Official Title: A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of the Marburg Chimpanzee Adenovirus Vector Vaccine, VRC-MARADC087-00-VP (cAd3-Marburg), in Healthy Adults

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Protocol RV 507

A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of the Marburg Chimpanzee Adenovirus Vector Vaccine, VRC-MARADC087-00-VP (cAd3-Marburg), 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
Walter Reed Army Institute of Research (WRAIR)
Clinical Trials Center (CTC)
Silver Spring, MD

In Collaboration With
VRC, NIAID, NIH

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

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IND #17930 – held by VRC, NIAID, NIH

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A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of the Marburg Chimpanzee Adenovirus Vector Vaccine, VRC-MARADC087-00-VP (cAd3-Marburg), in Healthy Adults

Study Design

This is a Phase I, open-label study to examine safety, tolerability and immunogenicity of an investigational Marburg vaccine given by intramuscular (IM) injection to healthy adults. The study is a dose escalation of VRC-MARADC087-00-VP, a chimpanzee adenovirus serotype 3 vector vaccine, which encodes wild type (WT) glycoprotein (GP) from Marburgvirus.

Table 1: RV 507 Study Design

Group	Participants	Day 0*
1	20	cAd3-Marburg at $1x10^{10}$ PU/mL
2	20	cAd3-Marburg 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 enrolled participants will be evenly split, with 20 in each of the two dosage groups for cAd3-Marburg. 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 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-MARADC087-00-VP is formulated at 1×10^{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 1×10^{10} PU/mL dose of cAd3-Marburg.

Participants

Healthy adult volunteers, 18 to 50 years old will be enrolled.

Study Duration

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

Study Objectives

Primary Objectives

- To evaluate the safety and tolerability of VRC-MARADC087-00-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-MARADC087-00-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-MARADC087-00-VP at 4 weeks after vaccination as assessed by GP ELISA and vector-specific neutralization assays, respectively.
- To evaluate the Marburg GP-specific T cell responses in VRC-MARADC087-00-VP at 4 weeks after vaccination as assessed by Intracellular cytokine staining (ICS).

Exploratory Objectives

- To evaluate the immunogenicity of VRC-MARADC087-00-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.
- To evaluate plasmablasts to follow lineage development of anti-GP antibodies.

Study Clinical Site

Clinical Trials Center (CTC), Room [redacted]
Translational Medicine Branch
Walter Reed Army Institute of Research (WRAIR)
[redacted]

Study Laboratories

U.S. Military HIV Research Program
Walter Reed Army Institute of Research
[redacted]

NIAID Vaccine Immunology Program (VIP)
[redacted]

NIAID VRC Immunology Laboratory
[redacted]

Service Laboratories

Quest Diagnostics Inc.
[redacted]oad
[redacted]

Study Data Management Center

EMMES Corporation
[redacted]

Reviewing IRB

Walter Reed Army Institute of Research IRB
(FWA00000015, IRB00000794)
[redacted]

LIST OF ABBREVIATIONS

Abbreviation	Term
AAE	Acquired angioedema
Ad5	Human adenovirus serotype 5
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
AoU	Assessment of understanding
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
cAd3-Marburg	Recombinant chimpanzee adenovirus type 3-vectored Marburg virus vaccine
cAd63	Recombinant chimpanzee adenovirus serotype63
CBC	Complete blood count
cGMP	Current Good Manufacturing Practices
CTC	Clinical Trials Center
DNA	Deoxyribonucleic Acid
EBOV	Species Zaire Ebolavirus
ELISA	Enzyme-linked immunosorbent assay
ELISPOT	Enzyme-linked immunospot
ERC	Ethical Review Committee
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 virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
IB	Investigator's Brochure
IBC	Institutional Biosafety Committee
ICH	International Conference on Harmonization
ICS	Intracellular cytokine staining
ICTV	International Committee on the Taxonomy of Viruses
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscular
IND	Investigational new drug
IRB	Institutional Review Board
LIMS	Laboratory Information Management System
MAbs	Monoclonal Antibodies

MARV	Marburg virus
MedDRA	Medical Dictionary for Regulatory Activities
MHF	Marburg hemorrhagic fever
MHRP	U.S. Military HIV Research Program
MVD	Marburg Virus Disease
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
PI	Principal Investigator
PM	Point mutation
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
RNA	Ribonucleic acid
SAE	Serious adverse event
SAS	Statistical Analysis System
SUSAR	Suspected, unexpected and serious adverse reaction
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 AND RATIONALE

1.1. Background: Marburg Infection

In 2013, the International Committee on the Taxonomy of Viruses (ICTV) Filoviridae Study Group and other experts published an updated taxonomy for filoviruses. Marburgvirus is one of three genera in the family Filoviridae, which, along with Ebolavirus and Cuevavirus, are known to induce viral hemorrhagic fever. Two distinct species included in the genus Marburgvirus are Marburg virus (MARV) and Ravn virus (RAVV) [1].

MARV is a negative-strand RNA virus composed of 7 genes encoding viral proteins, including a single glycoprotein (GP) [2-5]. The virus is responsible for causing Marburg virus disease (MVD), formerly known as Marburg hemorrhagic fever, in humans. Two large outbreaks of MARV have occurred in Africa. Case fatality rates were over 80% in the Democratic Republic of Congo from 1998-2000 and Angola in 2005 [5]. Another outbreak occurred in Uganda in 2012, resulting in 23 clinical cases and 15 deaths with a case fatality rate of 65%. On 19 October 2017, the Ugandan Ministry of Health officially declared an outbreak of MVD in eastern Uganda. As of 14 November, there have been three fatal cases, with over 100 individuals being monitored for potential infection. Cross-border surveillance activities are ongoing in Uganda as well as Kenya where one confirmed case had traveled prior to his death [6].

Though less well known than Ebolavirus, MARV was the first filovirus identified. Currently there are no approved vaccines or therapeutics to treat individuals infected with MARV. Human infection can occur from exposure to Rousettus bats, the natural host of MARV, found in mines or caves [5]. MARV 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 [5].

MVD has an incubation period of 2 to 21 days followed by a rapid and abrupt onset of non-specific symptoms such as fever, extreme fatigue, gastrointestinal complaints, abdominal pain, anorexia, headache, myalgias and/or arthralgias, and diarrhea can persist for a week. Many patients develop severe hemorrhagic manifestations, including hemorrhagic rash, epistaxis, mucosal bleeding, hematuria, hemoptysis, hematemesis, melena, conjunctival hemorrhage, tachypnea, confusion, somnolence, and hearing loss between 5 and 7 days after infection. Laboratory findings include low white blood cell and platelet counts and elevated liver enzymes [5]. In general, the symptoms last for about 7 to 14 days, after which recovery may occur. Death can occur 8 to 9 days after the onset of symptoms and is usually preceded by severe blood loss and shock [7, 8]. MARV has been isolated from the semen and ocular fluid of convalescent patients.

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 MVD, both humoral and cellular immunity are detected, however, their relative contribution to protection is unknown [9]. While recent outbreaks of MVD have been localized to regions of Africa, there is a potential threat of spread to other countries given the frequency of international travel.

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. As of January 2017, no effective therapies or FDA-licensed vaccines exist for any member of

Filoviridae family of viruses, although a vaccine for Ebolavirus may be on the horizon based upon several promising clinical trials [10].

1.2. Rationale for Development of VRC-MARADC087-00-VP Vaccine

A vaccination strategy to achieve immediate protective immunity in most recipients with a single vaccination 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 using a single vaccine administration would serve both needs, but boosting may be needed for long-term protective immunity.

The Vaccine Research Center (VRC), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) has developed a recombinant chimpanzee adenovirus Type 3-vectored Marburgvirus vaccine, VRC-MARADC087-00-VP (cAd3-Marburg), with the primary goal of developing rapid immunity followed by durable immunity. The vaccine encodes wild type (WT) glycoprotein (GP) from Marburg virus. The development of this vaccine is based on previous human experience with filovirus antigens in investigational filovirus vaccines, previous human experience with the cAd3 vaccine vector, and preclinical studies including challenge studies with this vaccine candidate.

The current Phase I study, RV 507, is primarily directed at assessing safety, tolerability and immunogenicity for the cAd3-Marburg vaccine construct that may provide rapid immunity with a single injection. Although there is no prior human experience with this specific cAd3-Marburg vaccine, both the cAd3 vector and the same Marburg Angola WT GP DNA insert have been evaluated in humans and no untoward safety events have been identified in non-human primate (NHP) preclinical studies.

1.2.1. Previous Human Experience with VRC Filovirus Vaccines

The VRC/NIAID/NIH has developed seven different investigational Ebola vaccines and one Marburg virus vaccine, 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 VRC Studies for Evaluation of Marburg and Ebola Vaccines

Study Identifier (Clinicaltrials.gov)	Study Design	Vaccine Product(s)	Dosage, route, x N administrations	Accrual Product/Placebo
VRC 204 [11] (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 [12] (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 [13, 14] (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 [15] (NCT00997607)	Phase Ib, randomized, placebo-controlled	VRC-EBODNA023-00-VP (Ebola DNA, WT GP)	4 mg IM x 3 doses	30/6

Study Identifier (Clinicaltrials.gov)	Study Design	Vaccine Product(s)	Dosage, route, x N administrations	Accrual Product/Placebo
		VRC-MARDNA025-00-VP (Marburg DNA, WT GP)	4 mg IM x 3 doses	30/6
		VRC-EBODNA023-00-VP (Ebola DNA, WT GP) and VRC-MARDNA025-00-VP (Marburg DNA, WT GP)	4 mg IM x 3 doses; both vaccines	30/6
RV 422 (NCT02354404)	Phase Ib, randomized, open label		(prime)	
		VRC-EBOADC069-00-VP (cAd3-EBO, WT GP)	$2x10^{10}$ PU IM x 1 dose	**30**/0
			$2x10^{11}$ PU IM x 1 dose	**30**/0
			(prime)	
		VRC-EBOADC076-00-VP (cAd3-EBOZ, WT GP)	$1x10^{10}$ PU IM x 1 dose	**15**/0
			$1x10^{11}$ PU IM x 1 dose	**15**/0
			(boost)	
		VRC-EBOMVA079-00-VP (MVA-EbolaZ)	$1x10^{8}$ PU IM x 1 dose	**66**/0
VRC 207 [16] (NCT02231866)	Phase I/Ib, open label	VRC-EBOADC069-00-VP (cAd3-EBO, WT GP)	$2x10^{10}$ PU IM x 1 dose	**10**/0
			$2x10^{11}$ PU IM x 1 dose	**10**/0
		VRC-EBOADC076-00-VP (cAd3-EBOZ, WT GP)	$1x10^{10}$ PU IM x 1 dose	**10**/0
			$1x10^{11}$ PU IM x 1 dose	**10**/0
		Further evaluate cAd3-EBOZ*		100 (final study accrual – 143*)
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
			(prime)	
		VRC-EBOADC069-00-VP (cAd3-EBO, WT GP)	$2x10^{11}$ PU IM x 1 dose	**13**/0
		+	+	
			(boost)	
		VRC-EBOMVA079-00-VP (MVA-EbolaZ)	$1x10^{8}$ PFU IM x 1 dose	
		[Received in VRC 207]	(prime)	
		[VRC-EBOADC069-00-VP]	$2x10^{10}$ PU x 1 dose	**ongoing**
		[VRC-EBOADC069-00-VP]	$2x10^{11}$ PU x 1 dose	**(up to 140)**/0
		[VRC-EBOADC076-00-VP]	$1x10^{10}$ PU x 1 dose	
		[VRC-EBOADC076-00-VP]	$1x10^{11}$ PU x 1 dose	
		+	+	
			(boost)	

Study Identifier (Clinicaltrials.gov)	Study Design	Vaccine Product(s)	Dosage, route, x N administrations	Accrual Product/Placebo
		VRC-EBOMVA079-00-VP (MVA-EbolaZ)	$1x10^8$ PFU x 1 dose	
Mali and Maryland [17] (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-EBOZ, 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 nested study (from above)	 **10**/0 **10**/0 **10**/0 **35**/0 **35**/0 **11**/0
		VRC-EBOADC076-00-VP (cAd3-EBOZ, WT GP) + MVA-BN®-Filo	$1x10^{10}$ 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 [18] (NCT02240875)	Phase Ia, open label, long term immunology	VRC-EBOADC076-00-VP (cAd3-EBOZ, 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) $2.5x10^{10}$ PU x 1 dose	 **20**/0 **20**/0 **20**/0 **8**/0 (7 days) **8**/0 (14 days)
		MVA-BN®-Filo	(boost) $1.5x10^8$ PU x 1 dose $3x10^8$ PU x 1 dose	 **34**/0 **12**/0
GSK monovalent ChAd3 Ebola Zaire [19] (NCT02289027)	Phase I/IIa, double-blind, placebo controlled, dose finding	VRC-EBOADC076-00-VP (cAd3-EBOZ, WT GP)	(potentially deployed) $2.5x10^{10}$ PU x 1 dose $5x10^{10}$ PU x 1 dose (non-deployed) $2.5x10^{10}$ PU x 1 dose $5x10^{10}$ PU x 1 dose	 **9**/0 **9**/0 **42**/**42**/2

*rAd5 is adenovirus type 5 vector
† viral particles
# 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 GP with the transmembrane deleted (ΔTM) from both Zaire and Sudan strains. At that time, deletion of the TM region of the GP was performed in order 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 cells in culture [20].

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 [12]. 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) [21].

DNA plasmid vaccines for both Ebola and Marburg GP were evaluated in VRC 206 (U.S.A) and RV247 - the first study of Ebola and Marburg vaccines ever conducted in Africa (Uganda) [13-15]. Between these two studies, a total of 70 study participants received three 4 mg injections of the VRC-MARDNA025-00-VP (Marburg WT GP DNA vaccine product); 30 of the 70 also received concomitant injections of Ebola GP DNA vaccines. Study injections were well tolerated with no significant local or systemic reactions. For the Marburg GP DNA vaccine alone group, the vaccine elicited antibody and T-cell responses specific to the glycoproteins; 32% and 52% response rates, respectively [15].

