World Health Organization

SOLIDARITY VACCINE TRIALS

CORE Protocol

A phase 1/2/3 study to evaluate the safety, tolerability, immunogenicity, and efficacy of vaccine candidates against (Filoviruses) disease in healthy individuals at risk of (Filoviruses) disease.

Version 5.0
July 2, 2023

R&DBlueprint
Powering research to prevent epidemics

Study information

Type of study	Phase 1, 2 and 3 randomised study
Registration of the study	
Study product(s) **Vaccine developer(s)**	
Co-Sponsor(s) **Representative of the Co-Sponsor(s)**	
Principal investigators (PI)	
Sub investigators (as defined in ICH guidelines)	
Study site	Areas with confirmed cases of (Filoviruses)
External monitors	Contract Research Organization

Table of Contents

Protocol signatures page

Principal Investigator

_____

Representatives of the Co-Sponsors

_____

_____

Dr Michael J Ryan
Executive Director
Health Emergencies Programme
WHO

STATEMENT OF COMPLIANCE

CORE Protocol
A phase 1/2/3 study to evaluate the safety, tolerability, immunogenicity, and efficacy of vaccine candidates against (Filoviruses) virus disease in healthy individuals at risk of (Filovirus) virus disease

The study will be carried out in accordance with the International Conference on Harmonisation Good Clinical Practice (ICH GCP).

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the WHO Ethical Review Committee, and the _____ Ethics Committee, and the and _____ National Drug Authority and approved.

Approval of both the protocol and the consent form must be obtained before any participant is enrolled.

Any amendment to the protocol will require review and approval by the above-mentioned Ethics Review Committees before the changes are implemented in the study.

In addition, all changes to the consent form will be approved by both Ethics review Committees; a determination will be made regarding whether new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

_____
Principal Investigator

Date : _____

Abbreviations

AE	Adverse event (not necessarily due to vaccination or (Filoviruses) disease)
cAd3	Chimpanzee adenovirus (type 3)
cAdOx1	Chimpanzee adenovirus Oxford (type 1)
CEPI	Coalition for Epidemic Preparedness Innovations
CI	Confidence Interval
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
eCRF	Electronic case record form
EBOV	*Ebolavirus* Ebola Zaire
ELISA	Enzyme Linked Immunosorbent Assay
ELISPOT	Enzyme linked Immunospot Assay
FLW	Front Line Worker
GCP	Good clinical practice (a set of guidelines on the conduct of studies)
HCW	Healthcare worker
ICH	International Conference on Harmonisation (responsible for GCP)
ICF	Informed Consent Form
IgG	Immunoglobulin type G
IgM	Immunoglobulin type M
LoA	Letters of Agreement
MARV	*Marburg)virus*
MVD	Marburg virus disease
MOH	In each country Ministry of Health
PBMC	Peripheral blood mononuclear cell
RT-PCR	Real time polymerase chain reaction
SAE	Serious Adverse Event (not necessarily due to vaccination or (Filoviruses) disease)
SAP	Statistical analysis plan
SOP ME	Standard Operating Procedures for the (Filoviruses) Trial
SUDV	*Ebolavirus* Ebola Sudan
SUSAR	Suspected Unexpected Serious Adverse Reaction (to vaccination)
TSC	Trial Scientific Committee
WHO	World Health Organization

1. INTRODUCTION

This vaccine study is a multistage and multiple-arm clinical study designed to assess the safety, immunogenicity, and efficacy of candidate Filoviruses virus (FV) vaccines in Africa. Certain African countries are prone to Ebola virus disease (EBOV) outbreaks caused by the most prevalent species Ebola Zaire (EBOV), and Ebola Sudan (SUDV) and Marburg virus disease (MVD) outbreaks caused by Marburg virus (MARV).

This adaptive multi-stage, multi-arm Solidarity Against (Filoviruses) Vaccine study protocol is designed as a living protocol that will be used to study the safety, immunogenicity, and efficacy of filovirus-candidate vaccines in African (Filoviruses)-prone countries. It will be a phase 1-2 study during the inter-epidemic periods, and phase 1-3 study during outbreaks.

