NDA (as applicable). The WRAIR HSPB will report serious unanticipated problems, follow up reports and DoD medical monitor reports to the USAMRDC ORP HRPO as per UWZ-C-636.

8.0 STATISTICAL CONSIDERATIONS

8.1 Overview

The primary objective of this study is to assess the safety and tolerability of cAd3-EBO S at two dose levels. The secondary objective is to evaluate the antibody and Ebola Sudan GP-specific T-cell responses to the GP insert and cAd3 vector at 4 weeks after vaccination. An exploratory evaluation of immunogenicity, including assays with samples collected at different study timepoints, profiling vaccine-induced mRNA expression, and isolating MAbs to determine epitope specificity, will also be performed. A total of 40 participants will be enrolled with 20 to receive a $1x10^{10}$ PU/mL dose and 20 to receive a $1x10^{11}$ PU/mL dose of the cAD3-EBO S and followed up through 48 weeks post -vaccination.

8.2 Sample Size and Accrual

8.2.1 Power and Sample Size Calculations for Safety

The goal of the safety evaluation for this study is to identify safety concerns associated with vaccination. Occurrence of solicited local and systemic reactogenicity symptoms, occurrence of adverse and serious adverse events will be assessed as the proportion of participants experiencing such safety event. Table 4 below shows 95% confidence intervals for 0, 1, 2, 5, and 10 participants with observed events in each group or among all study participants.

Table 4. Exact 95% Confidence Intervals for the Proportion of Participants Experiencing a Safety Event

Group	Sample Size	Number of Participants with an Event(s) Observed				
		0	1	2	5	10
Each Individual Study Group	20	0% (0%-16.8%)	5% (0.1%-24.9%)	10% (1.2%-31.7%)	25% (8.6%-49.1%)	50% (27.2%-72.8%)
All participants	40	0% (0%-8.8%)	2.5% (0.06%-13.2%)	5% (0.6%-16.9%)	12.5% (4.2%-26.8%)	25% (12.7%-41.2%)

If no participants experience an event, the upper limit of a two-sided exact 95% CI would be 16.8% for an individual group and 8.8% for the entire study group. While this study is not necessarily powered to detect differences between groups, we would have 82% power to detect a difference of 40% (p1=0.1 and p2=0.50) using Barnard's exact unconditional test at a 5% two-sided level of significance.

Changes in laboratory measures from baseline will also be described. For continuous safety measures, Table 5 below shows minimum detectable changes from baseline to a specified time point using a paired t-test with a two-sided 5% level test.

Table 5 Minimum Detectable Differences, in Standard Deviations, for Change From Baseline to a Single Time (2-sided α=0.05)

Group	Sample Sizes	Power		
		80%	85%	90%
1 (1 x 10^{10} PU/mL)	15	0.78	0.83	0.9
2 (1 x 10^{11} PU/mL)	20	0.66	0.71	0.76
All Active	35	0.49	0.52	0.56

If comparing the two study groups, we would have 80% power to detect a difference of 0.91 standard deviations using a two-sample t-test with a two-sided 5% alpha and assuming equal variances.

8.2.2 Power and Sample Size Calculations for Immunogenicity

The precision and power calculations for safety shown in Table 4 and Table 5 also apply to immunogenicity results. Results of immunogenicity assessments can be shown as proportion of responders (Table 4 applied) or continuous measures (Table 5 applied). For example, if we observe 10 positive responses from an ELISA assay in an individual group, the 95% exact confidence interval of the true response rate will range from 0.272 to 0.728. Note that immunogenicity is a secondary objective for this protocol.

8.3 Statistical Analysis

All analyses will be described overall and by vaccination group (Group 1 and Group 2). The safety and immunogenicity analysis will include all vaccinated participants. All statistical analyses will be performed using Statistical Analysis System (SAS), R, or S-Plus statistical software. No formal multiple comparison adjustments will be employed for safety endpoints or secondary endpoints.

8.3.1 Baseline Demographics

Baseline demographics and laboratory measurements will be summarized for individual groups and overall. Categorical variables will be reported in numbers and percents with exact 95% Clopper-Pearson confidence intervals. Continuous variables will be reported in means and standard deviations or medians and IQR as appropriate.

8.3.2 Safety Analysis

Safety and tolerability will be assessed by both clinical and laboratory monitoring. If comparisons are performed between groups, then Barnard's exact unconditional test will be performed for binary variables and t-tests (or Wilcoxon Rank Sum as appropriate) for continuous measures.

Reactogenicity

The number and percentage of participants experiencing each type of reactogenicity sign or symptom will be tabulated by study group and severity. Exact 95% Clopper-Pearson confidence intervals will be calculated for each set of events. For a given sign or symptom, each participant's reactogenicity will be counted once under the maximum severity for all assessments.

Adverse Experiences
Adverse experiences are coded into Medical Dictionary for Regulatory Activities (MedDRA) system organ classes and preferred terms. The number and percentages of participants experiencing each specific adverse event will be tabulated by dose level, severity and relationship to treatment. For the tabulation of the adverse experiences by system organ class, a participant was counted only once in a given body system. For example, a participant reporting gastritis and diarrhea will be reported as one participant, but the symptoms will be listed as two separate AEs within the class. A complete listing of adverse experiences for each participant will provide details including preferred term, system organ class, severity, relationship to treatment, onset time, duration and outcome.

Local Laboratory Values
Boxplots of local laboratory values will be generated for baseline values and for values measured during the course of the study. Each boxplot will show the 1st quartile, the median, and the 3rd quartile. Outliers, or values outside the boxplot, will also be plotted. If appropriate, horizontal lines representing boundaries for abnormal values will be plotted. Tables will be provided for changes from baseline.

8.3.3 Immunogenicity Analysis
Immunogenicity analysis will consist of all vaccinated participants. If assay data are qualitative (i.e., positive or negative) then analyses will be performed by tabulating the frequency of positive response for each assay at each time point that an assessment is performed. Binomial response rates will be presented with their corresponding exact 95% confidence interval estimates. Barnard's unconditional exact tests will be used to compare the two groups to each other. For quantitative results, mean and standard deviation will be calculated. One-sample t-tests will be used to assess the changes from baseline. Two-sample t-tests will be used to compare the two study groups. Missing responses will be assumed to be missing at random, i.e., conditional on the observed data the missingness is independent of the unobserved responses. Graphical descriptions of the longitudinal immune responses will also be given.

Some immunologic assays have underlying continuous or count-type readout that is often dichotomized into responder/non-responder categories. For these assays, graphical and tabular summaries of the underlying distributions will be made. These summaries may be performed on transformed data (*e.g.*, log transformation) to better satisfy assumptions of symmetry and homoscedasticity.

8.3.4 Interim Analyses
Safety Reviews: The PSRT will review safety data routinely throughout the study. The study will utilize both electronic database features and reviews by designated safety review personnel to identify in a timely manner if any of the safety pause rules of the study are met. The SMC will review study data on an annual basis from the time the study opened.

Immunogenicity Review: Periodic analyses of immunogenicity for each group may be performed during the study for the purpose of informing future vaccine-related decisions in a timely manner once there are at least 3 participants in the group with the 4 weeks post vaccination follow-up completed. The results will not influence the conduct of the trial in terms of early termination or later safety or immunogenicity endpoint assessments.

9.0 SAMPLE AND DATA MANAGEMENT

9.1 Plan for Use and Storage of Biological Samples

9.1.1 Use of Samples, Specimens and Data

Samples, specimens and data collected under this protocol will be used to conduct protocol-related safety and immune response evaluations, exploratory laboratory evaluations related to the type of infection the study agent was designed to prevent, exploratory laboratory evaluations related to vaccine or infectious disease research in general and for research assay validation. Genetic testing will be performed in accordance with the information included in the study informed consent for genetic testing (Appendix 2c). Results from genetic testing will not be provided to participants as the test results are not validated for clinical use. All safety labs will be performed at the study site.

Immunogenicity of the vaccine will be evaluated as humoral and cellular immune responses assessed by ELISA and intracellular cytokine staining (ICS) assay. The ELISA assay will be performed at the VRC or VIP and the exploratory evaluation of Ebola-specific neutralizing antibodies will be conducted at the VRC, using previously published methods [21]. The pre-existing and post-vaccination presence of cAd3 neutralizing antibody also will be evaluated [32]. The ICS assay quantitates the frequency of CD4+ and CD8+ cells that produce interleukin-2, interferon-gamma and/or tumor necrosis factor in response to pools of overlapping peptides representing Ebola GP antigens and is based upon previously published methods [35].

Other evaluations of vaccine-induced immune responses may be conducted as exploratory evaluations. Specific peptides may be used to detect T-cell responsiveness by an enzyme-linked immunospot (ELISpot) assay, modified from a previously published method [33]. Genetic factors associated with immune responses may also be evaluated; isolation of MAbs to determine epitope specificity and functional capacity may be performed; and time courses of immune responses may be analyzed including durability of cAd3 neutralizing antibody titers, mediators of inflammation following vaccination, and, for the first week, vaccine-induced mRNA expression profiles.

Stored samples from vaccine study participants may also be used in the future for evaluation of immune response to the vaccine as measured by other assays. The experimental laboratory procedures for the exploratory objectives may be conducted using fresh or stored samples at the NIH or at the laboratories of its affiliates and/or collaborators (see Appendix 13).

9.1.2 Storage and Tracking of Blood Samples and Other Specimens

All of the stored study research samples will be labeled with a participant ID number that only the site can link to the participant. Samples will be stored at VIP or at the VRC Immunology Laboratory in Building 40; all are secure facilities with limited access. Data will be kept in password-protected computers. Only investigators or their designees will have access to the samples and data. Samples will be tracked in the Laboratory Information Management System (LIMS) database or using another software designed for this purpose (e.g., Freezerworks).

9.1.3 Disposition of Samples, Specimens and Data at Completion of the Protocol

At the time of protocol termination, samples will remain at VIP, VRC or, after IRB approval, transferred to another repository. At this time, a list of all participants who refused future use of their samples will be generated from the study database and the corresponding samples will be destroyed. Data will be archived by the VRC in compliance with all requirements for retention of research records, or after the IRB and the IND sponsor approval, may be either destroyed or transferred to another repository.

9.1.4 Loss or Destruction of Samples, Specimens or Data

Any loss or unanticipated destruction of samples (for example, due to freezer malfunction) or data (for example, misplacing a printout of data with identifiers) that compromises participant confidentiality or the scientific integrity of the study will be reported to the IRB in accordance with Section 7.7. The PI will also notify the IRB if the decision is made to destroy the remaining samples.

9.2 Study Documentation and Storage

The investigator will maintain a list of appropriately qualified persons to whom trial duties have been delegated.

Source documents are original documents, data, and records from which the participant's data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, radiographs, and correspondence.

The investigator and staff are responsible for ensuring maintenance of a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives of USAMRDC ORP HRPO, WRAIR, FDA, the U.S. DoD, MUSPH IRB, UNCST, NDA, the sponsor, and other regulatory agencies. Essential documents for all study participants are to be maintained by the investigators in a secure storage facility. Elements include:

- Participant files containing completed informed consent forms, and copies of source documentation
- Study files containing the protocol will include all amendments and copies of correspondence between the study site, protocol team and the IRB
- All Essential Documents outlined in the ICH Good Clinical Practice Guideline.

In addition, all original source documentation must be maintained and be readily available for monitoring or auditing purposes.

All essential documentation will be collected by EMMES in the Regulatory Tracking System and should be retained for the same period of time required for medical record retention. The FDA requires study records to be retained for 2 years after marketing approval or refusal (21 CFR 312.62), the NIH requires study record retention for a minimum of 7 years after study closure, and the UNCST guidelines require records to be retained for a minimum of 5 years post-study closure. Study records will be retained for at least as long as is required by the FDA, NIH and UNCST record retention requirements. No study document or data should be destroyed

without prior written agreement between VRC, the MHRP Consultants and the PI. Should the PI wish to assign the study records to another party or move them to another location, VRC must be notified in writing of the new responsible person and/or new location.

The VRC may request to receive a copy of all essential documents. FDA form 1572, CVs and IRB approvals must be submitted to the VRC as IND Sponsor.

9.3 Data Collection

Clinical research data will be collected in a secure electronic data management system through a contract organization, EMMES (Rockville, MD). Data entered into the electronic data system shall be performed by authorized individuals. Corrections to the electronic data system shall be tracked electronically (password protected) with time, date, individual making the correction, and what was changed.

The investigator is responsible for assuring that the data collected is complete, accurate, and recorded in a timely manner. Source documentation (the point of initial recording of information) should support the data collected in the system, and must be signed and dated by the person recording and/or reviewing the data. Extracted data without participant identifiers will be sent to the Protocol Statistician for statistical analysis.

This data will not contain participant names or Social Security or other national identification number, but is referenced only by the study specific identification code.

Every attempt must be made to adhere to the approved protocol and to obtain and record all data requested for each participant at the specified times. However, ethical considerations or other events may result in the failure to obtain and record certain data, or to record data at the times specified. If this occurs, the events and, the reasons for the event must be clearly documented on the CRF for deviations and reported as applicable.

Analysis files are created on a periodic basis and made available to the MHRP Consultants, PI, and AIs. Other collaborators may be given access to these analysis files, or data gathered from them, at the direction of the PI.

10.0 ETHICAL CONSIDERATIONS

10.1 Risks

10.1.1 Risks of the cAd3 Ebola Vaccines and Diluent

Potential side effects resulting from intramuscular injection include pain, stinging, arm discomfort, redness of the skin, soreness, itchiness, swelling or mild bruising at vaccine injection sites. Study participants can receive medications such as acetaminophen, NSAIDs, or antihistamines as required.

Participants may exhibit general signs and symptoms associated with administration of a vaccine including fever, chills, rash, aches and pains, nausea, headache, dizziness and fatigue. These side effects will be monitored, but are generally short term and do not require treatment. As with all vaccines, an allergic reaction is possible and will be managed as per site SOP for anaphylaxis. To mitigate this risk, participants will remain under observation in the clinic for at least 30 minutes post-injection.

Chimpanzee adenoviral vector vaccines have been generally safe in healthy adults at dosages up to 10^{11} PU per injection in completed and ongoing clinical trials [17, 28, 29]. Systemic reactogenicity typically occurs on the day of or day after vaccination and may include headache, malaise, myalgia, chills, and fever. When present, fever onset occurs within 1 day of vaccination and typically resolves within 24 hours of onset. A pattern of fever occurring later than 1 day after vaccination or lasting longer than 1 day may require evaluation for additional etiology.

Risks of the vaccine to pregnant and nursing women and to the unborn fetus are unknown.

There may be other unknown side effects.

10.1.2 Other Risks

Blood drawing with needles, like injections, may cause pain, bruising, feeling lightheaded, fainting, and, rarely, infection at the site where the blood is taken.

The risk to pregnant women and fetuses is currently unknown. As such, women of reproductive potential will be required to agree to use birth control for sexual intercourse beginning at least 21 days prior to enrollment and continue through 24 weeks after the study injection. Because this is a research study, women of reproductive potential will be asked to notify the site immediately upon learning of a pregnancy during this study and will be tested for pregnancy prior to administration of the study injection. The amount of blood drawn will be reduced at follow-up visits for pregnant participants as blood will only be drawn for safety testing. The participant will be contacted to ask about the outcome of a pregnancy that begins during the study.

It is possible that the standard medical tests performed as part of this research protocol will result in new diagnoses. Depending upon the medical findings and consequences of being provided with the new medical information about health status, the study participant may view this aspect of study participation as either a risk or a benefit. Any such information will be shared and discussed with the participant and, if requested by the participant, will be provided to the participant for review by the primary health care provider for further workup and management.

10.2 Benefits

Although study volunteers may benefit from clinical testing and physical examinations, study participants will receive no direct benefit from participation.

In light of the recent Ebola outbreak in 6 countries in West Africa that killed more than 5,160 people (of an estimated 14,000 cases) and its potential for international spread, the general population in Uganda (and West Africa in particular), may benefit from information gained from the development of a vaccine against Ebola. Further, Uganda has itself experienced 3 outbreaks of Ebola between 2000 and 2012 with a case fatality rate ranging from 25% to 71%. While prior outbreaks of EVD have been localized to various regions within Africa, there is a continued potential threat of spread to other countries given the frequency of international travel.

Others may benefit from knowledge gained in this study that may aid in the development of an Ebola virus vaccine.

10.3 Informed Consent

The study informed consents are provided in Appendix 2. The main study consent describes the IP to be used and all aspects involved in protocol participation.

Before a volunteer may participate in the study, it is the investigator's responsibility to obtain written informed consent from the potential participant, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or study medications are administered. Information will be given in both oral and written form whenever possible as deemed appropriate by the IRBs. The investigator or designee (e.g., study coordinator) shall give the participant ample opportunity to inquire about details of the study, discuss with other people and ask any questions before dating and signing the consent forms. Participant information and consent form language will be at a reading level fully comprehensible to the prospective participants. Informed consent will be obtained in accordance with 21CRF 50, DoD Common rule, 32 CFR 219, ICH harmonized Tripartite Guideline for GCP (E6), the principles of the Belmont Report, UNCST guidelines, and all applicable regulations.

Each participant's signed informed consent documents will be kept on file by the investigator for inspection by Regulatory Authorities and/or Regulatory Compliance persons. Each participant will receive a copy of the signed and dated written informed consent document along with a copy of the volunteer event schedule. The informed consent process will be documented in the CRFs.

The legal age at which individuals can provide their own consent to participate in research is 18 years. Consent forms will be available in English and Luganda. The volunteer will sign and date the consent form. Illiterate participants will not be enrolled into this study for safety purposes. Participants must be able to read and comprehend all written information in the informed consent forms and must be able to accurately document any symptoms on the diary cards so as to inform the investigators about any adverse events or reactions that may be associated with the study vaccine.

Three (3) different consent forms and one withdrawal form will be used for this study:

i. Main Informed Consent Form (Appendix 2a)
ii. Future Use Informed Consent Form (Appendix 2b)

iii. Informed Consent for Genetic Testing (Appendix 2c)

The participant may terminate participation in the study at any time for any reason without penalty. Additionally, in the event that the participant is unable or unwilling to adhere to the protocol design, the investigator may terminate their participation for safety purposes.

10.4 Language

All written information and other material to be used by participants and investigative staff must use vocabulary and language that are clearly understood. Accordingly, the consent and all other written materials will be translated into Luganda in addition to English and will be submitted to the IRBs for review and approval.

10.5 Compensation

Participants will be compensated for time and inconvenience in accordance with the local standards and legal obligations for compensation required by the study site. Any applicable guidelines by IRBs/ECs for compensation of research participants will be sought and followed.

Participants will receive 50,000 Ugandan shillings for time, inconvenience and transportation costs associated with each scheduled visit, and 20,000 Ugandan shillings for each unscheduled visit to address safety concerns. Compensation for unscheduled visits will be at the Investigator's/ designee's discretion.

10.6 Policy Regarding Research-Related Injuries

Participants who experience illness or injury arising from participation in the study will receive medical care for such illness or injury until cure or stabilization with costs for such care provided by a limited set-aside fund and a clinical trials medical insurance policy that will be obtained by MHRP (HJF). While it is anticipated that the combination of the set-aside fund and the insurance policy is more than enough to pay for the research related injury medical care cost associated with this study, there is a limit to the amount of coverage available. The study sponsor, MUWRP, and the U.S. DoD will not provide long-term medical care or financial compensation for stabilized research-related injuries. This will not waive a participant's rights.

10.7 Participant Confidentiality

The PI will maintain participant research records at the site for this study. All participants will receive study numbers that are known only to the investigators and study staff. All samples and documents (with the exception of the consent forms) will be labeled only with a participant's study number and not personal information. The link between a participant ID number and participant identifiable information will be maintained in a secure, locked file cabinet in a locked room which is accessible only to the PI/designees. Clinical and research records may be reviewed by representatives of USAMRDC ORP HRPO, WRAIR, FDA, the U.S. DoD, MUSPH, UNCST, NDA, the sponsor, and other regulatory agencies as part of their responsibilities for insuring the protection of research participants.