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 [21]. 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 testing, VRC-EBODNA023-00-VP (Ebola DNA WT), was a recombinant DNA vaccine composed of 2 plasmids, each encoding for the 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 developed; and in collaboration with Crucell, an adenovirus type 5 (rAd5) vector expressing the GP of Marburg Angola was produced. When cynomolgus macaques were challenged with a lethal dose of Marburg Angola virus at 5 weeks post-injection, those vaccinated with 1) a heterologous DNA-GP/rAd5-GP prime-boost, 2) a single injection of rAd5-GP, or 3) several sequential injections of a DNA-GP-only vaccine were all prevented from dying [22].

In follow-up to the NHP DNA vaccine studies, human studies (VRC 206 and RV247) both demonstrated that the plasmid DNA vaccines encoding for Ebola WT GP and Marburg WT GP were safe and immunogenic but repetitive DNA-GP vaccinations with 3 or 4 doses were needed to achieve higher response rates to some of the antigens. Importantly, the evaluation of WT GP constructs has not been associated with coagulopathy or serious adverse events [13-15].

Emergence of the 2014 Ebola epidemic rapidly advanced the next candidate Ebolavirus vaccine into clinical evaluation. The vaccine antigen was chosen based on the data from evaluation of the

WT GP antigen; the chimpanzee Ad3 vector (cAd3) was selected because it has little to no pre-existing immunity in human populations, and the cAd3 expressed antigens elicit comparable immune response to the same antigens expressed by rAd5 vectors. This vaccine (cAd3 EBO GP) was also demonstrated to be safe and immunogenic in humans [16-19].

Based on the human data from the investigational vaccines, listed in Table 2, a logical approach to further development of a Marburg vaccine candidate would be clinical assessment of the same cAd3 vector delivering encoded Marburg WT GP also sequences previously evaluated in the VRC DNA Marburg WT GP plasmid vaccine.

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) [23] and malaria [24], 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 infection in the NHP model.

Serological studies showed a low seroprevalence in human sera for antibodies to cAd3 [25] 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 [26, 27] [and unpublished VRC data]. The cAd3-based vaccines were capable of inducing an immune response comparable to human Ad5 vectored vaccines [26, 27]. VRC investigators showed that cAd3 vectors had similar levels of potency as rAd5 using multiple 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 the 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 [23]. Chimpanzee adenoviral vector type 3 vaccines have been safe in healthy adults at dosages up to 2×10^{11} PU per injection in completed and ongoing clinical trials [23, 24].

Published data in support of evaluating cAd3 vectors for a next generation Marburg vaccine comes from the Phase I, dose-escalation, open-label trial of cAd3-EBO performed by Ledgerwood, *et. al.* [16]. 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. Other studies evaluating this product in U.S., Swiss

and Malian adults showed the Ebola cAd3 vaccine to be safe and immunogenic [16-19]. Similar cAd3 Marburg GP doses will be tested in this slowly enrolling, staged, dose-escalation study.

In summary, use of the recombinant, non-replicating cAd3 vector for construction of the cAd3-Marburg vaccine is based on its properties to induce immune responses as readily as rAd5, but with little to no pre-existing immunity in human populations. The encoded WT GP antigens were chosen based on preclinical data and may provide protective immunity against Marburgvirus species and on their demonstrated safety in humans when expressed by a DNA plasmid.

1.3. Preclinical Studies Supporting Safety of cAd3 Constructs

The vaccine vector cAd3 has undergone several preclinical evaluations for other vaccine viral antigens. First, the vaccine vector, cAd3, was evaluated by others in an investigational HCV vaccine study; in support of clinical testing, nonclinical evaluations were performed for the vaccine, AdCh3-HCV (BB-IND 14818, Okairos, Inc.). In addition, a nonclinical toxicology study with VRC cAd3-HIV Vaccine (VRC-HIVADC064-00-VP) was performed by VRC/NIAID to support a clinical study. The toxicology studies demonstrated expected local inflammatory reactions, which were transient and failed to demonstrate unusual toxicities.

The March 2014 Ebola outbreak in West Africa [28] prompted the VRC/NIAID to accelerate initiation of the first chimp adenovirus vector clinical study – evaluation of VRC-EBOADC069-00-VP – a mix of two vectors: one expressing the WT GP Zaire and one expressing the WT GP Sudan. In April 2014, the VRC/NIAID proposed to the FDA that the prior nonclinical and clinical studies (AdCH3-HCV, cAd3-HIV) supported evaluation of cAd3-EBO through a staged, dose escalation Phase I study design without the conduct of a GLP toxicity study. The FDA concurred with the VRC proposal to proceed immediately with evaluation of the cAd3-EBO vaccine in a Phase I clinical trial. The VRC/NIAID with its collaborating researchers then sought and received approval to evaluate the cAd3 EBO GP Zaire vaccine alone as a vaccine under the same IND. This was designated VRC-EBOADC076-00-VP (cAd3-EBOZ).

Details of additional prior relevant nonclinical and clinical studies are summarized in the Investigator's Brochure.

1.4. Nonclinical Protection Studies

Several non-GLP studies were performed in cynomolgus macaques to select filovirus constructs for further development and to provide animal proof- of-concept data before Phase I clinical studies. Research-grade materials, made with the same constructs as clinical material, for 1) Ebola - cAd3 EBO Z (containing GP from Ebolavirus Zaire), 2) Ebola - cAd3 EBO S (containing GP from Ebolavirus Sudan), 3) Ebola - cAd3-EBO (composed of a 1:1 ratio of cAd3 EBO Z and cAd3 EBO S), 4) Marburg – rAd5 Marburg GP, 5) Marburg GP DNA, and 6) cAd3 Marburg GP were used in the viral challenge studies summarized in Table 3 [22, 29]. In totality, these studies support Phase I clinical testing of the cAd3-Marburg vaccine; the protection studies in cynomolgus macaques are ordered in relevance to RV507.

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 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 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 protection against lethal challenge of Marburg Angola after either a Marburg GP DNA vaccine, a single IM dose of Marburg GP rAd5-vector vaccine, or both	100% protection from death when vaccinated with 4 IM 4mg dose of Marburg GP plasmid, or one IM dose of Marburg GP rAd5 at 10^{11} vp, or 3 IM 4mg dose of Marburg GP plasmid followed by one IM dose of Marburg GP rAd5 at 10^{11} 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 Marburg Angola virus in cynomolgus macaques after single IM dose of cAd3-MARV and demonstrate durability of immune responses 12 months after vaccination.	100% of animals challenged at 6 months and 75% challenged at 12 months survived
Demonstrate protection against lethal challenge of Marburg Angola after a single IM dose of cAd3-MARV	100% protection after a single IM dose of cAd3-MARV GP at $1x10^{10}$ vp when challenged at 5 weeks post-immunization

1.4.1. Protection against lethal MARV Challenge and Durability of Immune Responses after Single IM Injection with cAd3-MARV

Rapid onset of protection from a single administration of cAd3-MARV was demonstrated in a 5-week immunization/challenge experiment. At four weeks post-immunization, all NHPs that received at 1 x 10^{10} vp of the vaccine had ELISA titers to the Marburg GP with a mean titer of about 3e10. The macaques were challenged at 5 weeks post-immunization, and all vaccinated animals survived whereas the unvaccinated NHP did not. A second study evaluated the durability of the protective activity following a single administration of the vaccine. Macaques were immunized IM, and immune responses were evaluated at 4 weeks post-immunization. All animals had plasma anti-GP titers comparable to the first experiment (Figure 1). Groups of 4 animals were challenged with Marburg Angola at 6 months and 12 months post-immunization.

Unvaccinated controls did not survive the challenge. In contrast, all animals challenged at 6 months and 75% challenged at 12 months survived (Figure 2). These data demonstrated the immediate and durable protective activity of the vaccine in NHP.

Figure 1 Vaccine-induced antibody responses and protection against infectious challenge with Marburg Angola in macaques

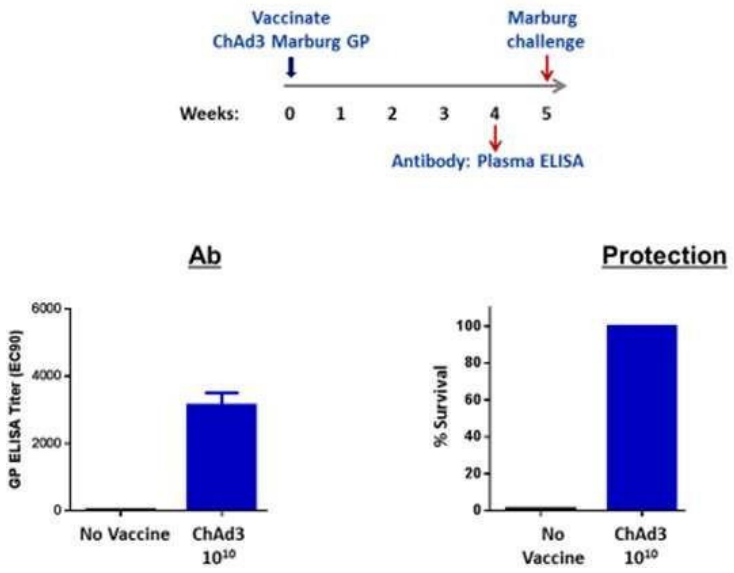

Figure 1: Animals (n=4) were vaccinated by the IM route with at 1 x1010 vp of ChAd3-MARV GP. Antibody responses were assessed by MARV GP ELISA at 4 weeks post vaccination and animals were challenged with 1000 PFU Marburg Angola 1 week later.

Figure 2 Durability of vaccine-induced antibody responses and protection against infectious challenge with Marburg Angola in macaques

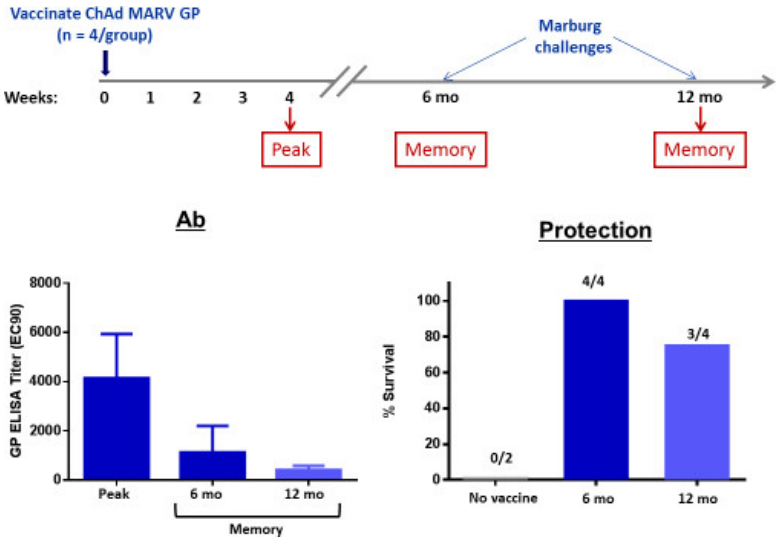

Figure 2: Animals (n=4/group) were vaccinated by the IM route with 1e10 particles of ChAd3-MARV GP. Antibody responses were assessed at the indicated time points and animals were challenged with 1000 PFU Marburg Angola 6 or 12 months post-vaccination.

1.4.2. Protection against Marburg Angola After a Marburg GP DNA Vaccine, an IM Dose of Marburg GP rAd5-vectored Vaccine, or Both

Each monkey in the DNA vaccine group (n=4) was injected intramuscularly with 4 mg MARV GP DNA vaccine at 0, 4, 8 and 23 weeks by Biojector® 2000 needle-free injection device. Monkeys in the MARV rAd5 only group were injected IM by needle and syringe with 10^{11} vp. Three animals received MARV GP DNA weeks 0, 4, and 8 as above then boosted 12 weeks after the third DNA injection at 20 weeks with rAd5 MARV GP. There was 100% protection from death in animals vaccinated with all three regimens [22].

1.5. Dose Justification for cAd3-MARV

Quantification of the vaccine is based on cAd3 PU, and the doses chosen for phase I testing are based on those 1) shown to be protective in the accepted challenge model and 2) demonstrated to be safe in animal toxicity studies. Doses between 10^{10} and 10^{11} PU of cAd3 were safe and demonstrated partial to complete protection in NHP challenge studies. The doses of cAd3 vector 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-MARADC087-00-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-MARADC087-00-VP when administered IM at a dose of 1 x 10^{11} PU to healthy adults.

2.2. Secondary Objectives

- To evaluate the antibody responses to the GP insert and cAd3 vector in VRC-MARADC087-00-VP at 4 weeks after vaccination as assessed by GP ELISA and vector-specific neutralization assays, respectively.

- To evaluate the Marburg GP-specific T cell responses in VRC-MARADC087-00-VP at 4 weeks after vaccination as assessed by ICS.

2.3. Exploratory Objectives

- To evaluate the immunogenicity of VRC-MARADC087-00-VP by various assay methods at some or all of the research sample collection timepoints 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.

- To evaluate plasmablasts to follow lineage development of anti-GP antibodies.

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 for all study groups:

- 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 antigen-specific and vector-specific neutralization assays 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 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 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 Marburg GP.

4.0 STUDY DESIGN AND METHODS

This is a Phase I open-label, dose escalation clinical trial to evaluate the safety, tolerability and immunogenicity of cAd3-vectored vaccines for Marburg WT GP in healthy adults. The study will be conducted at the WRAIR CTC in Silver Spring, Maryland, USA.

Twenty participants will be enrolled in each of the two dosage groups for cAd3-Marburg. 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 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. For the first 3 participants in each group, only one participant per day will be enrolled.

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 participants 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. Proof of identity includes a valid U.S. government-issued or state-issued photo ID such as a driver's license, military ID, or U.S. passport.

4. Able and willing to provide a personal mobile phone number or home phone number at which the participant can be reliably contacted. Participants will be contacted primarily for study visit 2A (Appendix 1), as a reminder of an upcoming visit, and after missed visits for rescheduling purposes.

5. Able and willing to complete the informed consent process and demonstrate understanding with a passing score (90% or greater) on the Assessment of Understanding (AOU) by the third attempt.