The study will be conducted both during the inter-epidemic periods as an individually randomized phase 1 and 2 study, with randomization among vaccine candidates, and as a ring vaccination study, phases 1-3, during outbreaks. The ring vaccine study during outbreaks will key on ring vaccination where the contacts of index cases (i.e., rings) will be randomized to either be immediately vaccinated or vaccinated with a 21-day delay. During phase 1 and phase 2 studies, safety and immunogenicity data will be collected on all vaccinated people regardless of whether they are in an immediate or delayed vaccination ring. Vaccine efficacy will be assessed during outbreaks by comparing data from the immediately vaccinated rings to the delayed vaccinated rings before they receive a vaccine.

The accrual of study participants will be additive over the inter-epidemic and outbreak periods. For the outbreak periods, data will accrue from one given outbreak to the next on a ring-by-ring basis until the power for efficacy evaluation is achieved for the phase 3 component of the study. New candidate vaccines can be added when they become available and receive clearance by the WHO prioritization committee and the applicable ethics and regulatory bodies in the research countries.

This study design was used in the *Ebola ca suffit* trial in Guinea in 2015 by the WHO (using a WHO Ethics Review Committee approved protocol) to evaluate a vaccine against Ebola virus. With necessary modifications, the present protocol is based closely on the *Ebola ca suffit* protocol.

Epidemiology of MVD, in each country

Marburgvirus, Sudanvirus and *Ebolavirus* are different genera in the family *Filoviridae* and vaccines and monoclonal antibodies that are effective against Zaire ebolavirus disease are unlikely to be of any use against other filovirus disease. But the epidemiology of MVD and SVD outbreaks is thought to be similar to that of Zaire ebolavirus disease.

Need for a study of the safety, immunogenicity and efficacy of vaccination

There is an urgent need to test the safety and efficacy of the currently proposed vaccine(s) that have been developed against filoviruses. There is no direct evidence as to whether they will be of any benefit at all to people who have recently been in contact with a case of filovirus disease (i.e., recent case-contacts). Since there is no established correlate of protection in humans (i.e., since laboratory studies alone cannot reliably predict efficacy in recent case-contacts), efficacy trials are urgently needed in the context of the current transmission patterns of filovirus disease.

During outbreaks, ring vaccination consists of the targeted vaccination of the recent contacts of an index case. This might protect the individual vaccinated or help create a small buffer zone of immunized people that could limit the propagation of the infection. Simulation and field studies have shown that ring vaccination around new cases can in some circumstances be effective and help contain outbreaks of infectious diseases with relatively low reproductive rates. This was true for smallpox and for Zaire ebolavirus disease [1-5], but there is no direct evidence as to whether it will be true for filovirus disease.

The proposed ring vaccination study involves a population at increased risk of infection as they have recently been in contact with a case of filovirus disease, so it may well provide useful information about the protection of such case contacts quickly, within just a few months. To judge by experience in the 2015 ring vaccination trial in Guinea, perhaps 5-10% of the rings of contacts around these index cases would be "informative" (i.e., would include at least one case of filovirus disease with the onset of symptoms 10 to 29 days after randomization). Even if the current outbreak is controlled within just a few months, such a trial could still be usefully informative if at least one of the candidate vaccines has a substantial protective effect – for example, if there were 6 vs 0 "informative" rings (delayed vs immediate vaccination) this result would be 2p=0.03, i.e., a conventionally significant difference between delayed and immediate vaccination.

In contrast, randomized trials in the general population, or in groups that have not been close to a recent case, would require large populations and extensive periods of time to generate results. The open-label cluster-randomized design of the study reflects 4 considerations:

1. The long delays and practical difficulties in undertaking delayed comparator-controlled trials (cluster-randomized or individually randomized) in a rapidly-changing outbreak;
2. The need to generate robust evidence regarding the efficacy and safety of ring vaccination for use in this or future outbreaks (and for regulatory authorization);
3. The potential unreliability of evidence obtained from non-randomized trials;
4. The importance of integrating randomized research studies into outbreak responses;
5. An open-label cluster-randomized ring vaccination trial can provide credible data on the efficacy of the study vaccine when used for ring vaccination in an outbreak situation. Ring vaccination has been used successfully to eradicate smallpox, and to limit Zaire ebolavirus outbreaks.

2. Overall design

This is a phase 1/2/3 study to evaluate the safety, tolerability, immunogenicity, and efficacy of candidate vaccines against (Filoviruses) disease in healthy individuals at risk of (Filoviruses) disease (contacts of a recently confirmed case, including health-care workers and front-line workers in affected areas).