Every effort will be made to keep the records as confidential as possible within the limits of the law. All data and medical information obtained about participants as individuals will be considered privileged and held in confidence. Research and clinical information relating to

participants will be shared with other investigators and the scientific community through presentation or publication; however, participants will NOT be identified by name or national registration number. Electronic data will be stored for at least 2 years after the IND is inactivated.

10.8 Future Use and Storage of Blood Samples

Each study participant will be asked to separately, and voluntarily consent to genetic testing and for their samples to be stored for future research studies that may be conducted after this study is completed. Future testing may involve genetic tests as indicated in the future use consent form. Results from genetic testing, whether for this study or from future genetic testing, will not be provided to participants as the results are not validated for clinical use. As stated above, the sample will be labeled only with the participant ID that can be linked to their study information. All samples for which future use consent has been obtained and for which additional material is available after study specified testing is complete will be stored for future testing at VIP.

11.0 REGULATORY REPORTING REQUIREMENTS

11.1 Protocol Deviation Reporting

A protocol deviation is defined as an isolated occurrence involving a procedure that did not follow the study protocol.

The timeline for reporting protocol deviations is determined by the categorization of the deviation: (1) emergent/significant or (2) non-emergent/minor. Protocol deviations arising of or leading to unanticipated problems should be reported in the appropriate timeframe according to the seriousness of the event as a significant deviation or a minor deviation. The unanticipated problem will be submitted as described in Section 7.7.

Emergent/significant deviations are departures from protocol that have a significant impact on the welfare or safety of a participant or on the integrity of the study data. Examples: providing the wrong lab result to a participant or failure to obtain a scheduled blood draw for multiple participants. Changes in protocol procedures may be initiated without prior IRB/ethical review committee (ERC) and VRC approval, only in cases where the change(s) is /are necessary to eliminate an immediate apparent hazard. Emergent/significant deviations should be reported promptly (within 48 hours) to the WRAIR HSPB and the IND sponsor and within 7 calendar days to the MUSPH IRB and NDA, upon becoming aware of the event. A written report is required to be submitted by the PI to the WRAIR HSPB and the VRC within 10 working days and to the MUSPH IRB and NDA within 7 calendar days of initial notification of the significant deviation. Deviations will be reported by the WRAIR HSPB to the USAMRDC ORP HRPO as per SOP-UWZ-C-636.

Non-emergent/minor deviations are routine departures that typically involve a participant's failure to comply with the protocol. Examples include missing scheduled visits and failing to complete a required questionnaire. Minor deviations will be reported to the MUSPH IRB, UNCST, and NDA in a cumulative summary report with the annual continuing review report and with the closeout report.

11.2 Safety Reports

The PI will be responsible for forwarding any Safety Reports issued by the study Sponsor to the MUSPH IRB and NDA in a timely manner.

11.3 Pregnancies

Each pregnancy must be reported *promptly* (within 24 hours of identification) by telephone or email to the PSRT. Pregnancies must be reported, within 48 hours of becoming aware of the event, to the WRAIR HSPB, the MUSPH IRB, and NDA.

11.4 Study Holds

The WRAIR HSPB, MUSPH IRB, and NDA will be immediately notified if any study pause criteria are met, as determined by the PSRT or SMC. The WRAIR HSPB will forward all study-hold reports to the USAMRDC ORP HRPO as per SOP-UWZ-C-636.

11.5 Protocol Modifications

Amendments to the protocol will be made only after consultation and agreement between NIAID VRC, the MHRP Consultants, and the PI. All protocol modifications (including but not limited to changes in the PI, inclusion/exclusion criteria, number of participants to be enrolled, study sites, or procedures) must be submitted as a written amendment to the MUSPH IRB, NDA and U.S. FDA for review and approval, and to the WRAIR HSPB for assessment of human subjects determination/acknowledgment, before implementation of the changes. Submissions to ethical and regulatory committees will be made after review and approval by the IND Medical Officer and the VRC IND Regulatory Representative. The WRAIR HSPB will submit any protocol amendments and modifications that potentially increase the risk to subjects or others to the USAMRDC ORP HRPO for review and approval prior to implementation.

The UNCST shall be notified of all MUSPH IRB approved protocol amendments.

Modifications or updates to the Investigational Brochures (IBs) will also be submitted to the MUSPH IRB, NDA (as specified above), and WRAIR HSPB for acknowledgment.

The Informed Consent Form must be revised to concur with any significant amendment that directly affects participants, and must also be reviewed and approved with the amendment. New participants enrolled in the study will be consented with the most recent approved consent form. Participants already enrolled in the study will be informed about the revision and asked to re-consent. This may be accomplished by repeating the consent process with the revised consent form with attention given to the changes, or it may be done using an addendum consent that states the revision or new information. The new document must be signed, placed in the study record, and a copy given to the participant.

Administrative changes to the protocol are corrections and/or clarifications that have no effect on the way the study is to be conducted. Such administrative changes will be submitted to the IRB for review and approval prior to implementation.

11.6 Continuing Reviews/Closeout Report

A continuing review report (CRR) will be submitted to the MUSPH IRB prior to the anniversary date determined at initial IRB review. If the continuing review is not approved by the MUSPH IRB by the anniversary date, all protocol activities must stop until such time as the approval is obtained.

A copy of the CRR and CRR approval notification from the IRB of Record will be submitted to the HRPO and the UNCST as these documents become available.

After all study-related activities, including data analysis are completed a final/closeout report will be submitted to the MUSPH IRB, UNCST and NDA. A copy of the approved closeout report, including any acknowledgment documentation and supporting documents will be submitted to the WRAIR HSPB as soon as these documents become available. A closeout report will be submitted after 5 years from study start or upon completion of the study, whichever occurs first. The WRAIR HSPB will forward CRR approval notifications and closeout report to the USAMRDC ORP HRPO as per SOP-UWZ-C-636.

Under current UNCST procedure, a protocol shall receive an approval for a period as may be granted. Prior to expiration of that period, the PI will submit a request for extension of the approval with rationale.

11.7 Reporting Requirements to the MRDC ORP HRPO

- Substantive modifications to the research protocol and any modifications that could potentially increase risk to participants must be submitted to the HRPO for approval prior to implementation. The USAMRDC ORP HRPO defines a substantive modification as a change in PI, change or addition of an institution, elimination or alteration of the consent process, change in the IRB of Record, change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc.), significant change in study design (i.e. would prompt additional scientific review) or a change that could potentially increase risks to participants.
- Any changes of the IRB used to review and approve the research will be promptly reported to the USAMRDC ORP HRPO.
- A copy of the IRB continuing review approval letter must be submitted to the HRPO as soon as possible after receipt of approval. For greater than minimal risk research, a copy of the continuing review report, current protocol and consent form at time of continuing review must also be provided.
- The final study report submitted to the IRB, including a copy of any acknowledgement documentation and any supporting documents must be submitted to the HRPO as soon as all documents become available.
- The following study events must be promptly reported to the HRPO by telephone [redacted] by email [redacted] or by facsimile [redacted] or mail to the US Army Medical Research and Materiel Command, ATTN: MCMR-RP[redacted]
    - All unanticipated problems involving risk to subjects or others.
    - Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the sponsor, or regulatory agencies.
    - Any instances of serious or continuing noncompliance with the federal regulations or IRB requirements.
    - The knowledge of any pending compliance inspection/visit by the Food and Drug Administration (FDA), Office for Human Research Protections, or other government agency concerning this clinical investigation or research.
    - The issuance of inspection reports, FDA Form 483, warning letters, or actions taken by any government regulatory agencies.
    - Change in participant status when a previously enrolled human participant becomes a prisoner must be promptly reported to the USAMRDC ORP HRPO. The report must include actions taken by the institution and the IRB.

11.8 Use of Information and Publication

It is expected that data from this study will be reported in both scientific journals and international scientific meetings. Confidentiality of participants will be maintained by the fact that individual results will not be reported or published, only group/aggregate results. All research data will be identified by the study number. The linkage between personal identifiers and study number will only be available in a confidential source document/database at the study site. The local health authorities will be informed of all scientific outcomes of the study and general prevalence and incidence data however, confidentiality will be maintained, and participant identities will not be released. Only aggregate information will be released. All publications resulting from this study will be cleared through the collaborating partners to this study.

WRAIR recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and at seminars or conferences. Any results of medical investigations and/or publication/lecture/manuscripts based thereon, shall be exchanged and discussed by the investigator, the sponsor representative(s) and the U.S. Army Medical Research and Materiel Command 60 days prior to submission for publication or presentation.

Results from investigations shall not be made available to any third party by the investigating team outside the publication procedure as outlined previously. WRAIR will not quote from publications by investigators in its scientific information and/or promotional material without full acknowledgment of the source (i.e., author and reference). All publications written by WRAIR investigators must be reviewed and approved by WRAIR Office of Research Technology and Applications (ORTA).

12.0 CONDUCT OF THE RESEARCH STUDY

This research study will be conducted in accordance with ICH GCP guidelines, UNCST guidelines, DOD Directive 3216.2, the Declaration of Helsinki, the Belmont Report, the U.S. Code of Federal Regulations 21 CFR 312, 812, 50 and 56, and all applicable local laws and regulations.

12.1 Regulatory Audits

The knowledge of any pending compliance inspection/visit by the US FDA, OHRP, or other government agency concerning this research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any regulatory agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements will be reported immediately to the IND sponsor, WRAIR HSPB, NDA and MUSPH IRB. The WRAIR HSPB will report knowledge of any pending inspections/audits by regulatory agencies to the USAMRDC ORP HRPO.

12.2 Protocol Monitoring Plan

Site visits by the study monitor will include a review of the following: study operations, the quality of data collected in the research records, the accuracy and timeliness of data entered in the database, and to determine that all process and regulatory requirements are met.

Site investigators will allow the study monitors, representatives of the VRC or designee, WRAIR HSPB, MUSPH IRB, NDA, UNCST, USAMRDC ORP HRPO, and the FDA to inspect study documents (e.g., consent forms, drug accountability and dispensing records, CRFs), and pertinent clinical records for confirmation of the study data.

Study data will be closed and final after data cleaning activities are completed and resolutions have been documented.

13.0 PRINCIPAL INVESTIGATOR AGREEMENT

1. I agree to follow this protocol version as approved by the IRBs/ERCs.
2. I will conduct the study in accordance with applicable IRB/ERC requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I will not modify the protocol without first obtaining an IRB/ERC approved amendment and new protocol version unless it is necessary to protect the health and welfare of study participants.
5. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local (UNCST) regulatory requirements. In accordance with the FDA Modernization Act and NIH policy, I will ensure the registration and reporting results of the trial on the www.clinicaltrials.gov website.
6. In accordance with Command Policy 2008-35, I will ensure that the Commanding General receives a pre-brief (or Executive Summary) and approves the study prior to execution.
7. I will ensure that the data (and/or specimens) are maintained in accordance with the data (and/or specimen) disposition outlined in the protocol. Any modifications to this plan should first be reviewed and approved by the applicable IRBs/ERCs.
8. I will promptly report changes to the research or unanticipated problems to the MUSPH IRB, the NDA (where applicable) and the WRAIR IRB immediately via the WRAIR Human Subjects Protection Branch at (301) 319-9940 (during duty hours) or to the usarmy.detrick.medcom-wrair.mbx.hspb@mail.mil and submit a written report within 10 working days of knowledge of the event.
9. I will prepare continuing review reports at an interval established by the IRB/ERC, and a study closure report when all research activities are completed.
10. I will immediately report to the WRAIR Human Subjects Protection Branch knowledge of any pending compliance inspection by any outside governmental agency.
11. I agree to maintain adequate and accurate records in accordance with IRB policies, Federal, state and local laws and regulations.

Principal Investigator Signature

05 MAR 2020

Date (DD/MM/YYYY)

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APPENDIX 1: SCHEDULE OF EVALUATIONS

RV 508 Schedule of Evaluations												
Visit		01	02	02A	02B	02C	02D	03	04	05	06	07
Week of Study		-8 to 0	W 0	W 1	W 1	W1	W2	W4	W 8	W 16	W 24	W 48
Day of Study		-56 to 0	D 0	D 1	D 3	D 7	D14	D 28	D 56	D 112	D 168	D 336
Clinical Evaluations	**Tube**	Screening[1]	Enrollment									
Informed Consent, Assessment of Understanding		X										
Physical exam and weight at screen; Vital signs, targeted exam at other visits		X	X		X	X	X	X	X	X	X	X
Medical history for eligibility at screen; interim history other visits		X	X		X	X	X	X	X	X	X	X
Study Vaccination[2]			X									
Begin/Review 7-Day Diary Card[6]			X		X	X	X					
Telephone contact; clinic visit if indicated				X								
Counseling on pregnancy prevention			X				X	X	X	X		
CBC w/total lymphocyte count	Anti-coagulant	3	3		3		3	3	3		3	
Pregnancy test: urine (or serum)[3]		X	X					X			X	
Creatinine and ALT	Coagulant	4	4		4		4	4	4			
HIV[5] and RPR		6										
Research Immunology												
Serum storage for antibody assays	Coagulant	12	12		12	12	12	12	12	12	12	12
Pre-Existing Vector Immunity testing		X										
PBMC and plasma for storage	Anti-coagulant	8.5	68			59.5	42.5	59.5	42.5	59.5	76.5	76.5
Intracellular RNA	PAXgene		3		6	6						
HLA type[4]	Anti-coagulant									17		
Daily Volume (mL)		**33.5**	**90**	**0**	**25**	**77.5**	**61.5**	**78.5**	**61.5**	**88.5**	**91.5**	**88.5**
Max. Cumulative Volume (mL)		**33.5**	**123.5**	**123.5**	**148.5**	**226**	**287.5**	**366**	**427.5**	**516**	**607.5**	**696**

Visit windows: 02A (+1 day); 02B (+2 days); 02C (+3 days); Visit 02D (±3 days); Visits 03 and 04 (±7 days); Visits 05, 06 and 07 (±14 days).

[1] Most screening evaluations must be no more than 56 days prior to Day 0 to be used for eligibility (pregnancy test from Day 0 must be used for eligibility). If clinical assessment on Day 0 suggests significant changes may have occurred since screening, then physical examination & laboratory studies done on Day 0 are used for eligibility. Day 0=day of enrollment and vaccine injection. Day 0 evaluations prior to first injection are the baseline for assessing adverse events subsequently.

[2] Complete post vaccination vitals and injection site assessment after the study injection (target to complete this within the interval 30 to 45 minutes post-vaccination). Subjects must remain in the clinic for at least 30 to 60 minutes after injection.

[3] Negative pregnancy test results must be confirmed for women of reproductive potential prior to administering the vaccine injection. Serum pregnancy testing at screening visit, urine pregnancy testing at enrollment visit and all follow-up visits where indicated. Serum taken from blood collected for HIV and RPR tests.

[4] HLA type blood sample is collected once at any time point in the study and is shown as a Visit 05 evaluation for convenience; however, if HLA type is already available in the medical record it does not need to be repeated. HLA type may also be obtained from a frozen sample.

[5] Includes pre/post-test counseling as per site SOP

[6] The Diary Card can be collected at any time between Visit 02C and Visit 02D (to include at an unscheduled visit) in order to obtain a complete day 7 assessment of any solicited symptoms.

APPENDIX 2: INFORMED CONSENT FORMS

APPENDIX 2A: MAIN INFORMED CONSENT FORM

MAIN STUDY INFORMED CONSENT FORM

Study Title: RV 508, "A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of Two Doses of an Ebola Sudan Chimpanzee Adenovirus Vector Vaccine, VRC-EBOADC086-00-VP (cAd3-EBO S), in Healthy Adults"

Sponsor: National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center (VRC)

Funding Agencies: NIH, the U.S. Military HIV Research Program (MHRP) and the U.S. Department of Defense (DoD)

Study Product Provided by: NIH/NIAID/VRC

Study Conducted by: Makerere University Walter Reed Project (MUWRP)

Principal Investigator: Betty Mwesigwa, MBChB, MSc Clinical Trials

INTRODUCTION

You are being invited to consider participating in this study because you are a healthy person who may meet the criteria to join this study. Before deciding to participate in this study, please read this document thoroughly. In doing so, you will understand the purpose and details of this study.

Before you decide whether or not to take part in this study, we would like to explain the purpose of the research study, how it may help you or others, any risks associated with participation, and our expectations of you. This process is called informed consent. It is important that you know the following:

a. Taking part is of your own free will (entirely voluntary).

b. If you decide not to participate you will not lose any of the benefits or rights you would normally have or be disadvantaged in any way.

c. You may decide not to participate in the study or you may decide to stop participating in the study at any time without loss of any medical care to which you are entitled now or in the future.

Please ask questions about anything you do not understand at any time. The clinic staff will talk to you about the information in this form. You can take as much time as you need to review this form and discuss your study participation with your family, friends, and community as you feel comfortable and appropriate, in order to decide whether or not you would like to participate. If you decide to participate in this study, you will review this document with a study staff and will be requested to sign and date at the end of this form to show that your questions have been answered and that you want to take part in the study. A copy of this signed/marked informed consent will be provided to you. This consent must be signed/marked before any study procedures are performed.

You will also have the opportunity to consent for future (currently unknown) use of your samples, and genetic testing. These will be explained to you, and you will sign a separate consent for each.

The technical name of the study vaccine is VRC-EBOADC086-00-VP, but we will refer to it as "cAd3-EBO S" or simply as the "Ebola vaccine." The study vaccine does not contain live or killed Ebola virus. It is **impossible** for the study vaccine to give you an Ebola virus infection.

This research study is funded by the U.S DoD and the NIAID/NIH. The MUWRP is conducting this research study in collaboration with the U.S. MHRP and NIAID/NIH in Kampala, Uganda.

PURPOSE AND BACKGROUND

This research study will evaluate an experimental vaccine for the Ebola Virus. "Experimental" means that it is not known if the vaccine works to prevent the Sudan strain of Ebola Virus Disease (EVD). Since it is not known if the vaccine works, it has not been approved by the US Food and Drug Administration (FDA) or the Uganda National Drug Authority (NDA). Vaccines are substances used to create immune responses (resistance) to an infection in order to prevent a disease. Immune responses are how your body recognizes and defends itself against bacteria, viruses, and substances that may be harmful to the body.

The main purpose of this study is to see if the experimental Ebola vaccine is safe and if it causes any side effects. Another goal is to study blood samples in the lab to see if and how the immune system responds in people who receive this vaccine.

The Ebola virus was discovered in 1976. It is named after a river in Africa close to where the virus was first discovered. Bats in certain parts of Africa carry the virus. EVD starts with fever and muscle aches. More severe symptoms are breathing problems, severe bleeding, kidney problems, and shock (loss of blood pressure). The infection may be mild, but it can also lead to death. The first two outbreaks of Ebola Hemorrhagic Fever in Africa in 1976 caused 340 deaths. In Africa, when there have been outbreaks of Ebola virus, 50% to 90% of infected people have died.

STUDY VACCINE

The experimental Ebola vaccine in this study was developed in a laboratory by the VRC at the NIH, located in Bethesda, Maryland USA. The experimental vaccine has previously been given to humans in combination with other Ebola vaccine products, but not by itself.

The cAd3-EBO S vaccine uses another virus, called chimpanzee Adenovirus 3 (cAd3), to deliver a piece of the Ebola Sudan virus to cells in your body. The adenovirus used to make the vaccine is from a strain that infects chimpanzees. This strain of adenovirus has been tested in people before and does not cause human adenovirus infections. It is further changed to make sure it cannot reproduce in a human body.

Once the Ebola Sudan virus piece is delivered to the cells in your body, your body will then make an immune response. You cannot become infected with or infect someone else with either Ebola or adenovirus from receiving the study vaccine.