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

7. 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:

8. Hemoglobin ≥ 11.5 g/dL for women; ≥13.0 g/dL for men.

9. White blood cells (WBC) = 3,300-12,000 cells/mm^3.

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

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

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

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

14. HIV-uninfected as evidenced by a negative FDA-approved HIV diagnostic blood test.

Female-Specific Criteria:

15. Negative β-HCG (human chorionic gonadotropin) pregnancy test; serum β-HCG at screening (or urine if screening is the same day as enrollment) and urine β-HCG at enrollment if woman is of reproductive potential.

16. 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. Immunosuppressive medications within 2 weeks prior to enrollment.

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 syphilis serology. False-positive results will also exclude a participant.
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 study visits, permitted windows for completing the visits, and evaluations performed at each visit are shown in Appendix 1. Total blood volume drawn from each participant will not exceed 550 mL in any 8-week period.

5.1.1. Recruitment

Healthy adult participants, male and female, military and civilian, will be recruited by non-coercive means through the WRAIR CTC. Participants will be recruited from the Baltimore-Washington, D.C. area through the WRAIR CTC according to applicable U.S. Army regulations (i.e., 32 CFR 219 and 21 CFR 50, 54, 56, and 312). Participants will be recruited by the use of WRAIR IRB approved advertisements such as newspaper advertisements, flyers, posters, generic radio advertisements, social media posts, and word of mouth and referrals from participants currently in studies. All recruitment materials will have been reviewed and approved by the WRAIR IRB prior to their use. All recruiting methods will direct the participant to contact the CTC via e-mail or phone, or to the CTC web site where the same contact information will be given.

Participants can also be recruited via WRAIR 2038, which is a generic screening protocol managed by the WRAIR CTC. Under this screening protocol, participants will undergo a generic screening visit with medical history, exam, vitals, lab tests, along with other potential screening tests.

If the participant is interested in learning about this clinical trial, they will need to attend a briefing and sign this study's informed consent form. If the participant consents, the screening documentation from WRAIR 2038 can be shared with this study to fulfill screening requirements, and a copy of said documents can be added to the participant's study file for this clinical trial.

5.1.2. Consent Procedures and Screening

Following the briefing sessions, volunteers who remain interested in the study will be scheduled for a screening visit. At the beginning of the screening visit, written informed consent will be obtained from the volunteer by the PI or their designee. 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 5). The consenting process will be documented in the case report forms (CRFs).

After providing signed informed consent the volunteer will complete an AOU. Volunteers are allowed to take the AOU three times, but must have a passing score (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 successfully pass the AOU will then be screened as per the study protocol.

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 (or urine if screening is the same day enrollment) pregnancy test for all females
- CBC with total lymphocyte count
- Creatinine
- ALT
- HIV testing (including pre/post-test counseling)
- Syphilis testing
- Pre-existing vector immunity testing
- Serum storage for antibody assays
- Peripheral blood mononuclear cells (PBMC) and plasma for storage

Screening evaluations for specific eligibility criteria (see Sections 4.1.1 and 4.1.2) must be completed within the screening visit window specified (Appendix 1) prior to enrollment, but may be repeated, if the initial laboratory result is not deemed medically significant, within the screening visit window in order to confirm eligibility. Samples for storage may also be collected within the screening visit window. Counseling on the potential risks of becoming pregnant during study participation 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.

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.

5.1.3. Day 0 Through Week 48

Day 0 is defined as the day of protocol enrollment and the 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, blood chemistries, and urinalysis done at screening must repeated, as appropriate, before the participant receives the experimental vaccine. 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 SOE 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 or 60 minutes post-injection (60 minutes for first 3 participants of each group and a minimum of 30 minutes for subsequent participants in each group).
7. Diary Card: Baseline in the evening on the day of injection; 7-day diary card 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 and archiving
13. Intracellular RNA

At intervals specified in the SOE, blood will be drawn for safety and immunologic assays. Total blood volume drawn from each participant will not exceed 550 mL in any 8-week period. Research blood samples will be processed and stored at VIP.

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 not are validated for clinical use. Any remnant cells, serum, or plasma will be stored for future exploratory virological and immunological assays as per individual participant's consent for future use.

5.2. Administration of the Study Injection

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 if 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. Procedures for follow-up in the clinic after vaccination are shown in Appendix 1.

Following the study injection, participants will be observed in the WRAIR CTC for a minimum of 30 or 60 minutes (60 minutes for first 3 participants of each group and a minimum of 30 minutes for subsequent participants in each group). Vital signs (temperature, blood pressure, and pulse) will be taken 30 or 60 minutes post-injection. 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.

In the event of a severe allergic reaction, the CTC is staffed with trained medical personnel and stocked with appropriate medical emergency equipment to provide acute care for conditions such as anaphylaxis. Further, if required, a formal emergency medical response service (fire department), capable of treating and transferring any life-threatening injuries to a higher level of medical care, is available in close proximity to the trial site.

5.2.1. 7-Day Solicited Reactogenicity and Follow-up

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. Solicited symptoms that persist after the end of day 7 will be considered an AE/SAE and will be reported (see section 7.5) and followed through resolution.

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, unusually tired, muscles aches (other than at injection site), headache, chills, nausea, and pain at injection site. Participants will also 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.

5.2.2. Management of Reactogenicity and Other Adverse Events

Events following injection that may require clinical evaluation include a fever of 38.5˚C/101.3˚F (Grade 2) or higher lasting greater than 24 hours, rash, urticaria, or significant impairment in the activities of daily living (ADL). Fever of any severity or any condition which in the judgment of

the clinician should be evaluated 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 11.5.

5.2.3. Management of Laboratory Abnormalities Following Vaccination

If the ALT, creatinine, hemoglobin and/or platelet count are 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.

5.3. 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-approved vaccines. Receipt of a licensed vaccine during study participation will be recorded in the study database. Otherwise, a record of concomitant medication changes throughout the study will not be recorded in the study database.

5.4. 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 Materiel Command's (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO), NIAID, the U.S. FDA, U.S. DoD or the Office for Human Research Protection (OHRP).

5.5. Early Discontinuation or Withdrawal of Study Participants

A participant may be discontinued from protocol participation for the following reasons:

1. Repeated failure to comply with protocol requirements
2. Participant requests withdrawal
3. Participant develops a medical condition that is a contraindication to continuing study participation
4. 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.

The investigator also has the right to withdraw a participant, e.g., because of worsening health status, intercurrent illness, or other event, which makes further follow-up impossible.

As this is a phase I open label study, participants may be replaced if they did not receive the study injection. A volunteer who has been assessed as eligible for the study through screening will take the place of the participant that did not receive the study injection. The participant who did not receive the study injection will not count toward the total participants enrolled in the study.

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 for safety. Blood draws will be conducted for safety purposes only. The PI or designated associate investigator 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 status of the child.

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. No study product will be administered to a participant who is incarcerated. The IRB will be notified of the period of incarceration. 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 will be counseled again about the potential risks of being a participant in the study. A note to the effect that the counseling was done will be written in the progress notes in the participant's binder.

Any participant who is incarcerated for more than 6 months will be re-consented to include taking and passing the AOU.

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, and then referred to their primary care physician or to a local free clinic. For civilian study participants, these new diagnoses of HIV or syphilis will be reported to the State of Maryland Public Health Department. In accordance with Maryland state law, all reportable diseases are reported to the Health Department, along with the participant's name, contact information, including address and telephone numbers, and the type of testing that was done on this participant. If the individual is an Active Duty service member, the participant's new diagnosis will be reported to the Preventive Medicine service at the Walter Reed National Military Medical Center for further counseling and referral to care within the Military Health System. As part of the informed consent process, participants will be informed that a positive HIV test or a positive syphilis test will prompt reporting, and that if the participant is Active Duty, their chain of command may be informed.

6.0 PHARMACY AND VACCINE ADMINISTRATION PROCEDURES

Study treatment is defined as VRC-MARADC087-00-VP (cAd3-Marburg). The study groups are shown in Table 1.

6.1. Study Product Formulation, Storage, and Preparation

6.1.1. Formulation

The recombinant chimpanzee adenovirus Type 3-vectored Marburg vaccine, VRC-MARADC087-00-VP (cAd3-Marburg) is composed of a cAd3 vector that expresses Marburg WT GP. The drug substance was manufactured by Advent S.r.l. (Pomezia, Italy, a subsidiary of Okarios, Inc.) and the vaccine, VRC-MARADC087-00-VP 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 Marburg drug substance filled into single dose vials at 1 x 10^{11} PU/mL. Vials are aseptically filled under cGMP to a volume of >1.0 mL to allow withdrawal of 1.0 mL for IM administration. This monovalent vaccine will be tested at two doses, 1 x 10^{10} PU/mL and 1 x 10^{11} PU/mL. Additional details on VRC-MARADC087-00-VP 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-Marburg vaccine to prepare the 1 x 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 3 mL glass vials at a fill volume >1.0 mL to allow withdrawal of 1.0 mL. Additional diluent VRC-DILADC065-00-VP composition and manufacturing information can be found in the Investigator Brochure.

6.1.2. Study Product Labels

The labels for the VRC-MARADC087-00-VP (cAd3-Marburg vaccine) 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: New Drug – Limited by Federal Law to Investigational Use"), and manufacturer information.

6.1.3. Study Product Storage

VRC-MARADC087-00-VP (cAd3-Marburg vaccine) will be stored at ≤-60°C, and VRC-DILADC065-00-VP (cAd3 diluent) will be stored will be stored at -45°C to -10°C in a qualified, continuously monitored, temperature-controlled freezer.

If deviations in storage temperature occur from the normal allowance for the pharmacy freezer, the storage temperature excursion will be promptly reported 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.

6.1.4. Preparation of Study Product for Injection

This section describes how the site will prepare study injections. Clinician instructions on how to select an arm and administer the injection are in Section 5.2.

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

Preparation will be done in a clean preparation unit 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-MARADC087-00-VP (cAd3-Marburg) at $1x10^{10}$ PU dose
Preparation of the $1x10^{10}$ PU dosage of cAd3-Marburg requires one serial dilution. Remove one vial of cAd3-Marburg vaccine and two vials of cAd3 diluent from the freezer and allow them to equilibrate to room temperature. Using 1 mL sterile syringes, draw up 1 mL of diluent from one diluent vial and 0.35 mL from the other diluent vial and inject these volumes into a 10 mL sterile vial. Then, using a 1 mL sterile syringe draw up 0.15 mL of the $1x10^{11}$ PU/mL vaccine and inject this into the 10 mL 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 $1.5x10^{10}$ PU VRC-MARADC087-00-VP in 1.5 mL and has a concentration of $1x10^{10}$ 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-MARADC087-00-VP (cAd3-Marburg) at $1x10^{11}$ PU dose
No dilution is needed for preparation of the $1x10^{11}$ PU dosage of cAd3-Marburg vaccine. Remove one vial of vaccine from the freezer and allow it to equilibrate to room temperature. Withdraw a total of 1 mL from the vial. One 1 mL injection of the preparation will be administered for each dose. Discard remnant vaccine in a vial in a biohazard container for incineration.

6.2. Study Product Accountability

6.2.1. 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.

6.2.2. Documentation

The site 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 will be used.

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

6.2.3. Disposition

The empty vials and the unused portion of a vial will be discarded in a biohazard containment bag and incinerated or autoclaved following the injection. Any unopened vials that remain at the end of the study will be destroyed at the discretion of the VRC in accordance with policies that apply to investigational agents. Partially used vials or expired prepared doses will not be administered to other participants nor used for *in vitro* experimental studies and will be discarded as indicated above.

7.0 PHARMACOVIGILENCE, SAFETY AND ADVERSE EVENT REPORTING

7.1. Definitions

Adverse Events

An adverse event (AE) is any untoward or unfavorable medical occurrence in a 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 study product, whether or not considered related to the study product. (International Conference on Harmonization (ICH) E6) (Synonym: Adverse Experience).

Serious Adverse Events

As defined in 21 CFR 312.32, 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.”

“Life-threatening” refers to an adverse event that at occurrence represents an immediate risk of death to the participant; it does not refer to an event that hypothetically might have caused death if it were more severe. 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 9). Arthralgia (joint pain) and arthritis AEs will be graded in accordance with the criteria in Appendix 10.

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 attribution to study vaccine. 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 a Marburg vaccine study, in the extremely unlikely circumstance of Marburg diagnosis in a study participant at any time throughout the study, this will be recorded on a “Marburg 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 9, 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 10) 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. 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.

7.3. 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: Principal Investigator 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, 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- MARADC087-00-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- MARADC087-00-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- MARADC087-00-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^{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 and VRC will be provided with documentation of the safety review and notification of the plan.

7.4. Criteria for Study Pause or Termination

The Principal Investigator 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 conduct the review, consult with the FDA, if needed, 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 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 3/4 pause reviews.

When indicated, safety data reports and changes in study status (study pauses) will be submitted to the IRB in accordance with Section 12.2 and institutional policy.

7.5. Reporting Serious and Unexpected Adverse Events

7.5.1. 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).

7.5.2. Expedited Reporting of SAEs 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. 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 or 15 calendar days, the investigator must submit additional information as soon as it is available.

7.5.3. 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. Per FDA guidance, the IND Sponsor will submit any unexpected fatal or life-threatening suspected adverse reactions to the FDA as a written IND Safety Report as soon as possible, but no later than 7 calendar days following the IND Sponsor's initial receipt of the information.

The IND Sponsor is responsible for providing copies of IND Safety Reports for submission to the WRAIR IRB.

7.5.4. Reporting Serious and Unexpected Adverse Events to WRAIR and HPRO

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

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 WRAIR IRB.

IND Safety Reports from the VRC will be simultaneously submitted to the FDA via the IND sponsor and to the WRAIR IRB via the PI/designee. WRAIR HSPB will forward to USAMRMC ORP HRPO as per SOP UWZ-C-636.

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

7.6. 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 WRAIR 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 IRB by phone (301-319-9940) or by email (Usarmy.detrick.medcom-wrair.mbx.hspb@mail.mil) and to the IND sponsor via email. The Principal Investigator will then submit a written report within 10 working days to the WRAIR IRB at the following address: Walter Reed Army Institute of Research, ATTN: Human Subject Protection Branch (HSPB), 503 Robert Grant Ave, Silver Spring, MD 20910.

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 WRAIR IRB. The WRAIR HSPB will report unanticipated problems to the USAMRMC ORP HRPO as per UWZ-C-636.

The DoD medical monitor should also review the unanticipated events and provide an independent assessment for submission to the sponsor and WRAIR IRB (as a local medical research monitor’s report). WRAIR HSPB will report these summaries to USAMRMC ORP HRPO.

8.0 STATISTICAL CONSIDERATIONS

8.1. Overview

The primary objective of this study is to assess the safety and tolerability of cAd3 Marburg at two dose levels. The secondary objective is to evaluate the antibody and Marburg 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, isolating MAbs to determine epitope specificity, and evaluating plasmablasts to follow lineage development of anti-GP antibodies, 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-Marbug and followed 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=0.5) 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%
Each Individual Study Group	20	0.66	0.71	0.76
All participants	40	0.45	0.49	0.53

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 at 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) or continuous measures (Table 5). 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 timepoint that an assessment is performed. Binomial response rates will be presented with their corresponding exact 95% confidence interval estimates. Barnard's exact unconditional 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.

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 may 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. Safety labs may be completed by Quest Diagnostics Inc.

Immunogenicity of the VRC-MARADC087-00-VP vaccine will be evaluated as humoral and cellular immune responses assessed by ELISA and intracellular cytokine staining (ICS) assay. Other measures of immunogenicity may be also conducted as exploratory evaluations. The ELISA assay will be performed at the VRC or VIP and the exploratory evaluation of Marburg-specific neutralizing antibodies will be conducted at the VRC, using previously published methods [12]. The pre-existing and post-vaccination presence of cAd3 neutralizing antibody also will be evaluated [27]. 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 Marburg GP antigens and is based upon previously published methods [30].

Other measures of immunogenicity 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 [31]. Genetic factors associated with immune responses may also be evaluated; isolation of MAbs to determine epitope specificity and function 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 and plasmablasts to follow lineage development of anti-GP antibodies.

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 16).

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, Gaithersburg, MD or at 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 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 institutional policies. 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, microfiches, 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 USAMRMC ORP HRPO, WRAIR IRB, FDA, the U.S. DoD, 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 (if kept)
- 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) and the NIH requires study record retention for a minimum of 7 years after study closure. Study records will be retained for at least as long as is required by the FDA and NIH 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 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 described applicable.

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

10.0 MEDICAL CARE FOR INJURY OR ILLNESS

All non-exempt research involving human participants shall, at a minimum, meet the requirement of 32 CFR 219.116(a)(6).

If a participant is injured because of participation in this research and is a DoD healthcare beneficiary (e.g. military spouse or dependent), the participant is entitled to medical care for that injury within the DoD healthcare system, as long as the participant remains a DoD healthcare beneficiary. This care includes, but is not limited to, free medical care at DoD hospitals or clinics.

If a participant is injured because of participation in this research and is not a DoD healthcare beneficiary, the participant is entitled to medical care for that injury at a DoD hospital or clinic; medical care charges for care at a military hospital or clinic will be waived. It cannot be determined in advance which military hospital or clinic will provide care. If the participant obtains care for research-related injuries outside of a DoD hospital or clinic, the study clinical trial insurance will be responsible for medical expenses. While it is anticipated that the insurance policy is enough to pay for the costs associated with this study, there is a limit to the amount of coverage available. If the limit is exceeded, the participant will have to pay non-covered costs.

For all participants: Transportation to and from DoD hospitals or clinics will not be provided, except in emergencies or situations where a non-DoD health care beneficiary requires a military escort for access to said hospitals or clinics. No reimbursement is available if the participant incurs medical expenses to treat research-related injuries. The study sponsor and the U.S. DoD will not provide long-term medical care or financial compensation for research-related injuries. The participant is not waiving any legal rights. The participant should contact the PI if the participant believes he or she has sustained a research-related injury. The participant should contact the PI for any questions.

11.0 ETHICAL CONSIDERATIONS

This research study will be conducted in compliance with the protocol, Good Clinical Practices (GCP) guidelines, and all applicable regulatory requirements.

11.1. Informed Consent

The study informed consents are provided in Appendix 2. The main study consent describes the investigational product 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 IRB. 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, 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. 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.

Four (4) 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)
iv. State of Maryland HIV Testing Consent Form (Appendix 2d)

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 reasons.

If the volunteer is an Active Duty service member, it is the volunteer's responsibility to obtain their supervisor's permission to participate in the study.

11.2. 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 USAMRMC ORP HRPO, WRAIR IRB, FDA, the U.S. DoD, 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 social security number. Electronic data will be stored for at least 2 years after the IND is inactivated.

11.3. Risks

11.3.1. Risks of the cAd3-Marburg Vaccine

Potential side effects resulting from intramuscular injection include pain, stinging, arm discomfort, redness of the skin 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 be observed in the clinic for 30 or 60 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 [16, 23, 24]. 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.

11.3.2. Other Risks

Blood drawing with needles, like injections, may cause pain, bruising, 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.

11.4. Benefits

Although study participants may benefit from clinical testing and physical examinations, study participants will receive no direct benefit from participation. Others may benefit from knowledge gained in this study that may aid in the development of a Marburg vaccine.

11.5. Compensation

Non-military and non-federally employed participants will receive $200 for their time, blood draws and inconvenience for the vaccination visit, $150 for each scheduled follow-up visit, and $50 for each screening visit. Participants will only receive $50 on Day 14 if they do not return their completed Diary Card, unless otherwise specified by the PI. Unscheduled visits may be compensated up to $100 each, at the discretion of the PI.

By regulation, active duty personnel and federal employees can be compensated only for visits in which blood draws occur, and then only $50 per visit, unless the visits occur during off-duty hours or when they are on leave and the individual has been granted approval for off duty employment in the study by their supervisory chain of command, according to the cognizant command's procedures. In such a circumstance, he or she will be paid the same as non-military/non-federal personnel.

11.6. Future Use and Storage of Specimens and Data

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, samples 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.

12.0 REGULATORY REPORTING REQUIREMENTS

12.1. 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 to the WRAIR IRB is determined by the categorization of the deviation: (1) emergent/significant or (2) non-emergent/minor. Protocol deviations arising from 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 7.6.

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 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 IRB and the IND sponsor, upon becoming aware of the event, by telephone or email. A written report is required to be submitted by the PI to the WRAIR IRB and the VRC within 10 working days of knowledge of the significant deviation. Deviations will be reported by the WRAIR HSPB to the USAMRMC 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 sponsor and the WRAIR IRB in a summary report with the annual continuing review report and the closeout report.

12.2. Safety Reports

Safety Reports issued by the study Sponsor will be forwarded to the WRAIR IRB and applicable regulatory bodies. The WRAIR HSPB will forward to USAMRMC ORP HRPO as per SOP-UWZ-C-636.

12.3. 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 IRB.

12.4. Study Holds

The PI will immediately notify the WRAIR IRB if any study pause criteria are met, as determined by the PSRT. The WRAIR HSPB will forward all study-hold reports to the USAMRMC ORP HRPO as per SOP-UWZ-C-636.

12.5. Continuing Review and Closeout Reports

The PI is responsible for submitting the required continuing review reports and associated documents to the WRAIR IRB for review and approval, allowing sufficient time for review and continuation determination prior to the established continuing review date. Summaries of

enrollment and safety reports will be provided in the continuing review report, as they are made available by the sponsor.

After all study related activities, including data analysis are completed, a closeout report will be submitted as required to the same bodies.

A closeout report will be submitted after 5 years or upon completion of the study, whichever occurs first. The WRAIR HSPB will forward CRRs and closeout report to the USAMRMC ORP HRPO as per SOP-UWZ-C-636.

12.6. Modification of Protocol

Any change or amendment to the protocol (including but not limited to changes in the principal investigator, inclusion/exclusion criteria, number of participants to be enrolled study sites, or procedures) will require a formal amendment to the protocol. Such amendment will be submitted to the WRAIR IRB, after review and approval by the IND Medical Officer and the VRC IND Regulatory Representative and prior to implementation. The WRAIR IRB will submit protocol amendments and modifications to the USAMRMC ORP HRPO as per SOP UWZ-C-636. Amendments that may potentially increase the risks to study participants or others will require review and approval by USAMRMC ORP HRPO prior to issuance of the WRAIR Commander Approval Authorization.

Modifications or updates to the investigational brochures (IBs) will also be submitted as protocol amendments to the WRAIR IRB for review and approval.

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.

The PI, WRAIR IRB, USAMRMC ORP HRPO, the U.S. DoD, the FDA, and the sponsor reserve the right to terminate the study. The investigator will notify the IRB in writing of the study's completion or early termination.

12.7. Reporting Requirements to the MRMC 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 USAMRMC ORP HRPO defines a substantive modification as a change in Principal Investigator, 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 USAMRMC 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 USAMRMC ORP HRPO. The report must include actions taken by the institution and the IRB.

12.8. Volunteer Registry Data Sheet

The US Army Medical Research and Materiel Command (USAMRMC) requires that investigators complete data sheets on all participants participating in this protocol for entry into the Command's Volunteer Registry Database. This Volunteer Registry Database Sheet (VRDS) contains items of personal information, such as participant's name, address, Social Security Number, study identity, and dates of participation.

The intent of this database is twofold: first, to readily answer questions about an individual's participation in research sponsored by the USAMRMC; and second, to ensure that USAMRMC can exercise its obligation to ensure that all research study participants are adequately warned (duty to warn) of risks and to provide new information as it becomes available. This information will be stored at USAMRMC for a minimum of 75 years and is kept confidential. The Volunteer Registry Data Sheet is a separate form and is not linked to the study database.

12.9. 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. 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).

13.0 CONDUCT OF THE RESEARCH STUDY

This research study will be conducted in accordance with ICH GCP 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.

13.1. Regulatory Audits

The knowledge of any pending compliance inspection/visit by the FDA, DHHS Office of Human Research Protections (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, must be promptly reported to the IND sponsor and the WRAIR IRB.

13.2. 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 IRB, USAMRMC ORP HRPO, U.S. DoD and the FDA to inspect study documents (e.g., consent forms, drug accountability and dispensing records, CRF), 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.

14.0 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 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 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.

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Principal Investigator Signature Date (DD/MM/YYYY)

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APPENDIX 1: SCHEDULE OF EVALUATIONS

RV 507 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									
RV 507 AoU, Informed Consent		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			X		X	X						
Telephone contact; clinic visit if indicated				X								
Counseling on pregnancy prevention		X	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]		2	X					X			X	
Creatinine and ALT	Coagulant	4	4		4		4	4	4			
HIV[5] and RPR		11										
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	30	80			60	40	80	60	60	80	80
Intracellular RNA	PAXgene		3		6	6						
HLA type[4]	Anti-coagulant								10			
Daily Volume (mL)		**62**	**102**	**0**	**25**	**78**	**59**	**99**	**89**	**72**	**95**	**91**
Max. Cumulative Volume (mL)		**62**	**164**	**164**	**189**	**267**	**326**	**425**	**514**	**586**	**681**	**773**

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 15 to 60 minutes post-vaccination). Subjects must remain in the clinic for a minimum of 30 or 60 minutes (60 minutes for first 3 participants of each group and a minimum of 30 minutes for subsequent participants in each group) 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.

[4] HLA type blood sample is collected once at any time point in the study and is shown as a Visit 04 evaluation for convenience. HLA type may also be obtained from a frozen sample.

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

APPENDIX 2: INFORMED CONSENT FORMS

APPENDIX 2A: MAIN INFORMED CONSENT FORM

MAIN STUDY INFORMED CONSENT FORM

Study Title: RV 507, "A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of the Marburg Chimpanzee Adenovirus Vector Vaccine, VRC-MARADC087-00-VP (cAd3-Marburg), 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 Agent Provided by: NIH/NIAID/VRC

Collaborating Institutions: Walter Reed Army Institute of Research (WRAIR), U.S. MHRP and NIH/NIAID/VRC

Principal Investigator: LTC Melinda Hamer, MD

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 informed consent will be provided to you. This consent must be signed 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-MARADC087-00-VP, but we will refer to it as "cAd3-Marburg" or simply as the "Marburg vaccine." The study vaccine does not contain live or killed Marburg virus. It is **impossible** for the study vaccine to give you a Marburg virus infection.

This research study is funded by the U.S DoD and the NIAID/NIH. The U.S. MHRP and the WRAIR Clinical Trials Center (CTC) are conducting this research study in Silver Spring, MD.

PURPOSE AND BACKGROUND

This research study will evaluate an experimental vaccine for the Marburg Virus. "Experimental" means that it is not known if the vaccine works to prevent Marburg Virus Disease (MVD). Since it is not known if the vaccine works, it has not been approved by the US Food and Drug Administration (FDA). 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 Marburg 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 Marburg virus was discovered in 1967 in a laboratory in Marburg, Germany. Bats probably carry the virus in certain parts of Africa. MVD 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 outbreak of Marburg in Germany and Yugoslavia in 1967 caused 7 deaths among 31 people who were infected. In 2005, an outbreak of Marburg virus in West Africa caused 227 deaths among the 252 people who were infected (90% fatality rate). In October 2017, the Ugandan Ministry of Health officially declared an outbreak of MVD in eastern Uganda. As of November 2017, there have been 3 fatal cases, with over 100 individuals being monitored for potential infection.

STUDY VACCINE

The experimental Marburg 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 studied in test tubes and animals. Both parts of this experimental Marburg vaccine have been separately tested in humans, but this is the first time that this combination of vaccine parts will be tested in humans.

One part of the Marburg vaccine, a virus called chimpanzee Adenovirus 3 (cAd3), is used to deliver a piece of the Marburg virus to cells in your body. The chimpanzee 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.