STUDY PARTICIPATION

If you agree to take part in the study you will receive one study injection at the enrollment visit (Visit 2). The vaccine injection will be given using a needle and syringe into an upper arm muscle. This is called an intramuscular (IM) injection.

About 40 participants will be enrolled into this study and will be divided into 2 groups. Both groups will have about 20 participants. Participants in Group 1 will receive a low dose of the vaccine and participants in Group 2 will receive a higher dose. Enrollment into Group 2 will not begin until after a safety review is completed for participants who received the lower dose of the vaccine and it is determined to be safe. The higher dose of the experimental Ebola Sudan vaccine is based on dose levels found to be safe in previous studies of similar vaccines that used the chimpanzee adenovirus. If you would like to know which group you are in, please ask the study clinician.

Vaccination Schedule:

RV 508 Study Groups		
Group	**Participants**	**Vaccine Dose**
1	20	cAd3-EBO S at $1x10^{10}$ PU IM
2	20	cAd3-EBO S at $1x10^{11}$ PU IM

STUDY DURATION

Participation in this study will last for about 48 weeks (almost 1 year) from the time of enrollment. There will be 1 screening visit and 10 study visits (1 visit for vaccination and 9 visits for follow-up). However, these do not include additional appointments if you have any side effects and if the study team requests you to come to the clinic. The screening and vaccination visits will each take approximately 2-3 hours. Other appointments will take approximately 1-2 hours. A schedule of events detailing your visits will be provided to you.

STUDY PROCEDURES

a) How do I join in this study?

You will have to sign this form acknowledging that you have read the form, that all your questions have been answered satisfactorily, and that you agree to participate in this study.

You may take part in this study if you are a healthy, male or female volunteer, between ages 18 and 50 with a body mass index (a ratio based on your weight and height) $\leq$ 40, available for a period of 48 weeks, able to provide proof of identity, willing to have the vaccine injection site and any vaccine reactions on your skin photographed, and agree to clinic staff visiting your home (as may be necessary). You must also be able to read this consent form, understand and complete this informed consent process, successfully complete an Assessment of Understanding (to see if you understand the information in this form), and be free of significant medical problems. Blood tests will be done to measure your hemoglobin (amount of blood), your white blood cells, and your liver and kidney function. Females will also be required to undergo pregnancy testing, to not be pregnant, to not be breastfeeding, and to plan not to become pregnant for at least 6 months after vaccination. Females must also agree to use a birth control method for at least 21 days prior to vaccination and for at least 6 months after vaccination.

You **cannot** participate in this study if you received an experimental Ebola or Marburg vaccine or have received a different cAd3 experimental vaccine. You also cannot participate if you have any of the following conditions:

- A history of a serious allergic reaction to any vaccines or allergic reaction to drugs like gentamycin, neomycin or streptomycin
- An autoimmune disease or deficiency or chronically recurring hives, asplenia (lack of normal spleen function) or a history of angioedema (facial swelling)
- HIV infection
- Active syphilis infection
- Diabetes (type I or II)
- Thyroid disease that is not well controlled
- High blood pressure or asthma that is not well controlled
- A bleeding problem or disorder
- Cancer
- A history of seizures or treatment for seizure disorder in the past 3 years

You also cannot participate if you have received any of the following:

- Drugs that may modify your immune system within 14 days prior to enrollment such as prednisone or dexamethasone
- Blood products within 112 days (16 weeks) prior to enrollment
- Any "live-attenuated" vaccine (e.g., oral polio, yellow fever, measles, etc.) within 28 days prior to enrollment in the present study or any other vaccine within 14 days prior to enrollment
- Experimental research drugs within 28 days prior to enrollment in the present study
- Drugs for treating or preventing Tuberculosis

You also may not participate in the study if the Investigators think you may have a history of any condition(s) that may interfere with your full participation in the study or that may impair your ability to provide informed consent.

It is important to remind you that to participate in this study you need to agree to home visits by the clinic staff. The clinic staff may visit your home if they are unable to reach you by phone, in order to remind you of your scheduled visit or for follow up.

b) Screening (Visit 1)

After you have reviewed the study consent form and have agreed to participate, the study staff will ask you to complete an Assessment of Understanding (AOU). The AOU will help the study staff to determine how well you have understood the information about this study and what is required for participation. You must complete 9 out of the 10 questions correctly at least once in 3 attempts. After the AOU, your medical history will be recorded and a thorough physical examination will be performed on you by a member of the study staff. In addition, you will have blood taken to check your HIV and syphilis status.

A serum (blood) pregnancy test will be required at the screening visit if you are female and able to become pregnant. The research staff will test your blood for HIV (human immunodeficiency virus), the

virus that causes AIDS. Prior to this blood test, you will receive counseling about HIV, AIDS, and prevention of HIV. If you are HIV infected, you will receive additional information about HIV and will be referred to our HIV Clinic or the Infectious Disease Institute (IDI) at Mulago or any other HIV Clinic of your choice.

It may be necessary to return to the clinic for a follow up appointment or to repeat tests if there are any abnormal laboratory results. If the physician discovers an illness or condition that requires treatment, you will be referred to a hospital or clinic that can provide further evaluation or treatment.

If you are eligible for participation in this study, you will be scheduled for an appointment for the vaccination visit within 56 days of the screening date. It is important to remind you that as part of the qualification for this study you have agreed to possible home visits by the clinic staff.

c) Enrollment and Follow-up Visits

The clinic staff will observe you for at least 30 to 60 minutes after the injection at the enrollment visit.

You will be asked to complete a diary card and look at your injection site in the evening on the day of the vaccination and then every day for the next 7 days. You will record your temperature, any symptoms, and describe any skin changes at the injection site each day. You will be provided with a thermometer to take your temperature and ruler to measure any injection-site skin changes. You may have to come to the clinic if you have a fever of 38.5˚C or higher that lasts more than 24 hours, a rash, hives, or difficulty in your usual daily activities (such as going to work, fixing a meal, laundry, etc.). You will be able to reach a study investigator at any time of day or night should you have any concerns.

If you develop any symptoms that are of concern to you or the study team, it may be necessary to come to the study clinic for an examination before your next scheduled visit. It is very important that you follow the instructions given to you by the clinic staff. You may also need to come to the clinic for any problem that the nurse or doctor thinks should be checked by exam, blood or other medical test.

At each visit, you will be checked for any health changes or problems since your last visit. You will be asked how you are feeling and what medications you may have taken. Blood will be drawn during clinic visits for testing of your health and your immune system.

The amount of blood drawn will vary from about 25 mL (about 5 teaspoons) to about 92 mL (6 tablespoons), depending on the visit. You might also be asked to have laboratory tests between regular visits if needed to check your health. The total amount of blood drawn during the 48 weeks of participation will be less than 700 mL (about 1.5 *tumpeco mugs*).

No more than a total of about one *tumpeco mug* (450 mL) will be drawn over any 3-month period during the study. Female participants will also have to give a urine sample for pregnancy test at some visits. You will be informed promptly if any health concerns are identified by the tests. You should avoid donating blood for at least one year after your study vaccination.

The study team will inform you of the results from your lab tests and medical examination at the next study visit. In cases where an abnormality may be of concern, the investigators will notify you as soon as possible. If any concerning abnormality is detected, you will be referred for appropriate testing, treatment and care as may be required.

d) Sample collection during the study

i. **Blood and urine specimens:** The investigators will obtain blood to test for any possible side effects as well as evaluate the immune response to the vaccine. Urine collected at study visits will be used for pregnancy tests for female volunteers.

ii. **HLA and genetic tests:** Part of the blood samples for this study will be used to analyze for HLA ('Human Leukocyte Antigen') type. HLA is a group of proteins present on the surface of all cells in the human body with an important role in the immune response to infection. Determining HLA type is necessary to be able to perform certain research studies. We will not notify you with the results of this test. The HLA test for this study is not a normal medical test and the test result will not be used for treatment purpose. You will be provided a separate form to consent or refuse genetic testing on your samples.

WHAT WILL HAPPEN TO MY SAMPLES AFTER THIS STUDY?

a) Sample Storage

During your participation in this study, blood samples will be collected from you as already explained. We will store left over blood samples in a secure central storage site (not in the clinic) in the USA for future research to learn more about Ebola virus, vaccines, the immune system, and/or other medical conditions. Only samples from participants who have provided consent for future use of their samples will be stored at the end of this study. If consent is not provided, the samples will be destroyed upon completion of tests for this study.

Please note that samples will only be transferred to another country after approval by the Uganda National Council of Science and Technology and your personal information will not be disclosed/ attached to these specimens (as described below).

b) Future Studies

You will have the opportunity to review, ask questions and provide consent (permission) for storage and use of your blood samples for future unknown use, in the "Future Use Blood Sample Consent Form." All future research that uses stored samples must be reviewed and approved by an Institutional Review Board (IRB), which is a committee that is responsible for overseeing the safety, welfare and rights of research participants.

c) Specimen Labeling

Specimens will be stored and labeled using a numeric barcode without your name attached. Only the site-investigator team is able to connect those numeric codes and your name. Personal Identification Information will be kept confidentially according to all applicable laws and regulations.

POSSIBLE RISKS OF STUDY PARTICIPATION

This section describes the risks associated with the experimental Ebola Sudan vaccine and other study procedures. There may be additional risks related to the experimental vaccine that are currently unknown. These unknown risks could affect you or, if applicable, your unborn child if you become pregnant. If the study investigators learn about new risks during this study, the study investigators will tell you.

Possible **risks from the injection:** Temporary stinging, pain, arm discomfort, redness, soreness, itchiness, swelling or bruising at the injection site on your arm. There is a very small chance of infection.

Possible **risks from any vaccine:** Fever, chills, rash, aches and pains, nausea, headache, dizziness, fatigue (feeling tired), and malaise (feeling unwell). Some people have allergic reactions to vaccines. These types of reactions are usually greatest within the first 24 hours after vaccination and may last 1 to 3 days.

Possible **risks of the experimental Ebola Sudan vaccine:** The risks of the experimental vaccine are unknown. The most common complaints in the first few days after receiving similar vaccines include sore arm, headache, muscle aches and feeling tired. A few people had a fever within a day after vaccination.

As with any vaccine, there may be a risk of skin rash, hives, or other unknown side effects. If you develop a reaction to the experimental vaccine on your skin, the investigators will take pictures of the reaction and the vaccine injection site. Every effort will be made to avoid photographing your face or any tattoos or birthmarks that may identify you in the photograph. Your name and other identifying information will not be associated with the photograph. All photographs will relate only to this study and will be the property of the sponsor.

There are currently no vaccines approved for use to protect against Ebola virus infection. Receipt of this experimental Ebola vaccine may affect your response to future vaccines against Ebola. It is unknown if you will develop an immune response, such as antibodies, after vaccination. It is unknown if your immune response would protect against EVD, have no effect on protection, or increase your risk of EVD. It is also unknown how long an immune response to the vaccine may last. You should continue to take all precautions against being exposed to body fluids of people who have an Ebola virus infection.

Unknown **safety risks:** There may be unknown side effects from the study vaccine – even serious or life-threatening risks – that we do not yet know about. Please tell the study staff about any side effect you think you are having as soon as possible. This is important for your safety.

Possible **risks of blood drawing:** Pain, bleeding, bruising, feeling lightheaded, fainting, or rarely, infection at the site where the blood is taken. To minimize the risks, trained health care providers will draw your blood.

Possible **risks from genetic testing:** Unintended release of information could be used by insurers or employers; discovering a gene that suggests risk of disease for you or your family; discovering undisclosed family relationships. To minimize the risks, results will only be labeled with a code, not your name or other identifying information.

Possible **risks to Pregnancy:** If you are pregnant, breast-feeding or want to become pregnant from 21 days before vaccination until 24 weeks (6 months) after the vaccination, you cannot participate in this study. We do not know the possible effects of the study vaccine on the unborn baby or nursing infant. Therefore, women who are able to become pregnant must have a negative pregnancy test before the study vaccination and agree to practice adequate birth control beginning at least 21 days prior to receiving the study injection until 24 weeks after the injection. Adequate methods of birth control include: condoms, male or female, with or without a spermicide; diaphragm or cervical cap with

spermicide; intrauterine device; all prescription methods (such as contraceptive pills, injections, patches and others); or a male partner who has previously undergone a vasectomy. You must notify the clinic staff immediately upon learning that you have become pregnant during this study. You must also notify the clinic if you suspect that you **might** be pregnant during this study. You will be asked to continue with the planned study follow-up visits for safety purposes and contacted later to learn about the outcome of any pregnancy that starts in the first 24 weeks after study vaccination.

Other **Risks:** You may not donate blood while participating in this research study or for one year after the date of the experimental vaccine injection.

Your samples will be shipped to collaborators outside of MUWRP to be analyzed. These samples will only be labeled with your study number, not your name or other personal information. Samples will only be shipped after approval from the MUWRP IRB.

WHAT IF THE RESEARCHERS LEARN NEW INFORMATION DURING THIS STUDY?

Results of this study or other scientific research may affect your willingness to continue to take part in this study. During the course of the study, you will be informed of any significant new findings (either good or bad), such as changes in the risks or benefits resulting from participation in the research or new alternatives to participation that might cause you to change your mind about continuing in the study. If new information is provided to you, your consent to continue participating in this study will be re-obtained.

BENEFITS FROM STUDY PARTICIPATION

You will receive no direct benefit from participating in this study because no one knows if the vaccine will work. However, you and others may benefit in the future from the information that will be learned from the study. The results of this study could play a role in whether the FDA will approve the vaccine for sale at some time in the future. You will not receive money or other compensation should this occur.

COMPENSATION FOR STUDY PARTICIPATION

You will be compensated Ug shs 50,000 for time and inconvenience associated with each scheduled visit and up to Ug shs 20,000 for each unscheduled visit. Unscheduled visits will be compensated only if the Principal Investigator/ designee finds it necessary. Other than medical care that may be provided and other payment specifically stated in this form, there is no other compensation available for you taking part in this study.

PERSONAL INFORMATION CONFIDENTIALITY

The Principal Investigator at this clinic, Dr. Betty Mwesigwa, will maintain research records of your taking part in this study.

All study volunteers will receive a study identification (SID) number. An SID is a unique number assigned to each participant, known only to the study team at the clinic and used to ensure the confidentiality of research information. All your study documents, samples and test results will not bear your name but will have your SID, the date, study number, group number and study visit number. Personal identifying information like your name and age collected at the time of enrollment will be

stored in a lockable cabinet to which only designated study team members will have access. These steps will ensure confidentiality of your personal information and minimize the chances of it becoming known to others.

Clinical and research records may be reviewed by representatives of the U.S. Army Medical Research and Development Command (USAMRDC), Office for Human Research Protections (OHRP), Human Research Protection Office (HRPO), U.S. DoD, WRAIR Human Subjects Protection Branch, Makerere University School of Public Health IRB, NIAID, the Uganda National Drug Authority (NDA), the Uganda National Council of Science and Technology, U.S. Food and Drug Administration, the Uganda Ministry of Health, and other agencies as part of their responsibilities for ensuring the protection of research volunteers. Representatives of all the above are bound by rules of confidentiality not to reveal your identity to others.

Complete confidentiality cannot be promised but every effort will be made to keep the records as confidential as possible within the limits of the law. All data and medical information obtained about you as an individual will be considered important and held in confidence.

Research and clinical information relating to you will be shared with other investigators and the scientific community through presentation or publication; however, you will not be identified by name or other personal information that could be used to identify you.

General clinical trial information will be kept in the database at the National Medical Library at the National Institutes of Health on http://www.clinicaltrials.gov. This website will not include information that can identify you. At most, the Web site will include a summary of the results.

SICKNESS OR INJURY AS A RESULT OF STUDY PARTICIPATION

If you get sick or injured due to the vaccination of this study, you will receive appropriate medical treatment and care until cure or stabilization as provided for by a limited fund (set aside for this study) and a clinical trials medical insurance policy for research-related injuries. While we anticipate the combination of the set-aside fund and the insurance policy is more than enough to pay for the costs associated with any study related injuries, there is a limit to the amount of coverage available. The study sponsor, MUWRP, and the U.S. DoD will not provide long-term medical care for stabilized research-related injuries.

The study team is responsible for the cost without using any personal health care package which belongs to the volunteer. MUWRP will pay costs up to the limit from set aside finds or through the insurance. However, you will not get any other compensation. You should discuss this thoroughly with the Principal Investigator or site clinicians before making a decision to participate in this study. If you have any questions about study-related sickness or injury, you can contact the following person:

Dr. Betty Mwesigwa
Makerere University Walter Reed Project
[redacted]
Kampala, Uganda
[redacted]

ENDING STUDY PARTICIPATION

You can choose not to participate or withdraw from the study at any time without any consequence to you. Although you may withdraw from the study at any time, the samples and data collected up to that time will be used in accordance with the protocol.

If you would like to withdraw from this study, please contact the Principal Investigator mentioned above. You will not lose any legal rights, including the rights for medical treatment and others if you withdraw from this study.

Although you may be willing to participate in the study, the investigators may not give you the vaccination if any of the following situations occur:

- Study is stopped.
- Study sponsors, the IRBs, the US FDA or the Uganda NDA request to terminate the study for unexpected reasons.
- You are unable to comply with the study requirements.
- You are not willing to have blood drawn although you are still willing to participate in other processes.
- You have a medical problem where continuing to be in the study would be harmful to you.
- Other incidents occurred and may be harmful to you if you continue being the study volunteer.

ALTERNATIVES

This study is not designed to treat any disease and no alternative currently exists. You may choose to not participate.

CONFLICT OF INTEREST STATEMENT

The NIH, including members of the VRC scientific staff, developed the experimental Ebola vaccine being used in this research study. The results of this study could play a role in whether the FDA will approve the vaccine for sale at some time in the future. If approved, the future sale of the vaccine could lead to payments to the NIH and to some of the NIH/VRC scientists. By US Law, government scientists are required to receive such payment for their inventions. Other participating investigators do not have a conflict of interest as a result of study participation. You will not receive money or other compensation should this occur. Please discuss with a study investigator any questions you may have about these issues. There is no conflict of interest with your doctors at this research site.

IF YOU NEED MORE INFORMATION OR HAVE ADDITIONAL QUESTIONS

If you have any question about this study or if you have any problems, you can contact the Principal Investigator Dr. Betty Mwesigwa at the research clinic on [redacted] or by telephone [redacted] or toll free on [redacted] or Immaculate Nakabuye on [redacted] or [redacted]

If you have any question and need to ask about your rights or you do not get appropriate treatment and care for sickness or injury which occur as a direct result of taking part in this study or the investigator does not treat you fairly in accordance with what is described in this consent form, you may make a complaint to the following bodies:

For information on

Regulatory questions	The Executive Secretary, at Uganda National Council of Science and Technology, [redacted] Kampala or on Tel number [redacted]
Human subject protection questions	Dr. Suzanne Kiwanuka at the Research and Ethics Committee, Makerere University School of Public Health, Mulago Hospital Complex or on [redacted]

Please keep a copy of this document in case you want to read it again.

STUDY VOLUNTEER STATEMENT

I have been asked to take part in RV 508, "A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of Two Doses of an Ebola Sudan Chimpanzee Adenovirus Vector Vaccine, VRC-EBOADC086-00-VP (cAd3-EBO S), in Healthy Adults".

The principal investigator Dr. Betty Mwesigwa or her representative has explained the significance of the testing, the duration of the study, the testing that I will undergo, the methods to be used, and the risks and dangers of participation. I have been given a chance to ask questions about this research study. All questions were answered to my satisfaction. If I have other questions about this research, I can ask: Dr. Betty Mwesigwa or Immaculate Nakabuye at the research clinic on [redacted] or by telephone [redacted] or toll free on [redacted]

I am signing below to indicate I wish to take part in this study, and my consent to follow the requirements of the study as much as possible. I will do my best to follow the recommendations of the study team, and I will report all problems occurring from this study to the study team. It has been explained to me that I can quit this study at any time, and I will not lose any benefits nor will I receive any penalty. If I decide to quit this study, I may be examined before leaving the study to ensure my good health. The medical care that I could receive as a result of sickness from being a part of this study have been explained to me and I have been offered a signed copy of this consent form.