The Marburg virus piece has also been tested in people. Once the Marburg virus piece is delivered to the cells in your body, your body may then make an immune response. You cannot become infected with or infect someone else with either Marburg 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 Marburg vaccine is based on dose levels found to be safe in previous studies of 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 507 Study Groups		
Group	**Participants**	**Vaccine Dose**
1	20	cAd3-Marburg at $1x10^{10}$ PU IM
2	20	cAd3-Marburg 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 less than an hour. 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 (a valid U.S. government-issued or state-issued photo ID such as a driver's license, military ID, or U.S. passport), and able to provide a personal cell phone number or home phone number at which you can reliably be contacted. Study investigators will use your phone number to follow-up with you a day or two after you receive the vaccination, to remind you of upcoming study visits, and to reschedule any missed appointments. You must also be able to read this consent form, understand and complete the

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.

Volunteers who are active duty military personnel must receive written approval from their supervisor prior to participating in the study, per WRAIR Policy Letter 12-28.

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. The results of these tests will be kept confidential; however, the study staff is required by law to report the results, if positive, to the local health authorities. The test results reported to local health authorities will contain your name, contact information (including address and telephone numbers), and the type of testing that was done on you as required by state law.

A serum (blood) pregnancy test will be required at the screening visit if you are female and able to become pregnant. The researchers 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 a hospital or clinic for medical treatment.

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 and you don't have a doctor, then the study staff will help you locate 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.

c) Enrollment and Follow-up Visits

If you are one of the first three participants in either vaccination group, the clinic staff will observe you for at least 60 minutes after the injection at the enrollment visit. Otherwise, the clinic staff will observe you for at least 30 minutes after the injection.

You will be asked to complete a diary card and look at your injection site at home 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 be asked to come to the clinic if you have a fever of 101.3˚F (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, 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 5 teaspoons (25 mL) to about 7 tablespoons (102 mL), 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 about 3 cups (773 mL).

You will not have more than 550 mL (less than 2.5 cups) of blood drawn over any 8-week 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) for future research to learn more about Marburg 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.

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 THIS STUDY PARTICIPATION

This section describes the risks associated with the experimental Marburg vaccine and other study procedures. There may be additional risks related to the experimental Marburg 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, 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, and fatigue. 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 Marburg 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. There are currently no vaccines approved for use to protect against Marburg virus infection. Receipt of this experimental Marburg vaccine may affect your response to future vaccines against Marburg. 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 MVD, have no effect on protection, or increase your risk of MVD. 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 a Marburg 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 as soon as possible about any side effect you think you are having that may be serious or cause concern. 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 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 WRAIR 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 WRAIR 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

Non-military and non-federally employed participants will be compensated $200 for time, blood draws and inconvenience for the vaccination visit, $150 for each scheduled follow-up visit, and $50 for each screening visit. Participants will be compensated up to $100 for each unscheduled visit, but only if the Principal Investigator/ designee finds it necessary. Participants who do not complete or lose the Diary Card will only be compensated $50 at visit 2D (14 days post-vaccination).

By regulation, military personnel and civilian government employees can only be compensated for visits at which blood draws occur, and then only $50 per visit, unless the visit occurs during off duty hours or when on leave with permission from a supervisor. Visits that occur during off duty hours or when on leave will be compensated at the same rate as non-military/non-federally employed participants as stated above.

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. Melinda Hamer, 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 Materiel Command (USAMRMC), the DoD, the NIAID, the WRAIR IRB, the FDA, the Office for Human Research Protections, and other regulatory 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.

Additionally, it is the policy of the USAMRMC that data sheets are to be completed on all study volunteers participating in research for entry into this Command's Volunteer Registry Data Base. The information to be entered into this confidential database includes your name, study number, date of birth, contact information, address, study title and dates participating in study, any adverse events related to the vaccine, and details of which study products you received. The intent of the data base is two-fold: first, to readily answer questions concerning an individual's participation in research sponsored by USAMRMC; and second, to ensure that the USAMRMC can exercise its obligation to ensure research study volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at USAMRMC for a minimum of 75 years. Please note that your name and study number will be stored separately from the USAMRMC volunteer registry database.

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 are injured because of your participation in this research and you are a DoD healthcare beneficiary (e.g., military spouse and their dependents), you are entitled to medical care for your injury within the DoD healthcare system as long as you remain a DoD healthcare beneficiary. This care includes, but is not limited to, free medical care at military hospitals or clinics.

If you are injured because of your participation in this research and you are not a DoD healthcare beneficiary, you are entitled to medical care for your injury at a military hospital or clinic. Medical care charges will be waived. It cannot be determined in advance which military hospital or clinical will provide care. If you obtain care for research-related injuries outside of an Army hospital or clinic, the study clinical trial insurance will be responsible for medical expenses. While we anticipate that the insurance policy is more than enough to pay for the costs associated with this study, there is a limit to the amount of coverage available. If the limit is exceeded, you will be responsible for paying the non-covered costs. The study sponsor and the DoD will not provide long-term medical care for research-related injuries.

For all participants, transportation to and from hospitals or clinics will not be provided. No reimbursement is available if you incur medical expenses to treat research-related injuries. No compensation is available for research-related injuries. You are not waiving any legal rights. If you believe you have sustained a research-related injury or if you have any questions about study-related sickness or injury, you can contact the PI:

Dr. Melinda Hamer
WRAIR CTC
[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 or the WRAIR CTC [redacted] 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 IRB, or the FDA 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 Marburg 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. Melinda Hamer [redacted] or the WRAIR CTC study staff [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 WRAIR IRB [redacted]; [redacted] or by e-mail [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 507 "A Phase 1 Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of the Marburg Adenovirus Vector Vaccine, VRC-MARADC087-00-VP (cAd3-Marburg), in Healthy Adults"

The principal investigator Dr. Melinda Hamer 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. Melinda Hamer [redacted] and the WRAIR CTC study staff [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 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 507, "A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of the Marburg Chimpanzee Adenovirus Vector Vaccine, VRC-MARADC087-00-VP (cAd3-Marburg), 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 Agent Provided by: NIH/NIAID/VRC

Collaborating Institutions: Walter Reed Army Institute of Research (WRAIR), U.S. MHRP and NIH/NIAID/VRC

Principal Investigator: LTC Melinda Hamer, MD

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. Some of the blood samples may be stored in the sponsor's laboratory for testing how your body fights Marburg 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 as 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 Marburg or Vaccines

Researchers are able to measure how the immune system responds by looking at blood samples. We will try to understand why Marburg disease progresses differently in some people. As new methods (or

ways) of measuring the body's immune response to Marburg 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 Marburg. 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 Marburg and how vaccines can prevent Marburg infection.

Your Samples Used for Future Research May Be Shipped to the Sponsor's Laboratory or to Regional Laboratories

Your samples will be stored in a secure central storage site (not at the WRAIR CTC) in the sponsor's laboratory. 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 study records at the WRAIR CTC. 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 contact 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, 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 Dr. Melinda Hamer b[redacted] or the WRAIR CTC study staff [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, contact the WRAIR IRB [redacted] or by e-mail [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 stored for future testing and then sign the consent form 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 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 507, "A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of the Marburg Chimpanzee Adenovirus Vector Vaccine, VRC-MARADC087-00-VP (cAd3-Marburg), 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 Agent Provided by: NIH/NIAID/VRC

Collaborating Institutions: Walter Reed Army Institute of Research (WRAIR), U.S. MHRP and NIH/NIAID/VRC

Principal Investigator: LTC Melinda Hamer, MD

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 Marburg and other diseases affected by Marburg 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 Marburg. 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 Marburg and to other diseases affected by Marburg.

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 May Be Shipped to the Sponsor's Laboratory or Other Regional Laboratories

In order to complete the genetic testing on your blood samples, they may be shipped and stored at the sponsor's laboratory. 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 to outside collaborators, 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 in 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. It is possible that if others found out genetic information about you that is learned from tests 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. However, the risk of this happening is extremely low, because your results will not be part of your study records at the WRAIR CTC.

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, 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 Dr. Melinda Hamer [redacted] or the WRAIR CTC study staff [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, contact the WRAIR IRB [redacted] or by e-mail [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 the consent form 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: STATE OF MARYLAND HIV TESTING CONSENT FORM

Informed Consent and Agreement to HIV Testing

I understand the following information, which I have read or has been read to me:

- Blood, or another body fluid or tissue sample, will be tested for human immunodeficiency virus (HIV) infection;
- Consent to be tested for HIV, the virus that causes AIDS, should be given FREELY;
- Results of this test, like all medical records, are confidential, but confidentiality cannot be guaranteed; and
- If positive test results become known, an individual may experience discrimination from family or friends and at school or work.

What a NEGATIVE Result Means:

- A negative test means that HIV infection has not been found at the time of the test.

What a POSITIVE Result Means:

- A positive HIV test means that a person is infected with HIV and can transmit the virus by having sex, sharing needles, childbearing (from mother to child), breastfeeding, or donating organs, blood, plasma, tissue, or breast milk.
- A positive HIV test DOES NOT mean a diagnosis of AIDS -- other tests are needed.

What Will Happen if the Test Is Positive:

- A copy of the Department of Health and Mental Hygiene's publication "Information for HIV Infected Persons" will be provided;
- The health department or my doctor will offer advice about services that are available;
- Women who are pregnant or may become pregnant will be told of treatment options which may reduce the risk of transmitting HIV to the unborn child;
- Information will be provided on how to keep from transmitting HIV infection;
- My name will be reported to the health department for tests that indicate HIV infection. This includes, but is not limited to: HIV Antibody (Western blot), HIV Viral Load (RNA or DNA quantification), HIV viral sequencing or HIV p24 antigen tests;
- My name will be reported to the health department if my doctor finds that I have AIDS;
- I will be offered assistance in notifying and referring my partners for services. If I refuse to notify my partners, a doctor may notify them or have a representative of the local health department do so. If a representative of the local health department notifies my partners, my name will not be used. Maryland law requires that when a local health department knows of my partners, it must refer them for care, support, and treatment.

I have been given a chance to have my questions about this test answered.

I hereby agree to be tested for HIV infection.

Print name of individual to be tested in the boxes below:

First Name Middle Init.

Last Name

Signature of Individual to be Tested
(or Authorized Substitute)

Date

Signature of Counselor or Health Care Provider

Date

APPENDIX 2E: WITHDRAWAL OF CONSENT FOR SAMPLE STORAGE

WITHDRAWAL OF CONSENT FOR SAMPLE STORAGE

Study Title: RV 507, "A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of the Marburg Chimpanzee Adenovirus Vector Vaccine, VRC-MARADC087-00-VP (cAd3-Marburg), 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 Agent Provided by: NIH/NIAID/VRC

Collaborating Institutions: Walter Reed Army Institute of Research (WRAIR), U.S. MHRP and NIH/NIAID/VRC

Principal Investigator: LTC Melinda Hamer, MD

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: ACTIVE DUTY SUPERVISOR'S APPROVAL

FOR WRAIR ACTIVE DUTY SERVICE MEMBERS: STATEMENT OF SUPERVISORS' APPROVAL

I would like to participate in the study, WRAIR Protocol RV 507, "A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of the Marburg Chimpanzee Adenovirus Vector Vaccine, VRC-MARADC087-00-VP (cAd3-Marburg), in Healthy Adults". I have reviewed the schedule of events for the study and do not believe that my participation will interfere with my normal duties.

- Compensation may vary depending on whether study events are done during normal duty hours or off-duty. If scheduled visits are to be done during duty hours, my supervisor will note by initialing on the study's 'schedule of events'.
- I will review the study and schedule with my chain-of command (listed below). I understand I need their approval to participate.
- I will inform my supervisor and the study team if I am a subject in another human research study.
- Copies of the form(s) will be placed in my study file.

Study Subject:

_____	_____	_____
(Print)	*(Sign)*	*(Date)*

Supervisory Chain-of-Command:

- I understand that participation in this study will require the federal employee's time and there may be side effects that might compromise their performance.
- I approve the Service member's participation in this study.

_____	_____	_____
Supervisor *(Print)*	*(Sign)*	*(Date)*
_____	_____	_____
Branch Director *(Print)* Or Equivalent	*(Sign)*	*(Date)*
_____	_____	_____
Company Commander *(Print)* Or Equivalent	*(Sign)*	*(Date)*

APPENDIX 4: FEDERAL EMPLOYEE DESIGNATION FORM

MCMR-UWZ
SUBJECT: WRAIR Policy Letter 12-28, Compensation to Federal Personnel When They Participate in Research as Human Subjects

INFORMATION SHEET REGARDING COMPENSATION TO FEDERAL PERSONNEL WHEN THEY PARTICIPATE IN RESEARCH AS HUMAN SUBJECTS

WRAIR Protocol RV 507/WRAIR #2438, "A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of the Marburg Chimpanzee Adenovirus Vector Vaccine, VRC-MARADC087-00-VP (cAd3-Marburg), in Healthy Adults".

If you are currently a federal employee (military or civilian) or become a federal employee while you are a research subject in this study, you need to be aware of certain payment restrictions due to U.S. laws. If you are a federal employee or become one during this study, please inform the study team right away.

As a federal employee, you can only receive payment for your participation in research supported by the Department of Defense (DoD) if you are on leave or off-duty. The laws requiring this are in place to ensure that federal employees are not paid twice for the same time period ("double-dipping"). There is one exception to this requirement: all research participants can receive up to $50 per blood draw even while on duty.

Please indicate below whether or not you are a federal employee, then sign and date this form. A copy of the signed form will be kept with the study records.

For Active Duty service members, the definitions of "on leave" and "off duty" are determined by your supervisor. Please talk with your supervisor about his/her requirements for your participation as a research subject. In order for any Active Duty service members to participate in research as human subjects, you must have your immediate supervisor, Branch Director and Company Commander sign the "Statement of Supervisors' Approval", Appendix B. You should utilize the provided study "Schedule of Events", which details the planned dates and duration of study visits, to discuss the study with your chain of command. You must submit Appendix B, signed and dated, to the study team before you can participate in the study. A copy of Appendix B will be placed in the study file.

If you have any questions or concerns about this federal policy, please do not hesitate to contact the WRAIR Human Subjects Branch (HSPB) by phone at 301-319-9940 or by email: usarmy.detrick.medcom-wrair.mbx.hspb@mail.mil.

Check your work designation below:

☐ I am a federal employee *(check one):*
- ☐ Civilian
- ☐ Active Duty military

☐ I am NOT a federal employee, but will inform the study staff if that changes during the study.

If you have any questions or concerns about this federal policy, please do not hesitate to contact the WRAIR HSPB by phone at 301-319-9940 or by email: usarmy.detrick.medcom-wrair.mbx.hspb@mail.mil

Participant signature:_____Date: _____

This Policy Letter supersedes **WRAIR Policy Letter 11-45,** dated 30 Sep 2011.

APPENDIX 5: 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	$50	
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 • Blood draw • Females: Pregnancy test & counseling	$200	
Week 1 **1 day post-vaccination** (+ 1 day)	**Visit # 2A** **(5 minutes)**	• Phone contact with clinic, clinic visit if necessary	$100 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	$150	
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	$150	
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	$150 ($50 if Diary Card is not completed or lost)	

Study Day Timeline	Visit ID	Procedures	Compensation*	Scheduled Date
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	$150	
Week 8 (± 7 days)	**Visit # 4** **(30 minutes)**	• Physical Exam (as required) • Updating medical history and assessments • Blood draw • Females: pregnancy prevention counseling	$150	
Week 16 (± 14 days)	**Visit # 5** **(30 minutes)**	• Physical Exam (as required) • Updating medical history and assessments • Blood draw • Females: pregnancy prevention counseling	$150	
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	$150	
Week 48 (± 14 days)	**Visit # 7** **(30 minutes)**	• Physical Exam (as required) • Updating medical history and assessments • Blood draw	$150	

*NOTE: WRAIR Policy Letter 12-28 states that Federal Employees who are on duty may only be compensated $50 per blood draw. Federal employees will be compensated the same way as non-Federal employees if their participation in this study is while "off duty" or on leave.

APPENDIX 6: VOLUNTEER REGISTRY DATA SHEET

VOLUNTEER REGISTRY DATA SHEET (USAMRMC 60-R)

THIS FORM IS AFFECTED BY THE PRIVACY ACT OF 1974

1. AUTHORITY: 5 USC 301; 10 USC 1071-1090; 44 USC 3101; EO 9397

2. Principal and Routine Purposes: To document participation in research conducted or supported by the U.S. Army Medical Research and Materiel Command. Personal information will be used for identification and location of participants.

3. Mandatory or Voluntary Disclosure: The furnishing of the SSN is mandatory and necessary to provide identification and to contact you if future information indicates that your health may be adversely affected. Failure to provide information may preclude your participation in the research study.

PART A - INVESTIGATOR INFORMATION
(To Be Completed by the Investigator)

PLEASE PRINT, USING INK OR BALLPOINT PEN

1. HRPO Study Number: A-17044.68

2. Protocol Title: "A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of the Marburg Chimpanzee Adenovirus Vector Vaccine, VRC-MARADC087-00-VP (cAd3-Marburg), in Health Adults"

3. Contractor/Awardee (Laboratory / Institute Conducting Study): Walter Reed Army Institute of Research (WRAIR) Clinical Trials Center (CTC)

4. Study Period: From: ____/____/____ To: ____/____/____

DD MM YY DD MM YY

5. Principal/Other Investigator(s) Names: LTC Melinda Hamer, MD

6. Location/Laboratory: WRAIR CTC

PART B - VOLUNTEER INFORMATION
(To Be Completed by the Volunteer)

PLEASE PRINT USING INK OR BALLPOINT PEN

7. SSN: ____/____/____ 8. Name: ____

9. Sex: M F_ 10. Date of Birth:___/___/____ 11.*MOS/Job Series:____ *12. Rank/Grade: ____

13. Permanent Home Address (Home of Record) or Study Location:

____
(Street) (P.O. Box/Apartment Number)

____
(City) (Country) (State) (Zip Code)

Permanent Home Phone Number: ____

14. *Local Address (If Different From Permanent Address):

____
(Street) (P.O. Box/Apartment Number)

____
(City) (Country) (State) (Zip Code)

Local Phone Number: ____

15. *Military Unit:____ Zip Code: ____

Organization:____ Post:____ Duty Phone Number: ____

PART C - ADDITIONAL INFORMATION
(To Be Completed by the Investigator)

PLEASE PRINT USING INK OR BALLPOINT PEN

16. Location of Study: _____

17. Is Study Completed?: Y:_____N: _____

Did volunteer finish participation?: Y: _____ N: ____

If YES, date finished:_____/____/_____

DD MM YY

If NO, date withdrawn:____/____/_____Reason Withdrawn: _____

DD MM YY

18. Did any Serious or Unexpected Adverse Incident or Reaction Occur?: Y:_____N: _____

If YES, explain: _____

_____

19. *Volunteer Follow-up: _____

Purpose:

Date: _____/____/_____ Was contact made?: Y: _____ N: _____

DD MM YY

If no action taken, explain:_____

20. *Hard Copy Records Retired: Place: _____

File NR: _____

21. *Product Information:

Product:_____Manufacturer:_____

Lot #:_____Expiration Date: _____

NDA #:_____IND/IDE #: _____

*Indicates that item may be left blank if information is unavailable or does not apply. Entries must be made for all other items.

Upon completion of the study, a copy of this form should be sent to the address below:

Commander
U.S. Army Medical Research and Materiel Command
ATTN: MCMR-ZB-P
Fort Detrick, MD 21702-5012

APPENDIX 7: 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 Marburg.
True ☐	False ☐	3.	There are no possible risks or side effects associated with receiving the Marburg vaccine.
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 the first vaccine through 24 weeks (6 months) after the first vaccination.
True ☐	False ☐	9.	There is a possibility that I can become infected with Marburg 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.
☐	☒	2.	The vaccine in this study will definitely protect me against Marburg.
☐	☒	3.	There are no possible risks or side effects associated with receiving the Marburg vaccine.
☒	☐	4.	There will be no direct benefit to me for participating in the study.
☒	☐	5.	I may leave the study at any time.
☒	☐	6.	Participation in the study will last for approximately 48 weeks (11 months).
☒	☐	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.
☒	☐	8.	Women participating in the study must use effective birth control 21 days prior to the first vaccine through 24 weeks (6 months) after the first vaccination.
☐	☒	9.	There is a possibility that I can become infected with Marburg from the study vaccine.
☒	☐	10.	I will be asked to keep a detailed diary of possible side effects for seven days after vaccination.

APPENDIX 8: BRIEFING SLIDES

WALTER REED ARMY INSTITUTE OF RESEARCH
(WRAIR)

Briefing for the Marburg Vaccine Study
RV 507/WRAIR #2438

Basic Information

Study Title: "A Phase I, Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of the Marburg Chimpanzee Adenovirus Vector Vaccine, VRC-MARADC087-00-VP (cAd3-Marburg), in Healthy Adults"

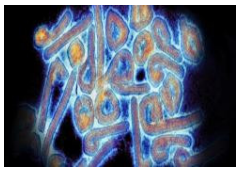
Study Location: Clinical Trials Center, WRAIR

Principal Investigator: LTC Melinda Hamer, MD

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?)
  - Immunogenicity (Can this vaccine produce an immune response in humans?)
    - Immune responses are the ways your body recognizes and defends itself against bacteria, viruses, or anything that appears harmful to the body

Background-Marburgvirus



- The Marburg virus is in the same virus family as Ebola
- The Marburg virus was first identified in 1967 in a laboratory in Germany, 9 years before Ebola was discovered
- Causes severe fevers with internal and external bleeding and has a significant risk of death, similar to the Ebola virus
- Found primarily in Southern Africa
  - 8 small outbreaks and 3 large outbreaks have occurred sporadically since the virus was identified
  - 1998-2000: 154 cases and 128 deaths (80% fatality rate) in Democratic Republic of Congo
  - 2004-2005: 227 cases and 252 deaths (90% fatality rate) in Angola
  - October 2017: Ugandan Ministry of Health declared an outbreak in Uganda. As of November, 3 deaths and 100 individuals being monitored for possible infection.
- It is not clear where these viruses originate from, but it is thought that bats are the most likely source of the human outbreaks that occur
- Once an outbreak occurs, the virus is spread from person to person through direct contact with an infected individual's blood or body fluids

Background-Marburgvirus

- Signs and Symptoms include:
  - Fever over 101.5 °F
  - Headache
  - Weakness and muscle aches
  - Abdominal pain
  - Diarrhea
  - Vomiting
  - Poor appetite
  - Bruising or bleeding
  - Multi-organ failure
  - Coma
  - Death
- Symptoms typically appear 2-21 days after becoming infected
- Up to 90% mortality

You can <u>NOT</u> get Marburg from the vaccine

Marburgvirus Vaccines

- This study looks to assess the vaccine called VRC-MARADC087-00-VP, also called “cAd3-Marburg”
- This experimental vaccine was created by the US National Institutes of Health (NIH) Vaccine Research Center (VRC)
- The vaccine consists of a virus, called chimpanzee adenovirus (cAd3), that has been modified (or changed) so that it cannot cause an adenovirus infection and so that it can deliver a piece of the Marburg virus to cells in your body. This tricks a person’s body into thinking it has seen the whole Marburgvirus, so that it can develop an immune reaction.
- The cAd3-Marburg vaccine has been studied in test tubes and animals. The cAd3 part and the Marburg part of the vaccine have been tested in humans on their own, but this is the first time that this combination of vaccine parts will be tested in humans.

Potential Risks and Discomforts from Participation

General Injection Risks

- 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*

General Vaccination Risks

- Also possible that you will get a fever, chills, rash, general itching, aches and pains, muscle pain, joint pain, vomiting, nausea, headache, dizziness, and fatigue (feeling tired), 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*

Potential Risks and Discomforts from Participation

General Vaccination Risks (continued)

- 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 or 60 minutes after the injection and you may need to stay longer if the study doctor thinks it is best for you

Experimental Vaccine Risks

- 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
- Receiving the vaccine does NOT mean you are protected against Marburg and you SHOULD continue to follow all recommended precautions against Marburg

Potential Risks and Discomforts from Participation

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

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 from Participation

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

Potential Benefits from Participation

There is no direct benefit to you by being in this study, (*we do not know if the study vaccine will work against Marburg 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)
- Have a valid U.S. government-issued or state-issued photo ID (such as a driver's license, military ID, or U.S. Passport)
- Are willing and able to provide a personal cell phone number or a home phone number at which you can reliably be contacted
- Are willing and able to provide informed consent
- Are HIV negative
- (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 or chronically recurring hives, asplenia (lack of normal spleen function) or a history of angioedema (facial swelling)
- 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 to any vaccines or allergic reaction to drugs like gentamycin, neomycin or streptomycin
- 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

Who Cannot Participate in the Study?

You cannot participate if you (continued):

- 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 or vaccines within 28 days prior to enrollment in the present study
  - Drugs for treating or preventing Tuberculosis

Overall Study Design

- Phase I open-label, dose-escalation clinical trial
- A total of 40 volunteers will be enrolled at the WRAIR CTC
  - 20 volunteers will receive a low dose of vaccine
  - 20 volunteers will receive a higher dose of vaccine

Group	Participants	Dose
1	20	cAd3-Marburg 1 x 10^{10} PU IM
2	20	cAd3-Marburg 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 the 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 102 mL (about 7 tablespoons)
- Over the whole study, the amount of blood that you will give is about 773 mL (about 3 cups)
- You will not have more than 550 mL of blood drawn over any 8-week 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 Marburg vaccine
- On the vaccination day, you will be in the clinic for **approximately 2** hours and will be required to remain at the clinic for 30 or 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 clinics 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!**

Compensation

- Compensation is dependent whether you are military personnel, a Federal employee or a civilian
- Non-military and non-federally employed participants will be compensated for their time, blood draws, and inconvenience at the following rates:
  - $50 for the screening visit
  - $200 for the vaccination visit
  - $150 for each scheduled follow-up visit ($50 at visit 2D if the Diary Card is lost or incomplete)
  - Up to $100 for each unscheduled follow-up visit, at the discretion of the Principal Investigator

Compensation (continued)

- Military and Federally employed participants will be compensated $50 for each visit at which a blood draw is done, unless the visit occurs during off duty hours or when on leave
  - If done during off duty hours or when on leave, military personnel will be compensated at a rate similar to non-military/ non-federally employed participants
- Military personnel must receive signed/written permission from their supervisor in order to participate in the 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

Conclusion

Thank you for your attention and consideration

Questions?

APPENDIX 9: TABLE FOR GRADING SEVERITY OF ADVERSE EVENTS

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

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".
- Severity grading definition for hypotension includes added clarifications such that an asymptomatic low blood pressure reading is not an adverse event.

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
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.

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	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 10: 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 12: ROLES AND RESPONSIBILITIES

Principal Investigator

The PI is responsible for the conduct of the RV 507 study at the WRAIR CTC. This is the person designated as taking overall responsibility within the team of researchers for the conduct and reporting of the RV 507 study. The site 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
- 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 will be reported to the required IRBs
- 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

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.

Laboratory Investigators

The lab investigator is responsible for laboratory analysis. Lab investigators will not have contact with study participants or personal identifiers.

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 IRB 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 the sponsor and to the WRAIR IRB by phone (301) 319-9940, or by email (usarmy.detrick.medcom-wrair.mbx.hspb@mail.mil). 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 USAMRMC 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's 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 participants' 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 agrees not to attempt to obtain any individually identifiable participant data

WRAIR/MHRP Regulatory Representatives

- Will serve as the point of contact on behalf of the WRAIR CTC for WRAIR regulatory purposes
- Responsible for ensuring compliance with the protocol and applicable US and DoD regulations
- Will not have contact with study participants and agrees not to attempt to obtain any individually identifiable participant data

APPENDIX 13: DIARY CARD

RV 507 Participant Diary Card

Walter Reed Army Institute of Research
Clinical Trials Center

Version 1.7
13 February 2019

Participant ID _____

Walter Reed Army Institute of Research
Clinical Trials Center
503 Robert Grant Avenue
Silver Spring, MD 20910
Phone: ***(301) 319-9660***
After Work Hours: ***(301) 319-9312***

Participant ID _____

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 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:
(301) 319-9660* OR *(301) 319-9312

Injection Site Pain Severity Scale

None = no pain

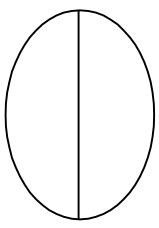
Mild = minimal pain; no limitation of use of arm.