I agree to participate in this study.

_____ _____

SIGNATURE OR MARK OF PARTICIPANT DATE

_____

PRINT NAME OF PARTICIPANT

_____ _____

SIGNATURE OF PERSON ADMINISTERING CONSENT DATE

_____

PRINT NAME OF PERSON ADMINISTERING CONSENT

APPENDIX 2B: FUTURE USE INFORMED CONSENT FORM

INFORMED CONSENT FOR FUTURE USE OF STORED SPECIMENS

Study Title: RV 508, "A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of Two Doses of an Ebola Sudan Chimpanzee Adenovirus Vector Vaccine, VRC-EBOADC086-00-VP (cAd3-EBO S), in Healthy Adults"

Sponsor: National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center (VRC)

Funding Agencies: NIH, the U.S. Military HIV Research Program (MHRP) and the U.S. Department of Defense (DoD)

Study Product Provided by: NIH/NIAID/VRC

Study Conducted by: Makerere University Walter Reed Project (MUWRP)

Principal Investigator: Betty Mwesigwa, MBChB, MSc Clinical Trials

During this study, you will be asked to provide blood. These blood samples will be stored for as long as possible and will be used according to your decision below. The blood samples will be stored in the United States (U.S.) for testing how your body fights Ebola infection and other future studies that we do not know about at this time. Some of the tests that may be conducted on your stored samples may not be developed yet, so the investigators cannot tell you all the tests that may be performed in the future.

There is a chance that the blood samples you are donating under this study may be used in other research studies and may have some commercial value. Your samples will not be sold or used directly to produce commercial products.

Should your donated sample(s) lead to the development of a commercial product, the study sponsor and inventor will own it and may take action to patent and license the product. Neither the sponsor nor the inventor intend to provide you with any compensation for your blood samples provided in this study, nor for any future value that the sample you have given may be found to have.

The blood samples will not be stored with any personal information. Your stored samples will be labeled by a code (such as a number) that only the study team can link to you. All personal information will be stored by the study investigator at the study site. Any identifying information about you will be kept confidential to the extent permitted by law.

You will not receive the results of future studies or future genetic tests involving your stored blood samples. The results of genetic tests will be for research purposes only. The genetic tests are not used in medical practice and have not been approved for use in making health care decisions.

Future Research on Your Samples Will Be Related to Ebola or Vaccines

Researchers are able to measure how the immune system responds by looking at blood samples. We will try to understand why Ebola disease progresses differently in some people. As new methods (or ways) of measuring the body's immune response to Ebola are made in the laboratory, we would like to test these methods on the samples we have already collected from you. We also know that sometimes genes,

passed down from your parents, can be important to a person's immune response to Ebola. Because of this, we may do genetic testing on your stored samples. We may use methods that have not been developed yet, so we cannot describe them to you now. We will only use your stored samples to learn more about how the immune system responds to Ebola and how vaccines can prevent Ebola infection.

Your Samples Used for Future Research Will Be Shipped to the USA

Your samples will be stored in a secure central storage site (not in the clinic) in the USA. The samples will not be labeled with your name, only with your Study Identification (SID) number. There is no time limit on how long your samples will be stored.

Your Privacy Will Be Protected

We will protect your privacy with any future research testing of your samples, just like we do with all research information from you during the main study. The samples will not be labeled with your name. Instead, they will have your study code. After this study ends, when the samples are requested for future research, the study code stays with them, or in some cases, it is removed before the samples are sent to be used, if this information is not necessary for the study.

An Institutional Review Board/Independent Ethics Committee Will Review Any Future Research on Your Samples

An IRB/Independent Ethics Committee, which is responsible for overseeing the safety, welfare and rights of research participants, must review and approve each research study that intends to use your samples in future studies.

There Will Be No Benefit to You If You Allow Us to Store Your Samples For Future Research

The researchers will not contact you or your health care provider with results from future studies or future genetic tests that use your samples. This is because the use of the samples is for research and the tests have not been approved for use in making health care decisions.

Your samples may contribute to a new invention or discovery. There is no plan for you to share any money or other benefits resulting from this invention or discovery.

There Are Few Risks Related to Storing Your Samples

When tests are done on the stored samples there is a small but possible risk to your privacy. It is possible that if others found out information about you that is learned from tests (such as information about your genes) it could cause you problems with your family (e.g., having a family member learn about a disease that may be passed on in families or learning who is the true parent of a child) or problems getting a job or insurance. The risk of this happening is extremely low, because your results will not be a part of your medical record and will not be given to the clinic. Also, it is possible that your SID could be removed from the samples. If your SID number is removed from any samples, we will not be able to link that sample to you.

You Can Agree Now to Let Us Use Your Samples For Future Testing and Still Change Your Mind Later

If you agree now, but decide later that you do not want us to use your samples for future research, please tell us. We will ask the storage facility to destroy any remaining samples that still have your SID on them so that they cannot be used for future research.

For More Information:

If you have questions about the use of your samples for future research, contact Dr. Betty Mwesigwa on [redacted] or toll free on [redacted]

If you have a problem that you think may be related to the use of your samples for future research, or if you want to withdraw your consent, contact Immaculate Nakabuye on [redacted]

If you have questions about your rights as a research participant, or problems or concerns about how you are being treated in this study, you may contact [redacted] the Research and Ethics Committee, Makerere University School of Public Health, Mulago Hospital Complex or o[redacted]

Once you have read this form and have had all of your questions satisfactorily answered, please initial and check the box next to your choice of whether or not you consent to have your blood samples stored for future testing, and then sign in the space provided below.

_____ ☐ I allow you to store and use my samples for future testing which may include genetic testing.
initials

_____ ☐ I **do not** allow you to store and use my samples for future testing.
initials

_____ _____
SIGNATURE OR MARK OF PARTICIPANT DATE

_____
PRINT NAME OF PARTICIPANT

_____ _____
SIGNATURE OF PERSON ADMINISTERING CONSENT DATE

_____
PRINT NAME OF PERSON ADMINISTERING CONSENT

APPENDIX 2C: INFORMED CONSENT FOR GENETIC TESTING

INFORMED CONSENT FOR GENETIC TESTING

Study Title: RV 508, "A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of Two Doses of an Ebola Sudan Chimpanzee Adenovirus Vector Vaccine, VRC-EBOADC086-00-VP (cAd3-EBO S), in Healthy Adults"

Sponsor: National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center (VRC)

Funding Agencies: NIH, the U.S. Military HIV Research Program (MHRP) and the U.S. Department of Defense (DoD)

Study Product Provided by: NIH/NIAID/VRC

Study Conducted by: Makerere University Walter Reed Project (MUWRP)

Principal Investigator: Betty Mwesigwa, MBChB, MSc Clinical Trials

As we told you in the main informed consent form for this study and in the consent form for storage of samples for future use, we will do some testing of your blood. Some of the testing that we will do will be genetic testing. This consent form tells you everything we know now about genetic testing using your blood samples.

You can decide whether or not to let us use your blood for genetic tests. Your decision does not affect your participation in the study or any care you receive at this clinic. If you decide to allow us to use your blood samples for genetic tests, we will ask you to sign this form. You will get a copy of the form to keep.

Your Blood Sample Is a Potential Source of Genetic Information

Researchers are able to measure how the immune system responds by looking at blood. We will try to understand why Ebola and other diseases affected by Ebola progress differently in some people and why some people are more likely to become infected than others. We know that sometimes genes, passed down from your parents, can be important to a person's immune response to Ebola. Because of this, we would like to do genetic testing on your blood samples. We will only perform genetic testing to learn more about how the immune system responds to Ebola and to other diseases affected by Ebola.

HLA and Genetic Testing: Some of the blood drawn from you, as part of this study will be used for a test called HLA type. HLA stands for 'Human Leukocyte Antigen', a group of proteins present on the surface of all cells on the human body and help the body's immune system respond to foreign, harmful substances. For research, HLA testing is used to try to identify factors associated with response to a vaccine, progression of a disease or related conditions. Determining HLA type is necessary to be able to perform certain research studies.

We will **not** notify you of the results of any genetic test. The genetic research tests we plan to conduct are not currently used in medical practice and have not been approved for use in making health care decisions.

Your Samples Used For Genetic Testing Will Be Shipped to the USA

In order to complete the genetic testing on your blood samples, they will be shipped and stored in the United States. There is no time limit on how long your samples will be stored.

Your Privacy Will Be Protected

We will protect your privacy with any genetic testing of your blood samples, just like we do with all research information from you during the study. The blood samples will not be labeled with your name. Instead, they will have your study identification (SID) number only. If your samples are sent outside Uganda, the SID number stays with them. Your genetic test results will only be connected to you by the SID number, known only to the study team, and not by your name or other personal information.

There Will Be No Benefit to You If You Allow Us to Use Your Samples For Genetic Testing

The researchers will not contact you or your health care provider with results from the genetic testing using your blood. This is because the use of the samples is for research and the tests have not been approved for use in making health care decisions.

Your samples may contribute to a new invention or discovery. There is no plan for you to share any money or other benefits resulting from this invention or discovery.

There Are Few Risks Related to Genetic Testing of Your Samples

Risk of genetic tests and HLA testing: The greatest risk associated with genetic testing is to your privacy. Genetic test results can be used to provide information about how susceptible you are to certain diseases. Used inappropriately, this information could be discriminatory (for example, by insurance companies). HLA typing can also be used to determine who the true parent of a child is (if compared to the child's HLA type). However, the risk of this happening is extremely low, because your results will not be part of your medical records and will not be provided to the clinic.

The blood samples that you provide will only be used to provide study investigators information about your immune system. The results will be coded to protect your identity. Your HLA (and other genetic tests) can only be connected to you by the coded study number and not by your name or other personal information. Neither you nor your doctor will be given the results of the tests.

For More Information:

If you have questions about the use of your samples for genetic testing, contact Dr. Betty Mwesigwa on [redacted] or toll free on [redacted]

If you have a problem that you think may be related to the use of your samples for genetic testing, or if you want to withdraw your consent, contact Immaculate Nakabuye on [redacted]

If you have questions about your rights as a research participant, or problems or concerns about how you are being treated in this study, you may contact [redacted] the Research and Ethics Committee, Makerere University School of Public Health, Mulago Hospital Complex or [redacted]

Once you have read this form and have had all your questions satisfactorily answered, please initial and check the box next to your choice of whether or not you consent to have your blood samples used for genetic testing, and then sign in the space provided below.

_____ ☐ I allow you to use my samples for genetic testing.
initials

_____ ☐ I **do not** allow you to do genetic testing on my samples.
initials

_____ _____
SIGNATURE OR MARK OF PARTICIPANT DATE

_____
PRINT NAME OF PARTICIPANT

_____ _____
SIGNATURE OF PERSON ADMINISTERING CONSENT DATE

_____
PRINT NAME OF PERSON ADMINISTERING CONSENT

APPENDIX 2D: WITHDRAWAL OF CONSENT FOR SAMPLE STORAGE

WITHDRAWAL OF CONSENT FOR SAMPLE STORAGE

Study Title: RV 508, "A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of Two Doses of an Ebola Sudan Chimpanzee Adenovirus Vector Vaccine, VRC-EBOADC086-00-VP (cAd3-EBO S), in Healthy Adults"

Sponsor: National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center (VRC)

Funding Agencies: NIH, the U.S. Military HIV Research Program (MHRP) and the U.S. Department of Defense (DoD)

Study Product Provided by: NIH/NIAID/VRC

Study Conducted by: Makerere University Walter Reed Project (MUWRP)

Principal Investigator: Betty Mwesigwa, MBChB, MSc Clinical Trials

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Volunteer Statement of withdraw of consent to have samples stored for future testing:

I _____ withdraw my consent to have my samples stored for future use. I do not want to donate blood samples for storage and future use. However, I would still like to continue taking part in the main study. It has been explained to me that when I sign at the bottom of this form, my samples will be used for all the tests specified for this present study, but no blood will be stored for future use.

It has been explained to me that withdrawing my consent to have my samples stored for future use will not make any difference to the care I am receiving now or in the future, or to any benefits that I am entitled to.

I have been given a chance to ask all the questions that I have about withdrawing my consent to have my samples stored. All of my questions were answered to my satisfaction. I was offered a signed copy of this consent.

_____ _____
SIGNATURE OR MARK OF PARTICIPANT DATE

_____
PRINT NAME OF PARTICIPANT

_____ _____
SIGNATURE OF PERSON ADMINISTERING CONSENT DATE

_____
PRINT NAME OF PERSON ADMINISTERING CONSENT

APPENDIX 3: VOLUNTEER EVENT SCHEDULE

Volunteer Event Schedule

Study Day Timeline	Visit ID	Procedures	Compensation	Scheduled Date
-56 to 0 days pre-vaccination	**Visit # 1** ***Screening Visit*** **(2 to 3 hours)**	• Informed Consent Process • Assessment of Understanding • Physical Exam, Weight, Height, Vitals • Complete Medical History • HIV Counseling and test • Syphilis test • Blood draw • Urine collection • Pregnancy test, if female	UG SHS 50,000	
Week 0 **Day 0**	**Visit # 2** **Enrollment and Vaccination** **(2 to 3 hours)**	• Physical Exam (as required) • Updating medical history and assessments • Vaccination • Discuss Diary Card (to be completed in the evening) • Blood draw • Females: Pregnancy test & counseling	UG SHS 50,000	
Week 1 **1 day post-vaccination** (+ 1 day)	**Visit # 2A** **(5 minutes)**	• Phone contact with clinic, clinic visit if necessary	UG SHS 20,000 if clinic visit is requested by study doctor	
Week 1 **3 days post-vaccination** (+ 2 days)	**Visit # 2B** **(30 minutes)**	• Physical Exam (as required) • Updating medical history and assessments • Blood draw • Diary Card review	UG SHS 50,000	
Week 1 **7 days post-vaccination** (+ 3 days)	**Visit # 2C** **(30 minutes)**	• Physical Exam (as required) • Updating medical history and assessments • Blood draw • Diary Card review	UG SHS 50,000	

Study Day Timeline	Visit ID	Procedures	Compensation	Scheduled Date
Week 2 **14 days post-vaccination** (± 3 days)	**Visit # 2D** **(30 minutes)**	• Physical Exam (as required) • Updating medical history and assessments • Blood draw • Females: pregnancy prevention counseling	UG SHS 50,000	
Week 4 (± 7 days)	**Visit # 3** **(30 minutes)**	• Physical Exam (as required) • Updating medical history and assessments • Blood draw • Urine collection • Females: Pregnancy test & counseling	UG SHS 50,000	
Week 8 (± 7 days)	**Visit # 4** **(30 minutes)**	• Physical Exam (as required) • Updating medical history and assessments • Blood draw • Females: pregnancy prevention counseling	UG SHS 50,000	
Week 16 (± 14 days)	**Visit # 5** **(30 minutes)**	• Physical Exam (as required) • Updating medical history and assessments • Blood draw • Females: pregnancy prevention counseling	UG SHS 50,000	
Week 24 (± 14 days)	**Visit # 6** **(30 minutes)**	• Physical Exam (as required) • Updating medical history and assessments • Blood draw • Urine collection • Pregnancy test, if female	UG SHS 50,000	
Week 48 (± 14 days)	**Visit # 7** **(30 minutes)**	• Physical Exam (as required) • Updating medical history and assessments • Blood draw	UG SHS 50,000	

APPENDIX 4: ASSESSMENT OF UNDERSTANDING

ASSESSMENT OF UNDERSTANDING

Please read each question and answer whether the statement is **True** or **False**.

True ☐	False ☐	1.	The main purpose of the study is to see if the experimental vaccine is safe.
True ☐	False ☐	2.	The vaccine in this study will definitely protect me against Ebola.
True ☐	False ☐	3.	I will be able to choose which dose of the vaccine I receive.
True ☐	False ☐	4.	There will be no direct benefit to me for participating in the study.
True ☐	False ☐	5.	I may leave the study at any time.
True ☐	False ☐	6.	Participation in the study will last for approximately 48 weeks (11 months).
True ☐	False ☐	7.	If I give permission, samples of my blood will be collected and stored in a research laboratory and may be used for future research studies.
True ☐	False ☐	8.	Women participating in the study must use effective birth control 21 days prior to receiving the vaccine through 24 weeks (6 months) after study vaccination.
True ☐	False ☐	9.	There is a possibility that I can become infected with Ebola from the study vaccine.
True ☐	False ☐	10.	I will be asked to keep a detailed diary of possible side effects for seven days after vaccination.

ASSESSMENT OF UNDERSTANDING ANSWER KEY

Please read each question and answer whether the statement is **True** or **False**.

True ☒	False ☐	1.	The main purpose of the study is to see if the experimental vaccine is safe.
True ☐	False ☒	2.	The vaccine in this study will definitely protect me against Ebola.
True ☐	False ☒	3.	I will be able to choose which dose of the vaccine I receive.
True ☒	False ☐	4.	There will be no direct benefit to me for participating in the study.
True ☒	False ☐	5.	I may leave the study at any time.
True ☒	False ☐	6.	Participation in the study will last for approximately 48 weeks (11 months).
True ☒	False ☐	7.	If I give permission, samples of my blood will be collected and stored in a research laboratory and may be used for future research studies.
True ☒	False ☐	8.	Women participating in the study must use effective birth control 21 days prior to receiving the vaccine through 24 weeks (6 months) after study vaccination.
True ☐	False ☒	9.	There is a possibility that I can become infected with Ebola from the study vaccine.
True ☒	False ☐	10.	I will be asked to keep a detailed diary of possible side effects for seven days after vaccination.

APPENDIX 5: BRIEFING SLIDES

A Presentation By:

Join Hands with Makerere University-Walter Reed Project
in Consultation with
The National Institutes of Health, Vaccine Research Center and the
United States Military HIV Research Program **to Develop an Ebola Vaccine**

Basic Information:

Study Title: "A Phase 1 Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of Two Doses of an Ebola Sudan Chimpanzee Adenovirus Vector Vaccine, VRC-EBOADC086-00-VP (cAd3-EBO S), in Healthy Adults"

Study Location: Makerere University-Walter Reed Project (MUWRP)

Principal Investigator: Betty Mwesigwa, MBChB, MSc in Clinical Trials

Purpose of this Presentation

To provide you with detailed information about:

- The Ebola vaccine study
- Risks and benefits associated with the study
- Who may and may not participate
- The study visits
- The study procedures
- Your rights as a participant

The Objectives of this Study

- The study will evaluate the following for this vaccine:
  - Safety (Is it safe in human beings?)
  - Tolerability (Can you easily endure the side effects?)
  - Immune responses
    - Immune responses are the ways your body recognizes and defends itself against bacteria, viruses, or anything that appears harmful to the body.

What Vaccine is Being Tested?

- The investigational Ebola vaccine being tested in this study is called VRC-EBOADC086-00-VP and is referred to as "cAd3-EBO S"
- This experimental vaccine was developed by the US National Institute of Health (NIH) and the Vaccine Research Center (VRC).

Potential Risks and Discomforts

General Injection Risks

You may get some side effects after vaccination:

- Stinging, itching, arm discomfort, injection site pain, soreness, tenderness and/redness, hardness, bruising and swelling at the site of injection. There is a very small chance of infection.
- *These reactions may occur with all types of injections.*

Potential Risks and Discomforts

General Vaccination Risks

- Also possible that you could get a fever, chills, rash, general itching, aches and pains, muscle pain, joint pain, vomiting, nausea, headache, dizziness, fatigue (feeling tired), and malaise (feeling unwell)
- Most side effects usually do not last very long (48-72 hrs) and do not require treatment.
- *You may take medications to help with pain control and inflammation after the injection, but please report their use to the study staff*
- It is rare, but you could have an allergic reaction to a vaccine, including a rash, hives, or difficulty breathing
- Some **allergic reactions can be life-threatening** therefore, you will need to stay at the clinic, where the staff will watch you for 30 to 60 minutes after the injection and you may need to stay longer if the study doctor thinks it is best for you

Potential Risks and Discomforts

Experimental Vaccine Risks

- There may be unknown risks with the use of the vaccine
- The most common complaints in the first few days after receiving similar vaccines include sore arm, headache, muscle aches, and feeling tired. A few people had a fever within a day after vaccination
- Receiving the vaccine does NOT mean you are protected against Ebola and you SHOULD continue to follow all recommended precautions against Ebola

Potential Risks and Discomforts

Other Risks, Hazards and Discomforts

- Drawing blood may cause pain and bruising, light-headedness or fainting and rarely, infection at the site where blood is drawn
- You may not donate blood while participating in this study or for one year after receiving the experimental vaccine
- An accidental release of genetic testing results could provide information that may be used against you, however to minimize this risk the results will only be labeled with a code, not your name or other identifying information

Potential Risks and Discomforts

Unknown Risks to Pregnancy and Fetus

- The risk to pregnant women, fetuses, and infants is unknown, therefore women who are pregnant, breast-feeding, or plan to become pregnant within 24 weeks (6 months) of receiving the vaccine cannot participate in the study
- Women who are capable of becoming pregnant will undergo pregnancy testing during the study and must agree to use adequate methods of birth control beginning 21 days prior to receiving the study vaccine until 24 weeks (6 months) after receiving the study vaccine

Potential Risks and Discomforts

Unknown Risks to Pregnancy and Fetus (continued)

- Adequate methods of birth control include:
  - Condoms (male or female), with or without a spermicide
  - Diaphragm or cervical cap with spermicide
  - Intrauterine device
  - All prescription methods (such as contraceptive pills, injections, patches and others)
  - A male partner who has previously undergone a vasectomy
- Should you become pregnant while enrolled in this study, you will not receive the vaccination
  - You will be followed up for your and your baby's safety

Safeguards

- You will be closely monitored by the study team.
- Blood tests will be conducted regularly throughout the study in order to detect any unforeseen or adverse reactions.
- You will be asked to return to the clinic for lab abnormalities or other concerns.

Benefits

There is no direct benefit to you by being in this study, (*we do not know if the study vaccine will work against Ebola infection*) however:

- You may learn more about your health,
- You and others may benefit in the future from the information that will be learned from the study. *The results of this study could play a role in future vaccine development.*

Who Can Participate in the Study?

You can participate if you:

- Are a man or woman between the ages of 18 and 50 years old
- Are available and willing to participate for the duration of the study visits and follow-up (48 weeks)
- Are healthy in the investigator's clinical judgment (lab test, exam, etc)
- Are able to provide proof of identity to the statisfaction of the investigator
- Are able and willing to provide fingerprints and have photographs taken including injection site photographs
- Are willing and able to provide informed consent
- Have reliable means to be contacted (for example a cell phone or through home visit)
- Are HIV negative
- Are not pregnant
- (If female and able to become pregnant) agree to use contraception from 21 days before vaccination to 24 weeks after vaccination

Who Cannot Participate in the Study?

You cannot participate if you:

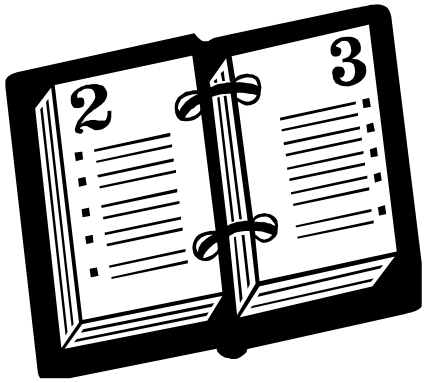
- Have received any other Ebola or Marburg vaccine, or cAd3-based vaccine in the past
- Have a bleeding problem or disorder
- Have an active syphilis infection
- Have an autoimmune disease or immunodeficiency
- Have diabetes (type I or II)
- Have thyroid disease that is not well controlled
- Have high blood pressure or asthma that is not well controlled
- Have cancer that is active, currently being treated, or not surgically cured
- Have a history of seizures
- Have a history of serious allergic reaction (anaphylaxis) to any vaccines or allergic reaction to drugs like gentamycin, neomycin or streptomycin

Who Cannot Participate in the Study?

You cannot participate if you (continued):

- Are pregnant, breastfeeding, or plan to become pregnant for 24 weeks after receiving the vaccine
- Have a history of clinically significant condition(s) that might interfere with participation or that may impair your ability to provide informed consent
- Have received any of the following:
  - Drugs that may modify your immune system within 14 days prior to enrollment e.g. Prednisolone or dexamethasone
  - Blood products within 112 days (16 weeks) prior to enrollment
  - Any "live-attenuated" vaccine (e.g. oral polio, yellow fever, measles, etc.) within 28 days prior to enrollment in the present study or any other vaccine within 14 days prior to enrollment
  - Experimental research drugs or vaccines within 28 days prior to enrollment in the present study
  - Drugs for treating or preventing Tuberculosis

The Study



Overall Study Design

- Phase I open-label, dose-escalation clinical trial
- Sponsored by the US NIH/NIAID/VRC in collaboration with the MHRP
- A total of 40 volunteers will be enrolled from Kampala, Uganda
  - 20 volunteers will receive a low dose of vaccine
  - 20 volunteers will receive a higher dose of vaccine

Group	Participants	Dose
1	20	cAd3-EBO S at 1 x 10^{10} PU IM
2	20	cAd3-EBO S at 1 x 10^{11} PU IM

- Interim safety reviews will be conducted throughout the study to ensure the safety of participants
- Once enrollment is completed for Group 1 and no safety issues are identified, enrollment into Group 2 will begin

Study Visit Procedures

Screening Visit

- You will review and voluntarily sign a consent form
- Your understanding of the study will be determined by you completing and passing an Assessment of Understanding.
- The study doctor will take your medical history and perform a physical exam
- Blood and urine samples will be taken to test your general health including testing for HIV and urine for pregnancy.

Study Visit Procedures

- If you are healthy and do not have any condition which prevents you from taking part in the study, based upon the screening visit, you will be asked to return to the clinic for a review of your laboratory and HIV results.
  - If the results of your screening medical evaluation identify a problem which prevents you from participating in the study, you will be referred to a health care provider, if needed.
- If you are eligible and still willing to participate, you will receive the vaccination at the second visit

Study Visit Procedures

- At every visit you will have blood drawn from a vein in your arm, ranging from a volume of about 25 mL (about 5 teaspoons) to about 92 mL (about 6 tablespoons)
- Over the whole study, the amount of blood that you will give is less than 700 mL (about 1.5 *tumpeco* mugs)
- You will not have more than 450 mL of blood drawn over any 3-month period during the study

Study Visit Procedures

Vaccination Day

- If you are eligible and willing to participate, you will receive the vaccination at visit 2
- The vaccination will be given (by needle & syringe) into the upper arm as a 1 mL dose of the experimental Ebola vaccine
- On the vaccination day, you will be in the clinic for about **2 – 3** hours and will be required to remain at the clinic for 30 to 60 minutes after vaccination (or longer if the study investigator thinks it's necessary)
- Should you develop any symptoms that are of concern to you or to the study team, you will be asked to return to the clinic

Study Visit Procedures

After the Vaccination

- You will be asked to complete a diary card at home in the evening on the day of vaccination and about the same time for the next seven (7) days
- You will return to the clinic 3 days after the vaccination, but the study team will contact you 1 day after the vaccination to see how you feel

Study Visit Procedures

Follow-Up Visits

- You will have 8 scheduled clinic visits after vaccination
- During each scheduled visit, the doctor will perform a brief medical history and physical exam, and remind you about contraception.
- Blood will be collected for routine laboratory safety studies and to identify the body's responses to the vaccine
- Remember: You can report any symptoms, problems or concerns you have to the study team **at any time!**

Your Rights as a Study Volunteer

Confidentiality

- All volunteers will be assigned study numbers that are known only to the investigators
- All research samples, lab results and study records will be identified by a study number and not by your name.
- All documents which bear your name will be securely locked in a cabinet, in a locked room with restricted access.
- Your study documents may be accessed by representatives of IRBs, the Sponsor and regulatory bodies e.g. NDA, UNCST

Ending Participation

Your participation may end for the following reasons:

- Decision by the investigator:
  - For safety reasons
  - Repeated failure to comply with instructions
- Decision by the sponsor or investigator to stop or cancel the study
- Decision by local regulatory authorities (NDA/ UNCST) and IRB (MUSPH) to stop or cancel the study
- You decide to withdrawal your consent

Compensation

- For taking part in this study you will receive 50,000 Ushs after each scheduled visit to compensate you for your time, transportation and inconveniences
- 20,000 Ushs for unscheduled visits to address safety concerns. Compensation for unscheduled visits will be at the investigator's discretion

Medical Care for Injury or Illness

- Should you be injured as a direct result of taking part in this research project, you will be provided medical care, at no cost to you until complete cure or stabilization of the research related injury
- You will not receive any compensation for injury and will not be asked to waive your legal rights
- You should discuss this issue thoroughly with the principal investigator before you enroll in this study

Final Reminders

- If you are pregnant or plan to become pregnant during the study, you will not be able to participate
- Your participation in the trial is completely voluntary and you may withdraw at any time for any reason
  - Your decision not to participate in the study, or a decision on your part to withdraw from the study will have no effect whatsoever on your healthcare and employment status
  - You may refuse to participate or you may withdraw from the study at any time without penalty or prejudice
- Close communication with study staff is key for your safety

QUESTIONS……CONCERNS

Site contacts

Principal Investigator: Dr. Betty Mwesigwa

[redacted]

Study Coordinator: Immaculate Nakabuye

[redacted]

Telephone: [redacted]

Website: www.muwrp.org

Additional contacts

Makerere University School of Public Health IRB: 0393 291397

Uganda National Council of Science and Technology: 0414-705525

National Drug Authority, Drug Information Department: 0414-255665

APPENDIX 6: GRADING SEVERITY OF ADVERSE EVENTS

FDA Guidance for Industry (September 2007): "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"

Modification to the FDA AE Grading Table
Individuals of African descent have lower neutrophil counts than individuals of other ethnicities. A study evaluating the reasons for ineligibility in phase I and II HIV vaccine trials in East Africa found that approximately one third of subjects were excluded because of neutropenia. The phase I and II studies used normal ranges from U.S. populations, not from African populations. If neutrophil ranges from East/South Africa populations were used instead, over one half of the subjects excluded because of hematologic abnormalities could have been included (ref.). Since this study will be conducted in part in East Africa, we will use the normal neutrophil range from East/South Africa (1.0 – 5.3 x 103 cells/ul, (ref.) for subjects in Uganda or other subjects of African descent. Grades for absolute neutrophil count in these subjects will be as follows:

	Grade 1	Grade 2	Grade 3	Grade 4
Absolute Neutrophil Count (cells/ul)	750 – 999	500 – 749	250 – 499	< 250

For other subjects, the usual FDA AE grading scale will be used as follows:

	Grade 1	Grade 2	Grade 3	Grade 4
Absolute Neutrophil Count (cells/ul)	–1,500 – 2,000	1,000-1,499	500 - 999	< 500

Assessment of Causality Relationship of an Adverse Event (AE) to Study Vaccine:

The relationship between an AE and the vaccine will be assessed by the investigator on the basis of his or her clinical judgment and the definitions below.

- **Definitely Related**. The AE and administration of study agent are related in time, and a direct association can be demonstrated.
- **Probably Related**. The AE and administration of study agent are reasonably related in time, and the AE is more likely explained by study agent than other causes.
- **Possibly Related**. The AE and administration of study agent are reasonably related in time, but the AE can be explained equally well by causes other than study agent.
- **Not Related**. There is not a reasonable possibility that the AE is related to the study agent.

For purposes of preparing data reports in which AE attributions are limited to "**Related**" or "**Not Related**", in this protocol, the "Definitely, Probably and Possibly" attributions will be mapped to the "Related" category. The definitions that apply when these two categories alone are used are as follows:

- **Related** – There is a reasonable possibility that the AE may be related to the study agent.
- **Not Related** – There is not a reasonable possibility that the AE is related to the study agent.

Grading the Severity of Adverse Events:
The FDA Guidance for Industry (September 2007): "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" is the basis for the severity grading of adverse events in this protocol. Several modifications were made to the table as follows:

- "Emergency room visit" is not automatically considered a life-threatening event; these words have been removed from any "grade 4' definition where they appear in the table copied from the guidance document.
- Any laboratory value shown as a "graded" value in the table that is within the institutional normal range will not be severity graded or recorded as an adverse event.
- Severity grading for hemoglobin decrease on the basis of the magnitude of decrease from baseline is not applicable at the grade 1 level; only absolute hemoglobin will be used to define grade 1. Increases in hemoglobin are AEs only for values above the upper limit of normal and are graded by the systemic illness clinical criteria.
- Severity grading definition for Grade 4 local reaction to injectable product (Erythema/Redness and Induration/Swelling) includes added text "requiring medical attention".
- 1 X ULN was removed from the definition for PT increase.
- Severity grading definition for hypotension includes added clarifications such that an asymptomatic low blood pressure reading is not an adverse event.
- Severity grading for neutropenia is provided for subjects of African descent based on normal ranges observed.

When not otherwise specified in the table, the following guidance will be used to assign a severity grade:

Grade 1 (Mild): No effect on activities of daily living
Grade 2 (Moderate): Some interference with activity not requiring medical intervention
Grade 3 (Severe): Prevents daily activity and requires medical intervention
Grade 4 (Potentially Life-threatening): Hospitalization; immediate medical intervention or therapy required to prevent death.
Grade 5 (Death): Death is assigned a Grade 5 severity.
Only the single adverse event that is assessed as the primary cause of death should be assigned "grade 5" severity.

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials
Modified from FDA Guidance - September 2007

A. Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Hospitalization
[1]Erythema/Redness	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis requiring medical attention
[2] Induration/Swelling	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis requiring medical attention
[3] Vital Signs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
[4] Fever (°C) (°F)	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	Hospitalization for arrhythmia
[5] Bradycardia - beats per Minute	50 – 54	45 – 49	< 45	Hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	Hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	Hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89 and symptomatic	80 – 84 and symptomatic and requiring oral fluids	< 80 and symptomatic and requiring IV fluids	Hospitalization for hypotensive shock
[6] Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

1. In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
2. Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.
3. Subject should be at rest for all vital sign measurements.
4. Oral temperature; no recent hot or cold beverages or smoking.
5. When resting heart rate is between 60 – 100 beats per minute, use clinical judgment when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.
6. When resting respiratory rate is greater than or equal to 17, use clinical judgment when characterizing tachypnea among healthy subject populations and consider baseline respiratory rate, relevant local normal values and other influences (e.g. elevation).

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	Hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	Hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	Hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	Hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	Hospitalization

Systemic Illness	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Hospitalization

B. Tables for Laboratory Abnormalities

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	100 – 110 110 – 125	111 – 125 126 – 200	>125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25–1.5 xULN**	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
**ULN" is the upper limit of the normal range.

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) decrease from baseline value - gm/dL	not applicable	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) decrease from baseline value – gm/dL	not applicable	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease – cell/mm^3-African descent	750-999	500-749	250-499	<250
Not of African descent	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.10 – 1.20 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
**ULN" is the upper limit of the normal range.

APPENDIX 7: DAIDS TABLE FOR GRADING SEVERITY OF ARTHRALGIA ADVERSE EVENTS

The following excerpt from the DAIDS AE Grading Table Corrected (Version 2.1-July 2017) will be used to grade reported events of joint pain (arthralgia). Solicited AEs involving arthralgias will be graded using the arthralgia criteria whereas unsolicited AEs involving arthralgias will be graded using the appropriate row based on the presence of symptoms.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis (objective findings on PE corresponding to the joint pain)	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions

APPENDIX 9: ROLES AND RESPONSIBILITIES

Principal Investigator

The PI is responsible for the conduct of the RV 508 study at MUWRP. This is the person designated as taking overall responsibility within the team of researchers for the conduct and reporting of the RV 508 study. The PI will help prepare study reports and article(s) for publication in collaboration with the protocol team. In addition, the PI is responsible for the day-to-day running of the research project.

The PI is responsible for ensuring that:

- The dignity, rights, safety and well-being of participants are given priority at all times.
- The study has obtained IRB approval prior to commencement
- All necessary submissions are made to the local IRB, as applicable
- The study will be conducted by the PI personally and/or members of his/her research team
- Each member of the research team, including PI, who has direct involvement with research participants and/or person-identifiable data, has completed all required training
- Procedures are in place to ensure collection of high quality, accurate data
- Serious Adverse Events and unanticipated problems will be reported to the required IRBs and PSRT
- Accurate records will be maintained and made available as required
- Continuing Review Reporting requirements are completed
- Counseling occurs for participants on HIV and pregnancy
- The consenting of participants is done correctly and prior to any study procedures

Associate Investigators

To act for the PI when the latter is unable to discharge their responsibilities owing to travel, leave, deployment, or other extenuating circumstances.

To assist the PI in all aspects of protocol execution.

Study Pharmacist

- Responsible for administering, dispensing, and accountability of study drug; assessment and management of adverse events; and review of arising data queries.

Laboratory Investigator

- Laboratory Investigator supervises clinical (CAP certified) and research laboratory activities for the study.
- Laboratory investigators will not have contact with study participants or personal identifiers and agree not to attempt to obtain any individually identifiable participant data

DoD Research Monitor

The DoD Research Monitor may perform oversight functions (e.g. observe recruitment, enrollment procedures, and the consent process for participants; oversee study interventions and interactions; review monitoring plans and UPIRTSO reports; oversee data collection, and analysis) and report their observations and findings to the IRB. The DoD research monitor may discuss the research protocol with the investigators, interview participants, and consult with others outside of the study about the research. The research monitor shall have authority to stop a research protocol in progress, remove individual participants from a research protocol, and take

whatever steps are necessary to protect the safety and well-being of participants until the IRBs can assess the monitor's report. Research Monitors shall have the responsibility to promptly report their observations and findings to the IRB. The DoD Research Monitor is required to review all unanticipated problems involving risks to subjects or others, serious adverse event (SAE) reports, and all participant deaths. The DoD Research Monitor at a minimum must comment on the outcomes of the event or problem and in case of a serious adverse event or death, comments on the relationship to participation in the study. They must also indicate whether he/she concurs with the details of the report provided by the PI.

The DoD Research Monitor should review all initial reports for SAEs, unanticipated problems involving risks to subjects or others, and all participant deaths in a timely manner (within 48 hours), and provide their own independent report. The Research Monitor will provide an unbiased written report of all unanticipated problems involving risks to subjects or others, and related SAEs and deaths, within 10 working days to the MUSPH IRB, NDA (where applicable), the sponsor, and to the WRAIR HSPB by phone [redacted] or by email [redacted] All Research Monitor reports for unrelated SAEs and deaths should be kept with the corresponding SAE reports at the study site.

The WRAIR HSPB will submit copies of these reports to the USAMRDC ORP HRPO as per SOP UWZ-C-636.

IND Medical Officer

The IND Medical Officer reviews and keeps abreast of adverse events and study pauses that may occur during the study (all adverse events, including deaths and serious or unexpected side effects, are reported to the IND Medical Officer via the PI) in order to ensure accurate and timely reporting to the FDA.