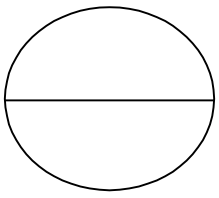
Moderate = notable pain; some limitation of use of arm.

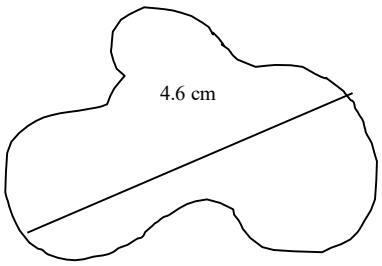
Severe = extreme pain; complete limitation of use of arm.

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, °F) Time Taken:_____PM

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

Temp:_____(oral, °F) 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				
Unusually Tired				
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: *(301) 319-9660* OR *(301) 319-9312*

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, °F) Time Taken:_____AM / PM *(circle)*

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

Temp:_____(oral, °F) 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				
Unusually Tired				
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: *(301) 319-9660* OR *(301) 319-9312*

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 2 after Vaccination

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

Temp:_____(oral, °F) Time Taken:_____AM / PM *(circle)*

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

Temp:_____(oral, °F) 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				
Unusually Tired				
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: *(301) 319-9660* OR *(301) 319-9312*

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 3 after Vaccination

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

Temp:_____(oral, °F) Time Taken:_____AM / PM *(circle)*

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

Temp:_____(oral, °F) 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				
Unusually Tired				
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: *(301) 319-9660* OR *(301) 319-9312*

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 4 after Vaccination

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

Temp:_____(oral, °F) Time Taken:_____AM / PM *(circle)*

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

Temp:_____(oral, °F) 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				
Unusually Tired				
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: *(301) 319-9660* OR *(301) 319-9312*

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 5 after Vaccination

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

Temp:_____(oral, °F) Time Taken:_____AM / PM *(circle)*

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

Temp:_____(oral, °F) 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				
Unusually Tired				
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: *(301) 319-9660* OR *(301) 319-9312*

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 6 after Vaccination

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

Temp:_____(oral, °F) Time Taken:_____AM / PM *(circle)*

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

Temp:_____(oral, °F) 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				
Unusually Tired				
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: *(301) 319-9660* OR *(301) 319-9312*

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 7 after Vaccination

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

Temp:_____(oral, °F) Time Taken:_____AM / PM *(circle)*

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

Temp:_____(oral, °F) 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				
Unusually Tired				
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: *(301) 319-9660* OR *(301) 319-9312*

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 | |

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		
Unusually Tired		
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 14: RECRUITMENT MATERIALS

WRAIR Clinical Trials Center
503 Robert Grant Ave
Silver Spring, MD 20910
Phone: 1-866-428-2788
Website: www.clinicaltrials.army.mil

Recruitment Script for Phone, Email and Electronic Use

Study Title: A Phase I, Open-label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of the Marburg Chimpanzee Adenovirus Vector Vaccine, VRC-MARADC087-00-VP (cAd3-Marburg), in Healthy Volunteers

Study Location: WRAIR Clinical Trials Center, 503 Robert Grant Ave, Silver Spring, MD 20910

What is Marburg virus?

Marburg virus (MARV) is a viral infection that was first recognized in 1967. It belongs to the same family of viruses as the Ebola virus. Currently there are no approved vaccines or therapeutics to treat individuals infected with MARV. Human infection can occur from exposure to Rousettus bats, the natural host of MARV, found in mines or caves.

Like Ebola, Marburg can cause people to quickly become very sick. There have been a couple of outbreaks in which over 80% of those who became ill have died. Marburg has mainly occurred in people living in or traveling to Southern Africa.

Study Information:

This study involves an experimental Marburg virus vaccine. **You cannot become infected with the Marburg virus from the vaccine.** This specific experimental Marburg vaccine has never been given to humans before, but it has been tested in animals. The two main molecules of the vaccine have been given separately to people before but not combined in one vaccine. We plan to enroll up to 40 volunteers in the study. The volunteers will be divided into 2 groups of 20. Each group will receive one injection, either a high dose or a low dose, on day 0. The vaccine injection will be given using a needle and syringe into an upper arm muscle.

The study's primary purposes are to look at the safety of the vaccine and the ability of your body to produce antibodies (proteins made by the body to protect against infection). This means if you were exposed to these viruses, your body would be able to more quickly respond to either prevent or lessen the effects of the infection.

Study Duration:

From the date of enrollment (day 0), there will be a total of 9 clinic visits over a 48-week period (approximately 11 months).

Study Overview:

- You will receive one dose of the vaccine on study day 0.
- There is a follow-up phone call on study day 1.
- There are 8 follow-up visits scheduled after vaccination. Follow-up visits will occur on study days 3, 7 & 14 post-vaccination and then on weeks 4, 8, 16, 24 & 48.
- Study procedures at the follow-up visits after the vaccination will consist of a brief physical exam, collection of blood, and a review of any symptoms that may have occurred.
- The final study visit is week 48.

Requirements and Restrictions:

You must meet ALL of the following requirements in order to participate in this study:

- You MUST be **18** to **50** years of age
- You MUST be in good general health
- You MUST be available and attend follow-up visits through 48 weeks after vaccination
- You MUST have a valid U.S. government-issued or state-issued photo ID (such as a driver's license, military ID, or U.S. Passport)
- You MUST be able and willing to provide a personal cell phone number or home phone number at which you can be reliably contacted.
- You MUST have a Body Mass Index (BMI) $\leq$ 40 *(This is a calculation based on your height and weight)*
- You MUST be able and willing to provide informed consent
- You **CANNOT** have received any other investigational Ebola or Marburg vaccine in a prior clinical trial or cAd3-based vaccine in the past.
- **FEMALES CANNOT** be pregnant, breastfeeding, or planning to become pregnant for 6 months after receiving the study vaccine. For safety reasons, females must also agree to use an effective form of birth control from at least 21 days prior to enrollment until at least 6 months after receiving the study vaccination.

- You **CANNOT** have a history of any of the following clinically significant conditions:
  - ✓ Serious allergic reaction to vaccines or allergic reaction to drugs like gentamycin, neomycin or streptomycin
  - ✓ Autoimmune disease or immunodeficiency or chronically recurring hives, asplenia (lack of normal spleen function) or a history of angioedema (facial swelling)
  - ✓ HIV infection
  - ✓ Active syphilis infection
  - ✓ Diabetes mellitus (type I or II)
  - ✓ Thyroid disease that is not well controlled.
  - ✓ High blood pressure or asthma that is not well controlled
  - ✓ Bleeding problem or disorder
  - ✓ Cancer that is active, currently being treated, or not surgically cured.
  - ✓ Seizure in the past 3 years or treatment for seizure disorder in the past 3 years.
  - ✓ Any current or past medical, psychiatric, or social condition that may interfere with your full participation in the study or that may impair your ability to provide informed consent as determined by the study physician.

- You **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 or vaccines within 28 days prior to enrollment in the present study
  - ✓ Drugs for treating or preventing Tuberculosis

There may be other reasons why you cannot participate in this study. Those will be discussed at your initial screening visit.

WRAIR Clinical Trials Center
503 Robert Grant Ave
Silver Spring, MD 20910
Phone: 1-866-428-2788
Website: www.clinicaltrials.army.mil

Possible Risks:

Potential side effects resulting from intramuscular injection include pain, stinging, arm discomfort, redness of the skin, or mild bruising at vaccine injection sites. Study 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. Risks of the vaccine to pregnant and nursing women and to the unborn baby are unknown. The risks of the experimental vaccine are also unknown, but the most common complaints in the first few days after receiving similar vaccines include a sore arm, headache, muscle aches, feeling tired and a fever within a day after vaccination.

Compensation:

If you qualify to participate in this study, you can receive up to $1,450.

Screening visit = $50
Vaccination visit = $200
Scheduled follow-up visits = $150 each*

*Study participants will only receive $50 on Day 14 if they do not return their completed Diary Card.

NOTE: Active military personnel and civilian government employees will receive only $50 for each visit at which a blood draw occurs, unless the visit occurs during off duty hours or when on leave with permission from a supervisor.

To learn more about this study or to schedule a screening appointment, contact the WRAIR CTC!

Call: 866-428-2788
Text: 301-215-0388
Email: Usarmy.detrick.medcom-wrair.mbx.clinical-trials@mail.mil
Hours: Monday-Friday, 6:00am-2:30pm

The WRAIR Clinical Trials Center is seeking

HEALTHY MEN & WOMEN

to participate in a Marburg vaccine study

Study Setting: Outpatient

Study Location: 503 Robert Grant Ave, Silver Spring, MD

Study Duration: 48 weeks (from time of enrollment)

Number of Visits: 10 clinic visits + 1 phone call

You will be paid for your participation in this study

To be eligible for this study you MUST:

- Be **18** to **50** years old
- Have no significant medical problems
- Have a **BMI ≤ 40**
- Live in the DC metro area
- **NOT** be pregnant, breastfeeding, or planning to become pregnant while enrolled in the study (for females).

There are other reasons you may not qualify for this study

WRAIR Clinical Trials Center

For more details call:

1-866-428-2788

Or visit our website at www.clinicaltrials.army.mil

The WRAIR Clinical Trials Center is seeking

HEALTHY MEN & WOMEN

to participate in a Marburg vaccine study

Study Setting: Outpatient

Study Location: 503 Robert Grant Ave, Silver Spring, MD

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- Have a **BMI ≤ 40**
- Live in the DC metro area
- **NOT** be pregnant, breastfeeding, or planning to become pregnant while enrolled in the study (for females).

There are other reasons you may not qualify for this study

WRAIR Clinical Trials Center

For more details call:

1-866-428-2788

Or visit our website at www.clinicaltrials.army.mil

The WRAIR Clinical Trials Center is seeking

HEALTHY MEN & WOMEN

to participate in a Marburg vaccine study

We're Searching for Volunteers*

To qualify you MUST meet the following criteria:

- Be 18 to 50 years old
- Have no significant medical problems
- Have a BMI ≤ 40
- Live in the DC metro area
- Females **CANNOT** be pregnant, breastfeeding, or planning to become pregnant while enrolled in the study.

Note: There are other reasons you may not qualify for this study.

Study setting: Outpatient
Study duration: 48 weeks
(from time of enrollment)
Number of visits: 10 clinic visits
+ 1 phone call

WRAIR Clinical Trials Center

*Volunteers will be paid for their participation in this study

For more information about this study call:

1-866-4-CTC-STUDY

WRAIR Clinical Trials Center | 503 Robert Grant Ave, Silver Spring, MD 20910 | 1-866-428-2788 | www.clinicaltrials.army.mil

The WRAIR Clinical Trials Center is seeking

HEALTHY MEN & WOMEN

to participate in a Marburg vaccine study

We're Searching for Volunteers*

To qualify you MUST meet the following criteria:

- Be 18 to 50 years old
- Have no significant medical problems
- Have a BMI ≤ 40
- Live in the DC metro area
- Females **CANNOT** be pregnant, breastfeeding, or planning to become pregnant while enrolled in the study.

Note: There are other reasons you may not qualify for this study.

Study setting: Outpatient
Study duration: 48 weeks
(from time of enrollment)
Number of visits: 10 clinic visits
+ 1 phone call
Compensation: Up to $1,450

*Volunteers will be paid for their participation in this study

WRAIR Clinical Trials Center

For more information about this study call:

1-866-4-CTC-STUDY

WRAIR Clinical Trials Center | 503 Robert Grant Ave, Silver Spring, MD 20910 | 1-866-428-2788 | www.clinicaltrials.army.mil

The WRAIR Clinical Trials Center is seeking

HEALTHY MEN & WOMEN

to participate in a Marburg vaccine study

WRAIR Clinical Trials Center

You will be paid for your participation in this study

To qualify for this study, you MUST:

- Be **18** to **50** years old
- Have no significant medical problems
- Have a BMI ≤ **40**
- Live in the DC metro area
- **NOT** be pregnant, breastfeeding, or planning to become pregnant while enrolled in the study (for females)

Note: There are other reasons you may not qualify for this study.