Clinical Research Staff

Under the guidance and supervision of the investigator, the duties of the Clinical Research Staff may include the following:

- Assisting in training other site personnel and other medical staff in understanding and implementing the protocol
- Recruiting and screening the potential study participants according to the protocol's inclusion and exclusion criteria
- Maintaining adequate source documentation (any document, or record where participant data are first recorded). All data noted in the CRF should be verifiable by supporting source documentation [21 CFR 312.62(b)]
- Completing the CRFs for the study accurately and completely as determined by the investigator
- Maintaining records of participant status in the study by using tools such as the enrollment log CRFs, etc.

WRAIR/MHRP/VRC Consultants

- Will serve as a liaison between the site and Sponsor
- Responsible for providing input for the study design and protocol development
- To oversee the process of study implementation, management, and monitoring to include data collection

- Serve as technical advisors and subject matter experts for study execution
- Agree not to attempt to obtain any individually identifiable participant data

VRC IND Representatives

- Will serve as the point of contact on behalf of the sponsor for the IND
- Responsible for ensuring compliance with the protocol and applicable US FDA regulations
- Assumes the responsibilities of the sponsor as detailed in 21 CFR 312 Subpart D
- Will not have contact with study participants and agree not to attempt to obtain any individually identifiable participant data

APPENDIX 10: DIARY CARD

RV 508 Participant Diary Card

Makerere University Walter Reed Project
Kampala, Uganda

Version 1.5
03 March 2020

Participant ID _____

[redacted]

Participant ID _____

General Symptoms Severity Scale

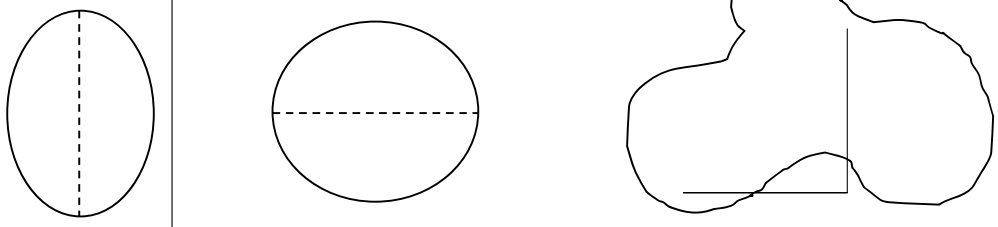
None= you have no symptoms
Mild= minimal symptoms; cause minimal or no interference with work, school, or self care activities.
Moderate=notable symptoms; required modification in activity; did not result in loss of work or cancellation of social activities
Severe = incapacitating symptoms; requiring bed rest and/or resulted in loss of work or cancellation of social activities.

For any Problems Call: [redacted]

Injection Site Pain Severity Scale

How to Measure Swelling and Redness at the Injection Site

1. Determine the widest part (or diameter) of the area.
2. Using the ruler that the clinic staff gave to you, measure the widest part of the area in centimeters (cm) as shown on the pictures below. Each small hash mark on the centimeter ruler equals one tenth (0.1) of a centimeter.
3. Measure the swelling (raised area) and the redness (red area) separately and record each measurement on the diary card.



Please complete this diary in black or blue ink only

Participant ID _____

Day of Vaccination

Date: ____/ _____/_____ (dd/mmm/yyyy)

The evening of the day of Vaccination:

Temp: _____ (oral, °C) Time Taken: _____ PM

If you have a fever and wish to take your temperature again, record your additional temperature:
Temp: _____ (oral, °C) Time Taken: _____ AM / PM *(circle)*

Temp: _____ (oral, °C) Time Taken: _____ AM / PM *(circle)*

Are you taking any medication? ☐ Yes ☐ No
If yes, please list medication(s):

Please use the symptom scale at the bottom of the page

Gen. Symptoms	None	Mild	Moderate	Severe
Joint Pain				
Feeling Unwell				
Muscle Aches (not at injection site)				
Headache				
Chills				
Nausea				

Injection Site Symptoms	None	Mild	Moderate	Severe
Local Pain				
Swelling Measure in cm	**__ __. __ cm**		Please record in cm, the largest width measurement of the swelling ***(Example: 2.5 cm)***	
Redness Measure in cm	**__ __. __ cm**		Please record in cm, the largest width measurement of the redness ***(Example: 2.5 cm)***	

Symptoms Severity Scale

None = no symptoms
Mild = minimal symptoms; cause minimal or no interference with work, school, or self care activities.
Moderate = notable symptoms; required modification in activity or medication; did not result in loss of work or cancellation of social activities.
Severe = incapacitating symptoms; requiring bed rest and/or resulted in loss of work or cancellation of social activities.

For any problems call: [redacted]

Injection Site Pain Severity Scale
None = no pain
Mild = minimal pain; no limitation of use of arm
Moderate = notable pain; some limitation of use of arm
Severe = extreme pain; complete limitation of use of arm

Participant ID |

Day 1 after Vaccination

Date: ____/ _____/_____ (dd/mmm/yyyy)

Temp: _____ (oral, °C) Time Taken: _____ AM / PM *(circle)*

If you have a fever and wish to take your temperature again, record your additional temperature:
Temp: _____ (oral, °C) Time Taken: _____ AM / PM *(circle)*

Temp: _____ (oral, °C) Time Taken: _____ AM / PM *(circle)*

Are you taking any medication? ☐ Yes ☐ No
If yes, please list medication(s):

Please use the symptom scale at the bottom of the page

Gen. Symptoms	None	Mild	Moderate	Severe
Joint Pain				
Feeling Unwell				
Muscle Aches (not at injection site)				
Headache				
Chills				
Nausea				

Injection Site Symptoms	None	Mild	Moderate	Severe
Local Pain				
Swelling Measure in cm	**__ __. __ cm**		Please record in cm, the largest width measurement of the swelling ***(Example: 2.5 cm)***	
Redness Measure in cm	**__ __. __ cm**		Please record in cm, the largest width measurement of the redness ***(Example: 2.5 cm)***	

Symptoms Severity Scale

None = no symptoms
Mild = minimal symptoms; cause minimal or no interference with work, school, or self care activities.
Moderate = notable symptoms; required modification in activity or medication; did not result in loss of work or cancellation of social activities.
Severe = incapacitating symptoms; requiring bed rest and/or resulted in loss of work or cancellation of social activities.

For any problems call: [redacted]

Injection Site Severity Scale

None = no symptoms
Mild = minimal pain; no limitation of use of arm
Moderate = notable pain; some limitation of use of arm
Severe = extreme pain; complete limitation of use of arm

Participant ID | |

Day 2 after Vaccination

Date: ____/ _____/_____ (dd/mmm/yyyy)

Temp: _____ (oral, °C) Time Taken: _____ AM / PM *(circle)*

If you have a fever and wish to take your temperature again, record your additional temperature:
Temp: _____ (oral, °C) Time Taken: _____ AM / PM *(circle)*

Temp: _____ (oral, °C) Time Taken: _____ AM / PM *(circle)*

Are you taking any medication? ☐ Yes ☐ No
If yes, please list medication(s):

Please use the symptom scale at the bottom of the page

Gen. Symptoms	None	Mild	Moderate	Severe
Joint Pain				
Feeling Unwell				
Muscle Aches (not at injection site)				
Headache				
Chills				
Nausea				

Injection Site Symptoms	None	Mild	Moderate	Severe
Local Pain				
Swelling Measure in cm	**__ __. __ cm**		Please record in cm, the largest width measurement of the swelling ***(Example: 2.5 cm)***	
Redness Measure in cm	**__ __. __ cm**		Please record in cm, the largest width measurement of the redness ***(Example: 2.5 cm)***	

Symptoms Severity Scale

None = no symptoms
Mild = minimal symptoms; cause minimal or no interference with work, school, or self care activities.
Moderate = notable symptoms; required modification in activity or medication; did not result in loss of work or cancellation of social activities.
Severe = incapacitating symptoms; requiring bed rest and/or resulted in loss of work or cancellation of social activities.

For any problems call: [redacted]

Injection Site Severity Scale
None = no symptoms
Mild = minimal pain; no limitation of use of arm
Moderate = notable pain; some limitation of use of arm
Severe = extreme pain; complete limitation of use of arm

Participant ID |

Day 3 after Vaccination

Date: ____/ _____/_____ (dd/mmm/yyyy)

Temp: _____ (oral, °C) Time Taken: _____ AM / PM *(circle)*

If you have a fever and wish to take your temperature again, record your additional temperature:
Temp: _____ (oral, °C) Time Taken: _____ AM / PM *(circle)*

Temp: _____ (oral, °C) Time Taken: _____ AM / PM *(circle)*

Are you taking any medication? ☐ Yes ☐ No
If yes, please list medication(s):

Please use the symptom scale at the bottom of the page

Gen. Symptoms	None	Mild	Moderate	Severe
Joint Pain				
Feeling Unwell				
Muscle Aches (not at injection site)				
Headache				
Chills				
Nausea				

Injection Site Symptoms	None	Mild	Moderate	Severe
Local Pain				
Swelling Measure in cm	**__ __. __ cm**		Please record in cm, the largest width measurement of the swelling ***(Example: 2.5 cm)***	
Redness Measure in cm	**__ __. __ cm**		Please record in cm, the largest width measurement of the redness ***(Example: 2.5 cm)***	

Symptoms Severity Scale

None = no symptoms
Mild = minimal symptoms; cause minimal or no interference with work, school, or self care activities.
Moderate = notable symptoms; required modification in activity or medication; did not result in loss of work or cancellation of social activities.
Severe = incapacitating symptoms; requiring bed rest and/or resulted in loss of work or cancellation of social activities.

For any problems call: [redacted]

Injection Site Severity Scale
None = no symptoms
Mild = minimal pain; no limitation of use of arm
Moderate = notable pain; some limitation of use of arm
Severe = extreme pain; complete limitation of use of arm

Participant ID _____

Day 4 after Vaccination

Date: ____/ _____/_____ (dd/mmm/yyyy)

Temp: _____ (oral, °C) Time Taken: _____ AM / PM *(circle)*

If you have a fever and wish to take your temperature again, record your additional temperature:
Temp: _____ (oral, °C) Time Taken: _____ AM / PM *(circle)*

Temp: _____ (oral, °C) Time Taken: _____ AM / PM *(circle)*

Are you taking any medication? ☐ Yes ☐ No
If yes, please list medication(s):

Please use the symptom scale at the bottom of the page

Gen. Symptoms	None	Mild	Moderate	Severe
Joint Pain				
Feeling Unwell				
Muscle Aches (not at injection site)				
Headache				
Chills				
Nausea				

Injection Site Symptoms	None	Mild	Moderate	Severe
Local Pain				
Swelling Measure in cm	**__ __. __ cm**		Please record in cm, the largest width measurement of the swelling ***(Example: 2.5 cm)***	
Redness Measure in cm	**__ __. __ cm**		Please record in cm, the largest width measurement of the redness ***(Example: 2.5 cm)***	

Symptoms Severity Scale

None = no symptoms
Mild = minimal symptoms; cause minimal or no interference with work, school, or self care activities.
Moderate = notable symptoms; required modification in activity or medication; did not result in loss of work or cancellation of social activities.
Severe = incapacitating symptoms; requiring bed rest and/or resulted in loss of work or cancellation of social activities.

For any problems call: [redacted]

Injection Site Severity Scale

None = no symptoms
Mild = minimal pain; no limitation of use of arm
Moderate = notable pain; some limitation of use of arm
Severe = extreme pain; complete limitation of use of arm

Participant ID |

Day 5 after Vaccination

Date: ____/ _____/_____ (dd/mmm/yyyy)

Temp: _____ (oral, °C) Time Taken: _____ AM / PM *(circle)*

If you have a fever and wish to take your temperature again, record your additional temperature:
Temp: _____ (oral, °C) Time Taken: _____ AM / PM *(circle)*

Temp: _____ (oral, °C) Time Taken: _____ AM / PM *(circle)*

Are you taking any medication? ☐ Yes ☐ No
If yes, please list medication(s):

Please use the symptom scale at the bottom of the page

Gen. Symptoms	None	Mild	Moderate	Severe
Joint Pain				
Feeling Unwell				
Muscle Aches (not at injection site)				
Headache				
Chills				
Nausea				

Injection Site Symptoms	None	Mild	Moderate	Severe
Local Pain				
Swelling Measure in cm	**__ __. __ cm**		Please record in cm, the largest width measurement of the swelling ***(Example: 2.5 cm)***	
Redness Measure in cm	**__ __. __ cm**		Please record in cm, the largest width measurement of the redness ***(Example: 2.5 cm)***	

Symptoms Severity Scale

None = no symptoms
Mild = minimal symptoms; cause minimal or no interference with work, school, or self care activities.
Moderate = notable symptoms; required modification in activity or medication; did not result in loss of work or cancellation of social activities.
Severe = incapacitating symptoms; requiring bed rest and/or resulted in loss of work or cancellation of social activities.

For any problems call: [redacted]

Injection Site Severity Scale
None = no symptoms
Mild = minimal pain; no limitation of use of arm
Moderate = notable pain; some limitation of use of arm
Severe = extreme pain; complete limitation of use of arm

Participant ID |

Day 6 after Vaccination

Date: ____/ _____/_____ (dd/mmm/yyyy)

Temp: _____ (oral, °C) Time Taken: _____ AM / PM *(circle)*

If you have a fever and wish to take your temperature again, record your additional temperature:
Temp: _____ (oral, °C) Time Taken: _____ AM / PM *(circle)*

Temp: _____ (oral, °C) Time Taken: _____ AM / PM *(circle)*

Are you taking any medication? ☐ Yes ☐ No
If yes, please list medication(s):

Please use the symptom scale at the bottom of the page

Gen. Symptoms	None	Mild	Moderate	Severe
Joint Pain				
Feeling Unwell				
Muscle Aches (not at injection site)				
Headache				
Chills				
Nausea				

Injection Site Symptoms	None	Mild	Moderate	Severe
Local Pain				
Swelling Measure in cm	**__ __. __ cm**		Please record in cm, the largest width measurement of the swelling ***(Example: 2.5 cm)***	
Redness Measure in cm	**__ __. __ cm**		Please record in cm, the largest width measurement of the redness ***(Example: 2.5 cm)***	

Symptoms Severity Scale

None = no symptoms
Mild = minimal symptoms; cause minimal or no interference with work, school, or self care activities.
Moderate = notable symptoms; required modification in activity or medication; did not result in loss of work or cancellation of social activities.
Severe = incapacitating symptoms; requiring bed rest and/or resulted in loss of work or cancellation of social activities.

For any problems call: [redacted]

Injection Site Severity Scale
None = no symptoms
Mild = minimal pain; no limitation of use of arm
Moderate = notable pain; some limitation of use of arm
Severe = extreme pain; complete limitation of use of arm

Participant ID |

Day 7 after Vaccination

Date: ____/ _____/_____ (dd/mmm/yyyy)

Temp: _____ (oral, °C) Time Taken: _____ AM / PM *(circle)*

If you have a fever and wish to take your temperature again, record your additional temperature:
Temp: _____ (oral, °C) Time Taken: _____ AM / PM *(circle)*

Temp: _____ (oral, °C) Time Taken: _____ AM / PM *(circle)*

Are you taking any medication? ☐ Yes ☐ No
If yes, please list medication(s):

Please use the symptom scale at the bottom of the page

Gen. Symptoms	None	Mild	Moderate	Severe
Joint Pain				
Feeling Unwell				
Muscle Aches (not at injection site)				
Headache				
Chills				
Nausea				

Injection Site Symptoms	None	Mild	Moderate	Severe
Local Pain				
Swelling Measure in cm	**__ __. __ cm**		Please record in cm, the largest width measurement of the swelling ***(Example: 2.5 cm)***	
Redness Measure in cm	**__ __. __ cm**		Please record in cm, the largest width measurement of the redness ***(Example: 2.5 cm)***	

Symptoms Severity Scale

None = no symptoms
Mild = minimal symptoms; cause minimal or no interference with work, school, or self care activities.
Moderate = notable symptoms; required modification in activity or medication; did not result in loss of work or cancellation of social activities.
Severe = incapacitating symptoms; requiring bed rest and/or resulted in loss of work or cancellation of social activities.

For any problems call: [redacted]

Injection Site Severity Scale

None = no symptoms
Mild = minimal pain; no limitation of use of arm
Moderate = notable pain; some limitation of use of arm
Severe = extreme pain; complete limitation of use of arm

Participant ID |

If you have any of the General or Injection Site Symptoms that is still ongoing after day 7, please complete stop dates below.

General Symptoms	Date the Symptom Ended	Maximum severity after day 7 (Mild, moderate or severe)
Joint Pain		
Feeling Unwell		
Muscle Aches (not at injection site)		
Headache		
Chills		
Nausea		

Injection Site Symptoms	Date the Symptom Ended	Maximum severity after day 7 (Mild, moderate or severe)
Local pain		
Swelling Measure in cm		**__ __. __ cm**
Redness Measure in cm		**__ __. __ cm**

Are you or have you taken any medication after day 7? If so, please record the name of the medication and the date you stopped taking the medication below, if applicable.

Name of Medication	Date You Stopped Medication

APPENDIX 11: RECRUITMENT MATERIALS

FLYER MESSAGE:

ARE YOU INTERESTED IN JOINING AN EBOLA VACCINE STUDY?

If you are aged 18-50 years and in good health

Call toll free number 0800-200058 for more information

OR

Visit Makerere University Walter Reed Project offices [redacted]

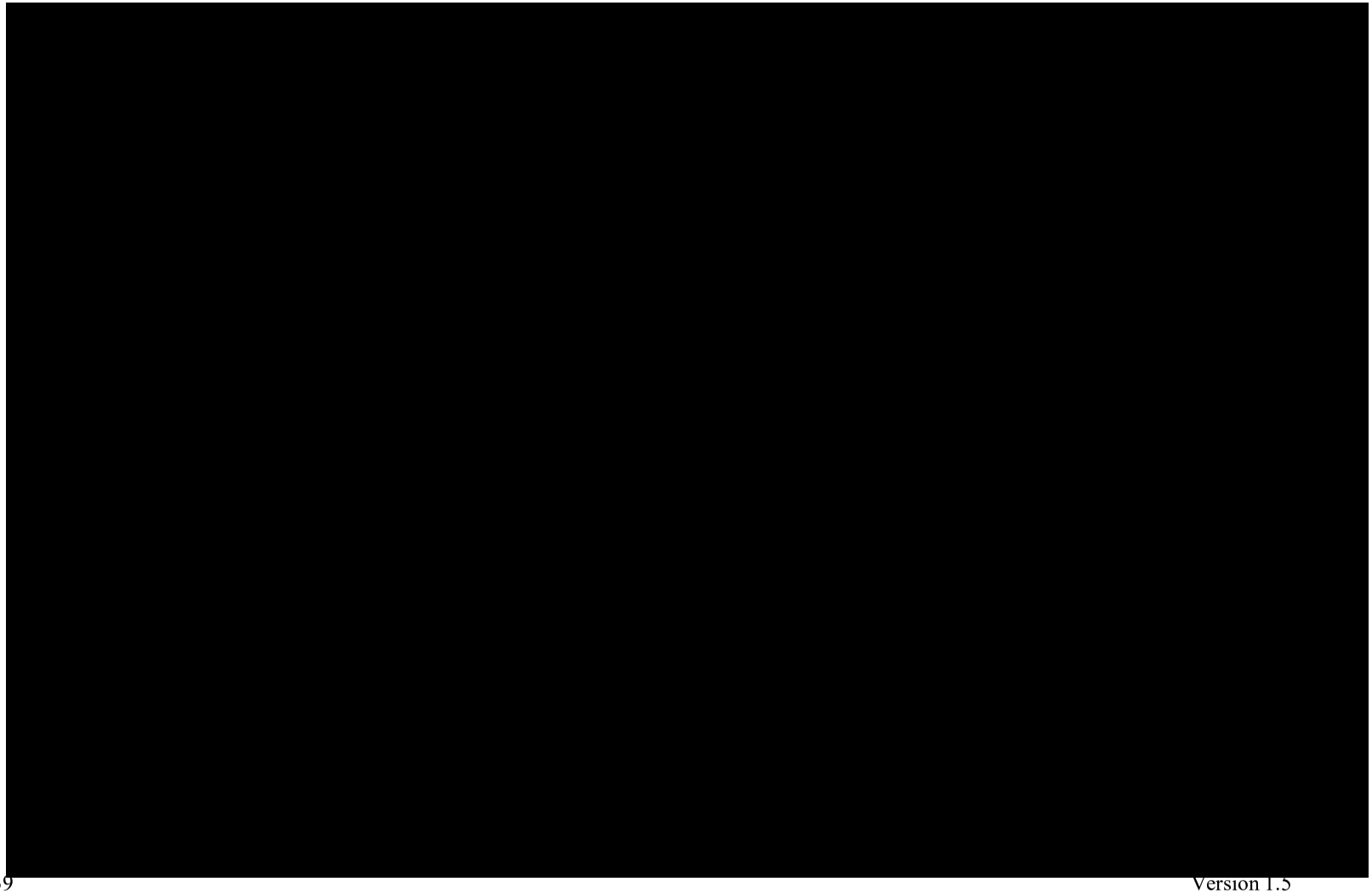
Join Ugandan Scientists in the Search for Vaccines Against Ebloa

NEWSPAPER ADVERT: Message concept:

VOLUNTEERS NEEDED NOW TO TEST INVESTIGATIONAL (Study)
VACCINE FOR THE PREVENTION OF EBOLA

The vaccine **DOES NOT** contain any virus and **CAN NOT** cause Ebola

Volunteers must be **aged 18- 50 years and in good health**



POSTER MESSAGE

The Search for a vaccine is on….

Volunteer to participate in a research study to test a vaccine against Ebola today

Adults aged 18-50 years and in good health needed

For more information/ directions, contact:
Makerere University Walter Reed Project offices, [redacted]

RADIO ANNOUNCEMENT

Message concept:

Makerere University Walter Reed Project is looking for volunteers to test an Investigational Vaccine for the **PREVENTION** of Ebola.

The Vaccine DOES NOT contain any virus and CAN NOT cause Ebola
(Repeat)

Interested individuals between the ages of 18 – 50 and in good health are invited to an Information Seminar this _____ at _____ pm, at the Makerere University Walter Reed Project offices [redacted]

OR can call toll free number [redacted] for directions/ more information (repeat phone number)

JOIN UGANDAN SCIENTISTS IN THE SEARCH FOR A VACCINE AGAINST EBOLA

RV 508 Sticker Message Content

SUPPORT THE SEARCH FOR A VACCINE AGAINST EBOLA

Makerere University Walter Reed Project, [redacted]
Toll free number [redacted]

APPENDIX 12: APPOINTMENT/EMERGENCY CONTACT CARD

MUWRP

MAKERERE UNIVERSITY WALTER REED PROJECT

APPOINTMENT CARD

Name: _____

Date: _____ Time: _____

For Emergencies that occur between 8:00am and 5:00pm, please call [redacted] **For Emergencies that occur before 8:00am or after 5:00pm, please call** [redacted]

APPENDIX 13: LIST OF EXTERNAL COLLABORATORS

MAIN STUDY INFORMED CONSENT FORM

Study Title: RV 508, "A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of Two Doses of an Ebola Sudan Chimpanzee Adenovirus Vector Vaccine, VRC-EBOADC086-00-VP (cAd3-EBO S), in Healthy Adults"

Sponsor: National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center (VRC)

Funding Agencies: NIH, the U.S. Military HIV Research Program (MHRP) and the U.S. Department of Defense (DoD)

Study Product Provided by: NIH/NIAID/VRC

Study Conducted by: Makerere University Walter Reed Project (MUWRP)

Principal Investigator: Betty Mwesigwa, MBChB, MSc Clinical Trials

INTRODUCTION

You are being invited to consider participating in this study because you are a healthy person who may meet the criteria to join this study. Before deciding to participate in this study, please read this document thoroughly. In doing so, you will understand the purpose and details of this study.

Before you decide whether or not to take part in this study, we would like to explain the purpose of the research study, how it may help you or others, any risks associated with participation, and our expectations of you. This process is called informed consent. It is important that you know the following:

a. Taking part is of your own free will (entirely voluntary).

b. If you decide not to participate you will not lose any of the benefits or rights you would normally have or be disadvantaged in any way.

c. You may decide not to participate in the study or you may decide to stop participating in the study at any time without loss of any medical care to which you are entitled now or in the future.

Please ask questions about anything you do not understand at any time. The clinic staff will talk to you about the information in this form. You can take as much time as you need to review this form and discuss your study participation with your family, friends, and community as you feel comfortable and appropriate, in order to decide whether or not you would like to participate. If you decide to participate in this study, you will review this document with a study staff and will be requested to sign and date at the end of this form to show that your questions have been answered and that you want to take part in the study. A copy of this signed/marked informed consent will be provided to you. This consent must be signed/marked before any study procedures are performed.

You will also have the opportunity to consent for future (currently unknown) use of your samples, and genetic testing. These will be explained to you, and you will sign a separate consent for each.

The technical name of the study vaccine is VRC-EBOADC086-00-VP, but we will refer to it as "cAd3-EBO S" or simply as the "Ebola vaccine." The study vaccine does not contain live or killed Ebola virus. It is **impossible** for the study vaccine to give you an Ebola virus infection.

This research study is funded by the U.S DoD and the NIAID/NIH. The MUWRP is conducting this research study in collaboration with the U.S. MHRP and NIAID/NIH in Kampala, Uganda.

PURPOSE AND BACKGROUND

This research study will evaluate an experimental vaccine for the Ebola Virus. "Experimental" means that it is not known if the vaccine works to prevent the Sudan strain of Ebola Virus Disease (EVD). Since it is not known if the vaccine works, it has not been approved by the US Food and Drug Administration (FDA) or the Uganda National Drug Authority (NDA). Vaccines are substances used to create immune responses (resistance) to an infection in order to prevent a disease. Immune responses are how your body recognizes and defends itself against bacteria, viruses, and substances that may be harmful to the body.

The main purpose of this study is to see if the experimental Ebola vaccine is safe and if it causes any side effects. Another goal is to study blood samples in the lab to see if and how the immune system responds in people who receive this vaccine.

The Ebola virus was discovered in 1976. It is named after a river in Africa close to where the virus was first discovered. Bats in certain parts of Africa carry the virus. EVD starts with fever and muscle aches. More severe symptoms are breathing problems, severe bleeding, kidney problems, and shock (loss of blood pressure). The infection may be mild, but it can also lead to death. The first two outbreaks of Ebola Hemorrhagic Fever in Africa in 1976 caused 340 deaths. In Africa, when there have been outbreaks of Ebola virus, 50% to 90% of infected people have died.

STUDY VACCINE

The experimental Ebola vaccine in this study was developed in a laboratory by the VRC at the NIH, located in Bethesda, Maryland USA. The experimental vaccine has previously been given to humans in combination with other Ebola vaccine products, but not by itself.

The cAd3-EBO S vaccine uses another virus, called chimpanzee Adenovirus 3 (cAd3), to deliver a piece of the Ebola Sudan virus to cells in your body. The adenovirus used to make the vaccine is from a strain that infects chimpanzees. This strain of adenovirus has been tested in people before and does not cause human adenovirus infections. It is further changed to make sure it cannot reproduce in a human body.

Once the Ebola Sudan virus piece is delivered to the cells in your body, your body will then make an immune response. You cannot become infected with or infect someone else with either Ebola or adenovirus from receiving the study vaccine.

STUDY PARTICIPATION

If you agree to take part in the study you will receive one study injection at the enrollment visit (Visit 2). The vaccine injection will be given using a needle and syringe into an upper arm muscle. This is called an intramuscular (IM) injection.

About 40 participants will be enrolled into this study and will be divided into 2 groups. Both groups will have about 20 participants. Participants in Group 1 will receive a low dose of the vaccine and participants in Group 2 will receive a higher dose. Enrollment into Group 2 will not begin until after a safety review is completed for participants who received the lower dose of the vaccine and it is determined to be safe. The higher dose of the experimental Ebola Sudan vaccine is based on dose levels found to be safe in previous studies of similar vaccines that used the chimpanzee adenovirus. If you would like to know which group you are in, please ask the study clinician.

Vaccination Schedule:

RV 508 Study Groups		
Group	**Participants**	**Vaccine Dose**
1	20	cAd3-EBO S at $1x10^{10}$ PU IM
2	20	cAd3-EBO S at $1x10^{11}$ PU IM

STUDY DURATION

Participation in this study will last for about 48 weeks (almost 1 year) from the time of enrollment. There will be 1 screening visit and 10 study visits (1 visit for vaccination and 9 visits for follow-up). However, these do not include additional appointments if you have any side effects and if the study team requests you to come to the clinic. The screening and vaccination visits will each take approximately 2-3 hours. Other appointments will take approximately 1-2 hours. A schedule of events detailing your visits will be provided to you.

STUDY PROCEDURES

a) How do I join in this study?

You will have to sign this form acknowledging that you have read the form, that all your questions have been answered satisfactorily, and that you agree to participate in this study.

You may take part in this study if you are a healthy, male or female volunteer, between ages 18 and 50 with a body mass index (a ratio based on your weight and height) $\leq$ 40, available for a period of 48 weeks, able to provide proof of identity, willing to have the vaccine injection site and any vaccine reactions on your skin photographed, and agree to clinic staff visiting your home (as may be necessary). You must also be able to read this consent form, understand and complete this informed consent process, successfully complete an Assessment of Understanding (to see if you understand the information in this form), and be free of significant medical problems. Blood tests will be done to measure your hemoglobin (amount of blood), your white blood cells, and your liver and kidney function. Females will also be required to undergo pregnancy testing, to not be pregnant, to not be breastfeeding, and to plan not to become pregnant for at least 6 months after vaccination. Females must also agree to use a birth control method for at least 21 days prior to vaccination and for at least 6 months after vaccination.

You **cannot** participate in this study if you received an experimental Ebola or Marburg vaccine or have received a different cAd3 experimental vaccine. You also cannot participate if you have any of the following conditions:

- A history of a serious allergic reaction to any vaccines or allergic reaction to drugs like gentamycin, neomycin or streptomycin
- An autoimmune disease or deficiency or chronically recurring hives, asplenia (lack of normal spleen function) or a history of angioedema (facial swelling)
- HIV infection
- Active syphilis infection
- Diabetes (type I or II)
- Thyroid disease that is not well controlled
- High blood pressure or asthma that is not well controlled
- A bleeding problem or disorder
- Cancer
- A history of seizures or treatment for seizure disorder in the past 3 years

You also cannot participate if you have received any of the following:

- Drugs that may modify your immune system within 14 days prior to enrollment such as prednisone or dexamethasone
- Blood products within 112 days (16 weeks) prior to enrollment
- Any "live-attenuated" vaccine (e.g., oral polio, yellow fever, measles, etc.) within 28 days prior to enrollment in the present study or any other vaccine within 14 days prior to enrollment
- Experimental research drugs within 28 days prior to enrollment in the present study
- Drugs for treating or preventing Tuberculosis

You also may not participate in the study if the Investigators think you may have a history of any condition(s) that may interfere with your full participation in the study or that may impair your ability to provide informed consent.

It is important to remind you that to participate in this study you need to agree to home visits by the clinic staff. The clinic staff may visit your home if they are unable to reach you by phone, in order to remind you of your scheduled visit or for follow up.

b) Screening (Visit 1)

After you have reviewed the study consent form and have agreed to participate, the study staff will ask you to complete an Assessment of Understanding (AOU). The AOU will help the study staff to determine how well you have understood the information about this study and what is required for participation. You must complete 9 out of the 10 questions correctly at least once in 3 attempts. After the AOU, your medical history will be recorded and a thorough physical examination will be performed on you by a member of the study staff. In addition, you will have blood taken to check your HIV and syphilis status.

A serum (blood) pregnancy test will be required at the screening visit if you are female and able to become pregnant. The research staff will test your blood for HIV (human immunodeficiency virus), the

virus that causes AIDS. Prior to this blood test, you will receive counseling about HIV, AIDS, and prevention of HIV. If you are HIV infected, you will receive additional information about HIV and will be referred to our HIV Clinic or the Infectious Disease Institute (IDI) at Mulago or any other HIV Clinic of your choice.

It may be necessary to return to the clinic for a follow up appointment or to repeat tests if there are any abnormal laboratory results. If the physician discovers an illness or condition that requires treatment, you will be referred to a hospital or clinic that can provide further evaluation or treatment.

If you are eligible for participation in this study, you will be scheduled for an appointment for the vaccination visit within 56 days of the screening date. It is important to remind you that as part of the qualification for this study you have agreed to possible home visits by the clinic staff.

c) Enrollment and Follow-up Visits

The clinic staff will observe you for at least 30 to 60 minutes after the injection at the enrollment visit.

You will be asked to complete a diary card and look at your injection site in the evening on the day of the vaccination and then every day for the next 7 days. You will record your temperature, any symptoms, and describe any skin changes at the injection site each day. You will be provided with a thermometer to take your temperature and ruler to measure any injection-site skin changes. You may have to come to the clinic if you have a fever of 38.5˚C or higher that lasts more than 24 hours, a rash, hives, or difficulty in your usual daily activities (such as going to work, fixing a meal, laundry, etc.). You will be able to reach a study investigator at any time of day or night should you have any concerns.

If you develop any symptoms that are of concern to you or the study team, it may be necessary to come to the study clinic for an examination before your next scheduled visit. It is very important that you follow the instructions given to you by the clinic staff. You may also need to come to the clinic for any problem that the nurse or doctor thinks should be checked by exam, blood or other medical test.

At each visit, you will be checked for any health changes or problems since your last visit. You will be asked how you are feeling and what medications you may have taken. Blood will be drawn during clinic visits for testing of your health and your immune system.

The amount of blood drawn will vary from about 25 mL (about 5 teaspoons) to about 92 mL (6 tablespoons), depending on the visit. You might also be asked to have laboratory tests between regular visits if needed to check your health. The total amount of blood drawn during the 48 weeks of participation will be less than 700 mL (about 1.5 *tumpeco mugs*).

No more than a total of about one *tumpeco mug* (450 mL) will be drawn over any 3-month period during the study. Female participants will also have to give a urine sample for pregnancy test at some visits. You will be informed promptly if any health concerns are identified by the tests. You should avoid donating blood for at least one year after your study vaccination.

The study team will inform you of the results from your lab tests and medical examination at the next study visit. In cases where an abnormality may be of concern, the investigators will notify you as soon as possible. If any concerning abnormality is detected, you will be referred for appropriate testing, treatment and care as may be required.

d) Sample collection during the study

i. **Blood and urine specimens:** The investigators will obtain blood to test for any possible side effects as well as evaluate the immune response to the vaccine. Urine collected at study visits will be used for pregnancy tests for female volunteers.

ii. **HLA and genetic tests:** Part of the blood samples for this study will be used to analyze for HLA ('Human Leukocyte Antigen') type. HLA is a group of proteins present on the surface of all cells in the human body with an important role in the immune response to infection. Determining HLA type is necessary to be able to perform certain research studies. We will not notify you with the results of this test. The HLA test for this study is not a normal medical test and the test result will not be used for treatment purpose. You will be provided a separate form to consent or refuse genetic testing on your samples.

WHAT WILL HAPPEN TO MY SAMPLES AFTER THIS STUDY?

a) Sample Storage

During your participation in this study, blood samples will be collected from you as already explained. We will store left over blood samples in a secure central storage site (not in the clinic) in the USA for future research to learn more about Ebola virus, vaccines, the immune system, and/or other medical conditions. Only samples from participants who have provided consent for future use of their samples will be stored at the end of this study. If consent is not provided, the samples will be destroyed upon completion of tests for this study.

Please note that samples will only be transferred to another country after approval by the Uganda National Council of Science and Technology and your personal information will not be disclosed/ attached to these specimens (as described below).

b) Future Studies

You will have the opportunity to review, ask questions and provide consent (permission) for storage and use of your blood samples for future unknown use, in the "Future Use Blood Sample Consent Form." All future research that uses stored samples must be reviewed and approved by an Institutional Review Board (IRB), which is a committee that is responsible for overseeing the safety, welfare and rights of research participants.

c) Specimen Labeling

Specimens will be stored and labeled using a numeric barcode without your name attached. Only the site-investigator team is able to connect those numeric codes and your name. Personal Identification Information will be kept confidentially according to all applicable laws and regulations.

POSSIBLE RISKS OF STUDY PARTICIPATION

This section describes the risks associated with the experimental Ebola Sudan vaccine and other study procedures. There may be additional risks related to the experimental vaccine that are currently unknown. These unknown risks could affect you or, if applicable, your unborn child if you become pregnant. If the study investigators learn about new risks during this study, the study investigators will tell you.

***Possible* risks from the injection:** Temporary stinging, pain, arm discomfort, redness, soreness, itchiness, swelling or bruising at the injection site on your arm. There is a very small chance of infection.

***Possible* risks from any vaccine:** Fever, chills, rash, aches and pains, nausea, headache, dizziness, fatigue (feeling tired), and malaise (feeling unwell). Some people have allergic reactions to vaccines. These types of reactions are usually greatest within the first 24 hours after vaccination and may last 1 to 3 days.

***Possible* risks of the experimental Ebola Sudan vaccine:** The risks of the experimental vaccine are unknown. The most common complaints in the first few days after receiving similar vaccines include sore arm, headache, muscle aches and feeling tired. A few people had a fever within a day after vaccination.

As with any vaccine, there may be a risk of skin rash, hives, or other unknown side effects. If you develop a reaction to the experimental vaccine on your skin, the investigators will take pictures of the reaction and the vaccine injection site. Every effort will be made to avoid photographing your face or any tattoos or birthmarks that may identify you in the photograph. Your name and other identifying information will not be associated with the photograph. All photographs will relate only to this study and will be the property of the sponsor.

There are currently no vaccines approved for use to protect against Ebola virus infection. Receipt of this experimental Ebola vaccine may affect your response to future vaccines against Ebola. It is unknown if you will develop an immune response, such as antibodies, after vaccination. It is unknown if your immune response would protect against EVD, have no effect on protection, or increase your risk of EVD. It is also unknown how long an immune response to the vaccine may last. You should continue to take all precautions against being exposed to body fluids of people who have an Ebola virus infection.

***Unknown* safety risks:** There may be unknown side effects from the study vaccine – even serious or life-threatening risks – that we do not yet know about. Please tell the study staff about any side effect you think you are having as soon as possible. This is important for your safety.

***Possible* risks of blood drawing:** Pain, bleeding, bruising, feeling lightheaded, fainting, or rarely, infection at the site where the blood is taken. To minimize the risks, trained health care providers will draw your blood.

***Possible* risks from genetic testing:** Unintended release of information could be used by insurers or employers; discovering a gene that suggests risk of disease for you or your family; discovering undisclosed family relationships. To minimize the risks, results will only be labeled with a code, not your name or other identifying information.

***Possible* risks to Pregnancy:** If you are pregnant, breast-feeding or want to become pregnant from 21 days before vaccination until 24 weeks (6 months) after the vaccination, you cannot participate in this study. We do not know the possible effects of the study vaccine on the unborn baby or nursing infant. Therefore, women who are able to become pregnant must have a negative pregnancy test before the study vaccination and agree to practice adequate birth control beginning at least 21 days prior to receiving the study injection until 24 weeks after the injection. Adequate methods of birth control include: condoms, male or female, with or without a spermicide; diaphragm or cervical cap with

spermicide; intrauterine device; all prescription methods (such as contraceptive pills, injections, patches and others); or a male partner who has previously undergone a vasectomy. You must notify the clinic staff immediately upon learning that you have become pregnant during this study. You must also notify the clinic if you suspect that you **might** be pregnant during this study. You will be asked to continue with the planned study follow-up visits for safety purposes and contacted later to learn about the outcome of any pregnancy that starts in the first 24 weeks after study vaccination.