StudySetting: Outpatient

StudyLocation: 503 RobertGrantAve
Silver Spring, MD 20910

StudyDuration: 48 weeks
(from time of enrollment)

NumberofVisits: 10 clinic visits
+ 1 phone call

For more information about this study call:

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Study Setting:	Outpatient
Study Location:	503 Robert Grant Ave Silver Spring, MD 20910
Study Duration:	48 weeks (from time of enrollment)
Number of Visits:	10 clinic visits + 1 phone call
Compensation:	Up to $1,450

For more information about this study call:

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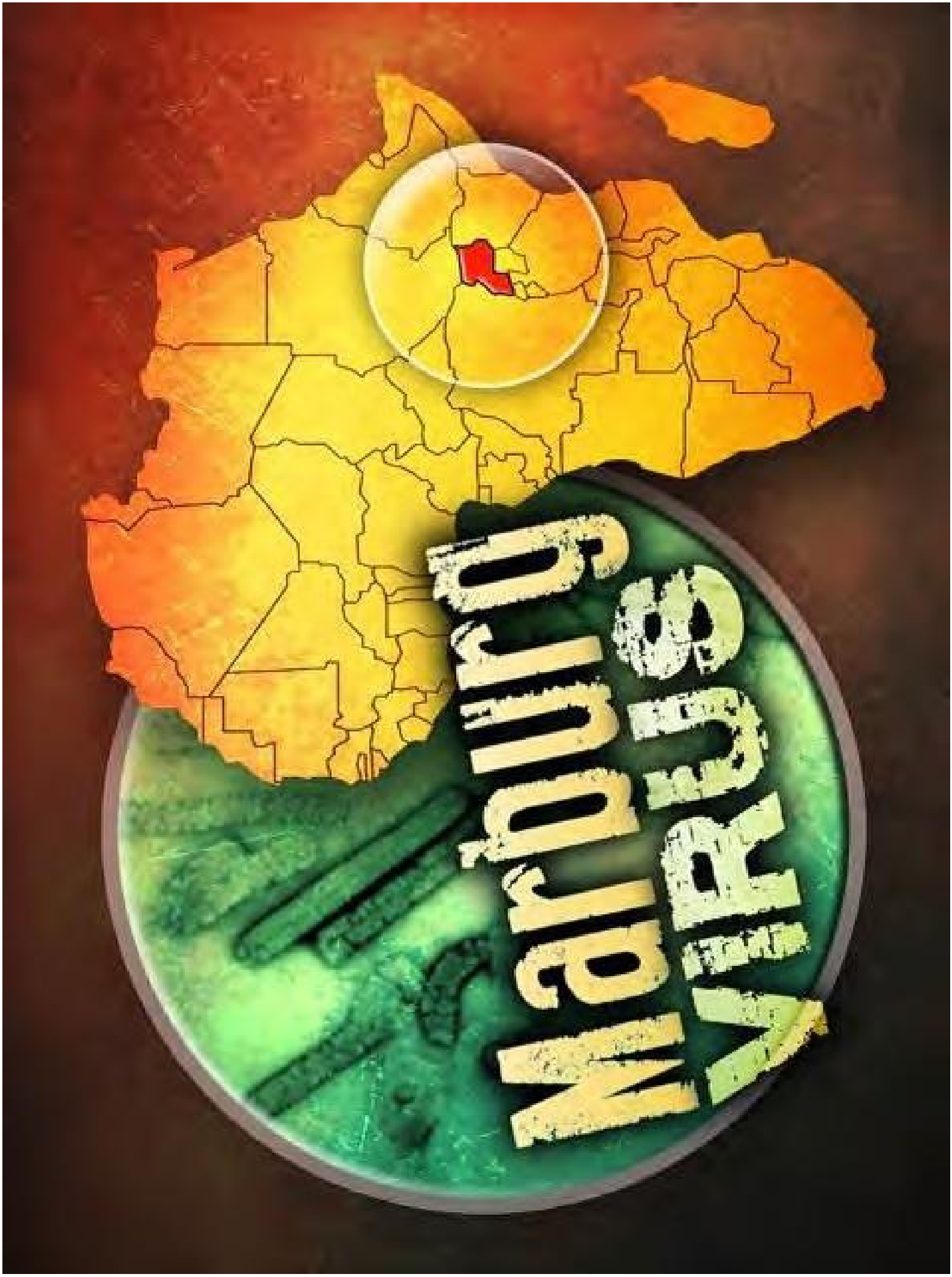
GROUND
ZERO

APPENDIX 15: APPOINTMENT/EMERGENCY CONTACT CARD

RV 507/WRAIR #2438
Marburg Vaccine Study
Participant ID#
Cardholder is a volunteer in a **Marburg VACCINE** study conducted by the
Walter Reed Army Institute of Research (WRAIR)
503 Robert Grant Ave, Silver Spring MD 20910

While in this study, false-positive Marburg serology can occur but no infection will be present.
If this volunteer develops any unexplained illness or symptoms that could possibly be related to vaccination please contact:
WRAIR Clinical Trials Center, 6:00 am – 2:30 pm
Monday - Friday at 301-319-9660

RV 507/WRAIR #2438
Marburg Vaccine Study

Between the hours of 2:30 p.m. and 6:00 a.m. Monday through Friday, and on weekends or holidays, please call the numbers provided below.

Dr. Hamer [redacted]

Dr. Ake [redacted]

APPENDIX 16: LIST OF EXTERNAL COLLABORATORS

MAIN STUDY INFORMED CONSENT FORM

Study Title: RV 507, "A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of the Marburg Chimpanzee Adenovirus Vector Vaccine, VRC-MARADC087-00-VP (cAd3-Marburg), 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 Agent Provided by: NIH/NIAID/VRC

Collaborating Institutions: Walter Reed Army Institute of Research (WRAIR), U.S. MHRP and NIH/NIAID/VRC

Principal Investigator: LTC Melinda Hamer, MD

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 informed consent will be provided to you. This consent must be signed 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-MARADC087-00-VP, but we will refer to it as "cAd3-Marburg" or simply as the "Marburg vaccine." The study vaccine does not contain live or killed Marburg virus. It is **impossible** for the study vaccine to give you a Marburg virus infection.

This research study is funded by the U.S DoD and the NIAID/NIH. The U.S. MHRP and the WRAIR Clinical Trials Center (CTC) are conducting this research study in Silver Spring, MD.

PURPOSE AND BACKGROUND

This research study will evaluate an experimental vaccine for the Marburg Virus. "Experimental" means that it is not known if the vaccine works to prevent Marburg Virus Disease (MVD). Since it is not known if the vaccine works, it has not been approved by the US Food and Drug Administration (FDA). 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 Marburg 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 Marburg virus was discovered in 1967 in a laboratory in Marburg, Germany. Bats probably carry the virus in certain parts of Africa. MVD 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 outbreak of Marburg in Germany and Yugoslavia in 1967 caused 7 deaths among 31 people who were infected. In 2005, an outbreak of Marburg virus in West Africa caused 227 deaths among the 252 people who were infected (90% fatality rate). In October 2017, the Ugandan Ministry of Health officially declared an outbreak of MVD in eastern Uganda. As of November 2017, there have been 3 fatal cases, with over 100 individuals being monitored for potential infection.

STUDY VACCINE

The experimental Marburg 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 studied in test tubes and animals. Both parts of this experimental Marburg vaccine have been separately tested in humans, but this is the first time that this combination of vaccine parts will be tested in humans.

One part of the Marburg vaccine, a virus called chimpanzee Adenovirus 3 (cAd3), is used to deliver a piece of the Marburg virus to cells in your body. The chimpanzee 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.

The Marburg virus piece has also been tested in people. Once the Marburg virus piece is delivered to the cells in your body, your body may then make an immune response. You cannot become infected with or infect someone else with either Marburg 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 Marburg vaccine is based on dose levels found to be safe in previous studies of 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 507 Study Groups		
Group	**Participants**	**Vaccine Dose**
1	20	cAd3-Marburg at $1x10^{10}$ PU IM
2	20	cAd3-Marburg 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 less than an hour. 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 (a valid U.S. government-issued or state-issued photo ID such as a driver's license, military ID, or U.S. passport), and able to provide a personal cell phone number or home phone number at which you can reliably be contacted. Study investigators will use your phone number to follow-up with you a day or two after you receive the vaccination, to remind you of upcoming study visits, and to reschedule any missed appointments. You must also be able to read this consent form, understand and complete the

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.

Volunteers who are active duty military personnel must receive written approval from their supervisor prior to participating in the study, per WRAIR Policy Letter 12-28.

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. The results of these tests will be kept confidential; however, the study staff is required by law to report the results, if positive, to the local health authorities. The test results reported to local health authorities will contain your name, contact information (including address and telephone numbers), and the type of testing that was done on you as required by state law.

A serum (blood) pregnancy test will be required at the screening visit if you are female and able to become pregnant. The researchers 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 a hospital or clinic for medical treatment.

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 and you don't have a doctor, then the study staff will help you locate 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.

c) Enrollment and Follow-up Visits

If you are one of the first three participants in either vaccination group, the clinic staff will observe you for at least 60 minutes after the injection at the enrollment visit. Otherwise, the clinic staff will observe you for at least 30 minutes after the injection.

You will be asked to complete a diary card and look at your injection site at home 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 be asked to come to the clinic if you have a fever of 101.3˚F (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, 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 5 teaspoons (25 mL) to about 7 tablespoons (102 mL), 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 about 3 cups (773 mL).

You will not have more than 550 mL (less than 2.5 cups) of blood drawn over any 8-week 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) for future research to learn more about Marburg 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.

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 THIS STUDY PARTICIPATION

This section describes the risks associated with the experimental Marburg vaccine and other study procedures. There may be additional risks related to the experimental Marburg 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, 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, and fatigue. 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 Marburg 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. There are currently no vaccines approved for use to protect against Marburg virus infection. Receipt of this experimental Marburg vaccine may affect your response to future vaccines against Marburg. 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 MVD, have no effect on protection, or increase your risk of MVD. 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 a Marburg 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 as soon as possible about any side effect you think you are having that may be serious or cause concern. 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 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 WRAIR 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 WRAIR 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

Non-military and non-federally employed participants will be compensated $200 for time, blood draws and inconvenience for the vaccination visit, $150 for each scheduled follow-up visit, and $50 for each screening visit. Participants will be compensated up to $100 for each unscheduled visit, but only if the Principal Investigator/ designee finds it necessary. Participants who do not complete or lose the Diary Card will only be compensated $50 at visit 2D (14 days post-vaccination).

By regulation, military personnel and civilian government employees can only be compensated for visits at which blood draws occur, and then only $50 per visit, unless the visit occurs during off duty hours or when on leave with permission from a supervisor. Visits that occur during off duty hours or when on leave will be compensated at the same rate as non-military/non-federally employed participants as stated above.

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. Melinda Hamer, 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 Materiel Command (USAMRMC), the DoD, the NIAID, the WRAIR IRB, the FDA, the Office for Human Research Protections, and other regulatory 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.

Additionally, it is the policy of the USAMRMC that data sheets are to be completed on all study volunteers participating in research for entry into this Command's Volunteer Registry Data Base. The information to be entered into this confidential database includes your name, study number, date of birth, contact information, address, study title and dates participating in study, any adverse events related to the vaccine, and details of which study products you received. The intent of the data base is two-fold: first, to readily answer questions concerning an individual's participation in research sponsored by USAMRMC; and second, to ensure that the USAMRMC can exercise its obligation to ensure research study volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at USAMRMC for a minimum of 75 years. Please note that your name and study number will be stored separately from the USAMRMC volunteer registry database.

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 are injured because of your participation in this research and you are a DoD healthcare beneficiary (e.g., military spouse and their dependents), you are entitled to medical care for your injury within the DoD healthcare system as long as you remain a DoD healthcare beneficiary. This care includes, but is not limited to, free medical care at military hospitals or clinics.

If you are injured because of your participation in this research and you are not a DoD healthcare beneficiary, you are entitled to medical care for your injury at a military hospital or clinic. Medical care charges will be waived. It cannot be determined in advance which military hospital or clinical will provide care. If you obtain care for research-related injuries outside of an Army hospital or clinic, the study clinical trial insurance will be responsible for medical expenses. While we anticipate that the insurance policy is more than enough to pay for the costs associated with this study, there is a limit to the amount of coverage available. If the limit is exceeded, you will be responsible for paying the non-covered costs. The study sponsor and the DoD will not provide long-term medical care for research-related injuries.

For all participants, transportation to and from hospitals or clinics will not be provided. No reimbursement is available if you incur medical expenses to treat research-related injuries. No compensation is available for research-related injuries. You are not waiving any legal rights. If you believe you have sustained a research-related injury or if you have any questions about study-related sickness or injury, you can contact the PI:

Dr. Melinda Hamer
WRAIR CTC
[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 or the WRAIR CTC [redacted] 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 IRB, or the FDA 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 Marburg 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. Melinda Hamer [redacted] or the WRAIR CTC study staff [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 WRAIR IRB [redacted] or by e-mail [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 507 "A Phase 1 Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of the Marburg Adenovirus Vector Vaccine, VRC-MARADC087-00-VP (cAd3-Marburg), in Healthy Adults"

The principal investigator Dr. Melinda Hamer 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. Melinda Hamer [redacted] and the WRAIR CTC study staff [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 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 507, "A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of the Marburg Chimpanzee Adenovirus Vector Vaccine, VRC-MARADC087-00-VP (cAd3-Marburg), 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 Agent Provided by: NIH/NIAID/VRC

Collaborating Institutions: Walter Reed Army Institute of Research (WRAIR), U.S. MHRP and NIH/NIAID/VRC

Principal Investigator: LTC Melinda Hamer, MD

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. Some of the blood samples may be stored in the sponsor's laboratory for testing how your body fights Marburg 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 as 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 Marburg or Vaccines

Researchers are able to measure how the immune system responds by looking at blood samples. We will try to understand why Marburg disease progresses differently in some people. As new methods (or

ways) of measuring the body's immune response to Marburg 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 Marburg. 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 Marburg and how vaccines can prevent Marburg infection.

Your Samples Used for Future Research May Be Shipped to the Sponsor's Laboratory or to Regional Laboratories

Your samples will be stored in a secure central storage site (not at the WRAIR CTC) in the sponsor's laboratory. 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 study records at the WRAIR CTC. 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 contact 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, 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 Dr. Melinda Hamer [redacted] or the WRAIR CTC study staff at [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, contact the WRAIR IRB [redacted] or by e-mail at [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 stored for future testing and then sign the consent form 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 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 507, "A Phase I Open-Label, Dose-Escalation Clinical Trial to Evaluate the Safety, Tolerability and Immunogenicity of the Marburg Chimpanzee Adenovirus Vector Vaccine, VRC-MARADC087-00-VP (cAd3-Marburg), 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 Agent Provided by: NIH/NIAID/VRC

Collaborating Institutions: Walter Reed Army Institute of Research (WRAIR), U.S. MHRP and NIH/NIAID/VRC

Principal Investigator: LTC Melinda Hamer, MD

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 Marburg and other diseases affected by Marburg 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 Marburg. 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 Marburg and to other diseases affected by Marburg.

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 May Be Shipped to the Sponsor's Laboratory or Other Regional Laboratories

In order to complete the genetic testing on your blood samples, they may be shipped and stored at the sponsor's laboratory. 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 to outside collaborators, 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 in 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. It is possible that if others found out genetic information about you that is learned from tests 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. However, the risk of this happening is extremely low, because your results will not be part of your study records at the WRAIR CTC.

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, 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 Dr. Melinda Hamer [redacted] or the WRAIR CTC study staff [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, contact the WRAIR IRB [redacted] or by e-mail [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 the consent form 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