Other **Risks:** You may not donate blood while participating in this research study or for one year after the date of the experimental vaccine injection.

Your samples will be shipped to collaborators outside of MUWRP to be analyzed. These samples will only be labeled with your study number, not your name or other personal information. Samples will only be shipped after approval from the MUWRP IRB.

WHAT IF THE RESEARCHERS LEARN NEW INFORMATION DURING THIS STUDY?

Results of this study or other scientific research may affect your willingness to continue to take part in this study. During the course of the study, you will be informed of any significant new findings (either good or bad), such as changes in the risks or benefits resulting from participation in the research or new alternatives to participation that might cause you to change your mind about continuing in the study. If new information is provided to you, your consent to continue participating in this study will be re-obtained.

BENEFITS FROM STUDY PARTICIPATION

You will receive no direct benefit from participating in this study because no one knows if the vaccine will work. However, you and others may benefit in the future from the information that will be learned from the study. The results of this study could play a role in whether the FDA will approve the vaccine for sale at some time in the future. You will not receive money or other compensation should this occur.

COMPENSATION FOR STUDY PARTICIPATION

You will be compensated Ug shs 50,000 for time and inconvenience associated with each scheduled visit and up to Ug shs 20,000 for each unscheduled visit. Unscheduled visits will be compensated only if the Principal Investigator/ designee finds it necessary. Other than medical care that may be provided and other payment specifically stated in this form, there is no other compensation available for you taking part in this study.

PERSONAL INFORMATION CONFIDENTIALITY

The Principal Investigator at this clinic, Dr. Betty Mwesigwa, will maintain research records of your taking part in this study.

All study volunteers will receive a study identification (SID) number. An SID is a unique number assigned to each participant, known only to the study team at the clinic and used to ensure the confidentiality of research information. All your study documents, samples and test results will not bear your name but will have your SID, the date, study number, group number and study visit number. Personal identifying information like your name and age collected at the time of enrollment will be

stored in a lockable cabinet to which only designated study team members will have access. These steps will ensure confidentiality of your personal information and minimize the chances of it becoming known to others.

Clinical and research records may be reviewed by representatives of the U.S. Army Medical Research and Development Command (USAMRDC), Office for Human Research Protections (OHRP), Human Research Protection Office (HRPO), U.S. DoD, WRAIR Human Subjects Protection Branch, Makerere University School of Public Health IRB, NIAID, the Uganda National Drug Authority (NDA), the Uganda National Council of Science and Technology, U.S. Food and Drug Administration, the Uganda Ministry of Health, and other agencies as part of their responsibilities for ensuring the protection of research volunteers. Representatives of all the above are bound by rules of confidentiality not to reveal your identity to others.

Complete confidentiality cannot be promised but every effort will be made to keep the records as confidential as possible within the limits of the law. All data and medical information obtained about you as an individual will be considered important and held in confidence.

Research and clinical information relating to you will be shared with other investigators and the scientific community through presentation or publication; however, you will not be identified by name or other personal information that could be used to identify you.

General clinical trial information will be kept in the database at the National Medical Library at the National Institutes of Health on http://www.clinicaltrials.gov. This website will not include information that can identify you. At most, the Web site will include a summary of the results.

SICKNESS OR INJURY AS A RESULT OF STUDY PARTICIPATION

If you get sick or injured due to the vaccination of this study, you will receive appropriate medical treatment and care until cure or stabilization as provided for by a limited fund (set aside for this study) and a clinical trials medical insurance policy for research-related injuries. While we anticipate the combination of the set-aside fund and the insurance policy is more than enough to pay for the costs associated with any study related injuries, there is a limit to the amount of coverage available. The study sponsor, MUWRP, and the U.S. DoD will not provide long-term medical care for stabilized research-related injuries.

The study team is responsible for the cost without using any personal health care package which belongs to the volunteer. MUWRP will pay costs up to the limit from set aside finds or through the insurance. However, you will not get any other compensation. You should discuss this thoroughly with the Principal Investigator or site clinicians before making a decision to participate in this study. If you have any questions about study-related sickness or injury, you can contact the following person:

Dr. Betty Mwesigwa
Makerere University Walter Reed Project
[redacted]

ENDING STUDY PARTICIPATION

You can choose not to participate or withdraw from the study at any time without any consequence to you. Although you may withdraw from the study at any time, the samples and data collected up to that time will be used in accordance with the protocol.

If you would like to withdraw from this study, please contact the Principal Investigator mentioned above. You will not lose any legal rights, including the rights for medical treatment and others if you withdraw from this study.

Although you may be willing to participate in the study, the investigators may not give you the vaccination if any of the following situations occur:

- Study is stopped.
- Study sponsors, the IRBs, the US FDA or the Uganda NDA request to terminate the study for unexpected reasons.
- You are unable to comply with the study requirements.
- You are not willing to have blood drawn although you are still willing to participate in other processes.
- You have a medical problem where continuing to be in the study would be harmful to you.
- Other incidents occurred and may be harmful to you if you continue being the study volunteer.

ALTERNATIVES

This study is not designed to treat any disease and no alternative currently exists. You may choose to not participate.

CONFLICT OF INTEREST STATEMENT

The NIH, including members of the VRC scientific staff, developed the experimental Ebola vaccine being used in this research study. The results of this study could play a role in whether the FDA will approve the vaccine for sale at some time in the future. If approved, the future sale of the vaccine could lead to payments to the NIH and to some of the NIH/VRC scientists. By US Law, government scientists are required to receive such payment for their inventions. Other participating investigators do not have a conflict of interest as a result of study participation. You will not receive money or other compensation should this occur. Please discuss with a study investigator any questions you may have about these issues. There is no conflict of interest with your doctors at this research site.

IF YOU NEED MORE INFORMATION OR HAVE ADDITIONAL QUESTIONS

If you have any question about this study or if you have any problems, you can contact the Principal Investigator Dr. Betty Mwesigwa at the research clinic on [redacted] or by telephone 0[redacted] or toll free on [redacted] or Immaculate Nakabuye on [redacted] or [redacted]

If you have any question and need to ask about your rights or you do not get appropriate treatment and care for sickness or injury which occur as a direct result of taking part in this study or the investigator does not treat you fairly in accordance with what is described in this consent form, you may make a complaint to the following bodies:

For information on

Regulatory questions	The Executive Secretary, at Uganda National Council of Science and Technology, [redacted] or on [redacted]
Human subject protection questions	[redacted] the Research and Ethics Committee, Makerere University School of Public Health, Mulago Hospital Complex or o[redacted]

Please keep a copy of this document in case you want to read it again.

STUDY VOLUNTEER STATEMENT

I have been asked to take part in RV 508, "A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of Two Doses of an Ebola Sudan Chimpanzee Adenovirus Vector Vaccine, VRC-EBOADC086-00-VP (cAd3-EBO S), in Healthy Adults".

The principal investigator Dr. Betty Mwesigwa or her representative has explained the significance of the testing, the duration of the study, the testing that I will undergo, the methods to be used, and the risks and dangers of participation. I have been given a chance to ask questions about this research study. All questions were answered to my satisfaction. If I have other questions about this research, I can ask: Dr. Betty Mwesigwa or Immaculate Nakabuye at the research clinic on [redacted] or [redacted]

I am signing below to indicate I wish to take part in this study, and my consent to follow the requirements of the study as much as possible. I will do my best to follow the recommendations of the study team, and I will report all problems occurring from this study to the study team. It has been explained to me that I can quit this study at any time, and I will not lose any benefits nor will I receive any penalty. If I decide to quit this study, I may be examined before leaving the study to ensure my good health. The medical care that I could receive as a result of sickness from being a part of this study have been explained to me and I have been offered a signed copy of this consent form.

I agree to participate in this study.

_____ _____

SIGNATURE OR MARK OF PARTICIPANT DATE

_____

PRINT NAME OF PARTICIPANT

_____ _____

SIGNATURE OF PERSON ADMINISTERING CONSENT DATE

_____

PRINT NAME OF PERSON ADMINISTERING CONSENT

INFORMED CONSENT FOR FUTURE USE OF STORED SPECIMENS

Study Title: RV 508, "A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of Two Doses of an Ebola Sudan Chimpanzee Adenovirus Vector Vaccine, VRC-EBOADC086-00-VP (cAd3-EBO S), in Healthy Adults"

Sponsor: National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center (VRC)

Funding Agencies: NIH, the U.S. Military HIV Research Program (MHRP) and the U.S. Department of Defense (DoD)

Study Product Provided by: NIH/NIAID/VRC

Study Conducted by: Makerere University Walter Reed Project (MUWRP)

Principal Investigator: Betty Mwesigwa, MBChB, MSc Clinical Trials

During this study, you will be asked to provide blood. These blood samples will be stored for as long as possible and will be used according to your decision below. The blood samples will be stored in the United States (U.S.) for testing how your body fights Ebola infection and other future studies that we do not know about at this time. Some of the tests that may be conducted on your stored samples may not be developed yet, so the investigators cannot tell you all the tests that may be performed in the future.

There is a chance that the blood samples you are donating under this study may be used in other research studies and may have some commercial value. Your samples will not be sold or used directly to produce commercial products.

Should your donated sample(s) lead to the development of a commercial product, the study sponsor and inventor will own it and may take action to patent and license the product. Neither the sponsor nor the inventor intend to provide you with any compensation for your blood samples provided in this study, nor for any future value that the sample you have given may be found to have.

The blood samples will not be stored with any personal information. Your stored samples will be labeled by a code (such as a number) that only the study team can link to you. All personal information will be stored by the study investigator at the study site. Any identifying information about you will be kept confidential to the extent permitted by law.

You will not receive the results of future studies or future genetic tests involving your stored blood samples. The results of genetic tests will be for research purposes only. The genetic tests are not used in medical practice and have not been approved for use in making health care decisions.

Future Research on Your Samples Will Be Related to Ebola or Vaccines

Researchers are able to measure how the immune system responds by looking at blood samples. We will try to understand why Ebola disease progresses differently in some people. As new methods (or ways) of measuring the body's immune response to Ebola are made in the laboratory, we would like to test these methods on the samples we have already collected from you. We also know that sometimes genes,

passed down from your parents, can be important to a person's immune response to Ebola. Because of this, we may do genetic testing on your stored samples. We may use methods that have not been developed yet, so we cannot describe them to you now. We will only use your stored samples to learn more about how the immune system responds to Ebola and how vaccines can prevent Ebola infection.

Your Samples Used for Future Research Will Be Shipped to the USA

Your samples will be stored in a secure central storage site (not in the clinic) in the USA. The samples will not be labeled with your name, only with your Study Identification (SID) number. There is no time limit on how long your samples will be stored.

Your Privacy Will Be Protected

We will protect your privacy with any future research testing of your samples, just like we do with all research information from you during the main study. The samples will not be labeled with your name. Instead, they will have your study code. After this study ends, when the samples are requested for future research, the study code stays with them, or in some cases, it is removed before the samples are sent to be used, if this information is not necessary for the study.

An Institutional Review Board/Independent Ethics Committee Will Review Any Future Research on Your Samples

An IRB/Independent Ethics Committee, which is responsible for overseeing the safety, welfare and rights of research participants, must review and approve each research study that intends to use your samples in future studies.

There Will Be No Benefit to You If You Allow Us to Store Your Samples For Future Research

The researchers will not contact you or your health care provider with results from future studies or future genetic tests that use your samples. This is because the use of the samples is for research and the tests have not been approved for use in making health care decisions.

Your samples may contribute to a new invention or discovery. There is no plan for you to share any money or other benefits resulting from this invention or discovery.

There Are Few Risks Related to Storing Your Samples

When tests are done on the stored samples there is a small but possible risk to your privacy. It is possible that if others found out information about you that is learned from tests (such as information about your genes) it could cause you problems with your family (e.g., having a family member learn about a disease that may be passed on in families or learning who is the true parent of a child) or problems getting a job or insurance. The risk of this happening is extremely low, because your results will not be a part of your medical record and will not be given to the clinic. Also, it is possible that your SID could be removed from the samples. If your SID number is removed from any samples, we will not be able to link that sample to you.

You Can Agree Now to Let Us Use Your Samples For Future Testing and Still Change Your Mind Later

If you agree now, but decide later that you do not want us to use your samples for future research, please tell us. We will ask the storage facility to destroy any remaining samples that still have your SID on them so that they cannot be used for future research.

For More Information:

If you have questions about the use of your samples for future research, contact Dr. Betty Mwesigwa on [redacted]

If you have a problem that you think may be related to the use of your samples for future research, or if you want to withdraw your consent, contact Immaculate Nakabuye on [redacted]

If you have questions about your rights as a research participant, or problems or concerns about how you are being treated in this study, you may contact [redacted] at the Research and Ethics Committee, Makerere University School of Public Health, Mulago Hospital Complex o[redacted]

Once you have read this form and have had all of your questions satisfactorily answered, please initial and check the box next to your choice of whether or not you consent to have your blood samples stored for future testing, and then sign in the space provided below.

_____ ☐ I allow you to store and use my samples for future testing which may include genetic testing.
initials

_____ ☐ I **do not** allow you to store and use my samples for future testing.
initials

_____ _____
SIGNATURE OR MARK OF PARTICIPANT DATE

_____
PRINT NAME OF PARTICIPANT

_____ _____
SIGNATURE OF PERSON ADMINISTERING CONSENT DATE

_____
PRINT NAME OF PERSON ADMINISTERING CONSENT

INFORMED CONSENT FOR GENETIC TESTING

Study Title: RV 508, "A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of Two Doses of an Ebola Sudan Chimpanzee Adenovirus Vector Vaccine, VRC-EBOADC086-00-VP (cAd3-EBO S), in Healthy Adults"

Sponsor: National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center (VRC)

Funding Agencies: NIH, the U.S. Military HIV Research Program (MHRP) and the U.S. Department of Defense (DoD)

Study Product Provided by: NIH/NIAID/VRC

Study Conducted by: Makerere University Walter Reed Project (MUWRP)

Principal Investigator: Betty Mwesigwa, MBChB, MSc Clinical Trials

As we told you in the main informed consent form for this study and in the consent form for storage of samples for future use, we will do some testing of your blood. Some of the testing that we will do will be genetic testing. This consent form tells you everything we know now about genetic testing using your blood samples.

You can decide whether or not to let us use your blood for genetic tests. Your decision does not affect your participation in the study or any care you receive at this clinic. If you decide to allow us to use your blood samples for genetic tests, we will ask you to sign this form. You will get a copy of the form to keep.

Your Blood Sample Is a Potential Source of Genetic Information

Researchers are able to measure how the immune system responds by looking at blood. We will try to understand why Ebola and other diseases affected by Ebola progress differently in some people and why some people are more likely to become infected than others. We know that sometimes genes, passed down from your parents, can be important to a person's immune response to Ebola. Because of this, we would like to do genetic testing on your blood samples. We will only perform genetic testing to learn more about how the immune system responds to Ebola and to other diseases affected by Ebola.

HLA and Genetic Testing: Some of the blood drawn from you, as part of this study will be used for a test called HLA type. HLA stands for 'Human Leukocyte Antigen', a group of proteins present on the surface of all cells on the human body and help the body's immune system respond to foreign, harmful substances. For research, HLA testing is used to try to identify factors associated with response to a vaccine, progression of a disease or related conditions. Determining HLA type is necessary to be able to perform certain research studies.

We will **not** notify you of the results of any genetic test. The genetic research tests we plan to conduct are not currently used in medical practice and have not been approved for use in making health care decisions.

Your Samples Used For Genetic Testing Will Be Shipped to the USA

In order to complete the genetic testing on your blood samples, they will be shipped and stored in the United States. There is no time limit on how long your samples will be stored.

Your Privacy Will Be Protected

We will protect your privacy with any genetic testing of your blood samples, just like we do with all research information from you during the study. The blood samples will not be labeled with your name. Instead, they will have your study identification (SID) number only. If your samples are sent outside Uganda, the SID number stays with them. Your genetic test results will only be connected to you by the SID number, known only to the study team, and not by your name or other personal information.

There Will Be No Benefit to You If You Allow Us to Use Your Samples For Genetic Testing

The researchers will not contact you or your health care provider with results from the genetic testing using your blood. This is because the use of the samples is for research and the tests have not been approved for use in making health care decisions.

Your samples may contribute to a new invention or discovery. There is no plan for you to share any money or other benefits resulting from this invention or discovery.

There Are Few Risks Related to Genetic Testing of Your Samples

Risk of genetic tests and HLA testing: The greatest risk associated with genetic testing is to your privacy. Genetic test results can be used to provide information about how susceptible you are to certain diseases. Used inappropriately, this information could be discriminatory (for example, by insurance companies). HLA typing can also be used to determine who the true parent of a child is (if compared to the child's HLA type). However, the risk of this happening is extremely low, because your results will not be part of your medical records and will not be provided to the clinic.

The blood samples that you provide will only be used to provide study investigators information about your immune system. The results will be coded to protect your identity. Your HLA (and other genetic tests) can only be connected to you by the coded study number and not by your name or other personal information. Neither you nor your doctor will be given the results of the tests.

For More Information:

If you have questions about the use of your samples for genetic testing, contact Dr. Betty Mwesigwa on [redacted] or toll free on [redacted]

If you have a problem that you think may be related to the use of your samples for genetic testing, or if you want to withdraw your consent, contact Immaculate Nakabuye on [redacted] or [redacted]

If you have questions about your rights as a research participant, or problems or concerns about how you are being treated in this study, you may contact [redacted] at the Research and Ethics Committee, Makerere University School of Public Health, Mulago Hospital Complex or o[redacted]

Once you have read this form and have had all your questions satisfactorily answered, please initial and check the box next to your choice of whether or not you consent to have your blood samples used for genetic testing, and then sign in the space provided below.

_____ ☐ I allow you to use my samples for genetic testing.
initials

_____ ☐ I **do not** allow you to do genetic testing on my samples.
initials

_____ _____
SIGNATURE OR MARK OF PARTICIPANT DATE

_____
PRINT NAME OF PARTICIPANT

_____ _____
SIGNATURE OF PERSON ADMINISTERING CONSENT DATE

_____
PRINT NAME OF PERSON ADMINISTERING CONSENT

WITHDRAWAL OF CONSENT FOR SAMPLE STORAGE

Study Title: RV 508, "A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of Two Doses of an Ebola Sudan Chimpanzee Adenovirus Vector Vaccine, VRC-EBOADC086-00-VP (cAd3-EBO S), in Healthy Adults"

Sponsor: National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center (VRC)

Funding Agencies: NIH, the U.S. Military HIV Research Program (MHRP) and the U.S. Department of Defense (DoD)

Study Product Provided by: NIH/NIAID/VRC

Study Conducted by: Makerere University Walter Reed Project (MUWRP)

Principal Investigator: Betty Mwesigwa, MBChB, MSc Clinical Trials

Volunteer Statement of withdraw of consent to have samples stored for future testing:

I _____ withdraw my consent to have my samples stored for future use. I do not want to donate blood samples for storage and future use. However, I would still like to continue taking part in the main study. It has been explained to me that when I sign at the bottom of this form, my samples will be used for all the tests specified for this present study, but no blood will be stored for future use.

It has been explained to me that withdrawing my consent to have my samples stored for future use will not make any difference to the care I am receiving now or in the future, or to any benefits that I am entitled to.

I have been given a chance to ask all the questions that I have about withdrawing my consent to have my samples stored. All of my questions were answered to my satisfaction. I was offered a signed copy of this consent.

_____ _____
SIGNATURE OR MARK OF PARTICIPANT DATE

_____
PRINT NAME OF PARTICIPANT

_____ _____
SIGNATURE OF PERSON ADMINISTERING CONSENT DATE

_____
PRINT NAME OF PERSON ADMINISTERING CONSENT