This study has two main components:
1. During the inter-epidemic period: Safety and Immunogenicity (phase 1 and 2)
2. During outbreaks: Safety and efficacy (phase 3) and for certain candidate vaccines (phase 1 and 2)

The study is designed to move seamlessly through the phases and collect needed data on each vaccine simultaneously.

During the inter-epidemic period **During outbreaks**

Phase 1 and 2 Individual randomization among vaccines (no placebo) *For candidate vaccines for which the independent Technical Advisory Committee on candidate vaccines prioritization* recommends, (and for which existing Phase 1 or Phase 2 data are insufficient)*		**Phase 1/2** ***Cluster-randomized (immediate versus delayed)*** *For candidate vaccines for which the independent Technical Advisory Committee on candidate vaccines prioritization * recommends (and for which existing Phase 1 or Phase 2 data are insufficient) in order to collect additional safety and immunogenicity information before unduly many volunteers are recruited.*		**Phase 3** ***Cluster-randomized (immediate versus delayed)*** ***To assess the effect of a candidate vaccine in protecting against laboratory-confirmed (Filoviruses) ebolavirus disease.*** *For candidate vaccines for which the independent Technical Advisory Committee on candidate vaccines prioritization *[1] recommends.*
1. Phase 1 (when needed). Enrolment of up to 100 (including HCWs/FLWs in affected areas and contacts of previous cases if feasible), subject to continuous DMC review. 2. Phase 2. Enrolment of up to 1000 HCWs/FLWs in affected areas.		1. Phase 1(when needed)- Enrolment of up to 200 (100 per arm) participants (contacts of filovirus disease cases including HCWs/FLWs), subject to continuous DMC review. 2. Safety analysis of Phase 1 data by DSMB (7 and 14 days post-vaccination) with formal recommendation on whether to continue to recruit. 3. Phase 2 - Enrolment continues (up to 1000 contacts) 4. These participants will also be included in Phase 3 analyses		1. Enrolment of additional participants (contacts of filovirus disease cases including HCWs/FLWs) 2. Analysis as defined in the Statistical Analysis plan

[1] *The Technical Advisory Committee on Candidate on Vaccines Prioritization will make recommendations based on the most current data from the vaccine developers

3. Study procedures

During the inter-epidemic period

In brief:

- The study team will seek all HCWs/FLWs in relevant areas and also create a new list of contacts of previous cases at any time in the past (no time-limited), including those briefly absent, who moved out, or who have died at the time the list is made. SOP ME-01
- A separate team will explain the study to all listed and eligible and invite them to provide their written informed consent using a printed information sheet.
- The eligible participants who consent will be included in the study until the set sample size is achieved.
- A vaccination team will offer vaccination to eligible and consenting participants. Qualified and protocol-trained nurses will vaccinate the participants at enrolment according to their randomization arm and as per SOP ME- 08.
- We will draw up to four 9 ml tubes of blood for the safety and immunogenicity studies. Samples will be tested by RT-PCR to ensure that they are negative for (Filoviruses) virus before further processing. Samples will be processed to obtain serum, plasma and peripheral blood mononuclear cells (PMBCs) and will be cryopreserved in liquid nitrogen or at -80°C. Humoral immunity parameters will be evaluated using virus neutralization assays, ELISA assays to measure filovirus-specific IgM and IgG and ELISPOT assays using overlapping peptide libraries as well as whole antigen to assess filovirus-specific T cell responses. Other assays to measure immune responses may also be performed. Outside of the indicated time-point schedule remaining blood samples from the safety of diagnostic tests collected on days 0/1 and 3 post-vaccination will be retained for future use (potentially to include exploratory research).s. Haematology and Chemistry labs will be monitored in the subset of participants who consented for the immunogenicity assays estimated to be about 100 per candidate vaccine and delayed comparator. SOP ME-24-28. See table below.
- Participants will be followed up on day 1(the day of vaccination) through day 8 and on days 14, 21, 28, and 56 for all solicited adverse events. Thereafter, follow-up will be on days 90, 180, and 365. SOP ME-16-17. [This timing will be adjusted, as appropriate, if multi-dose vaccines are evaluated.]
- To facilitate the study, no paperwork is required, and enrolment and randomization is done via a cloud-based GCP-compliant computer system.
- An independent quality assurance team will continuously monitor the study records. In addition, an independent Data and Safety Monitoring Board will keep the accumulating results under continuous review.

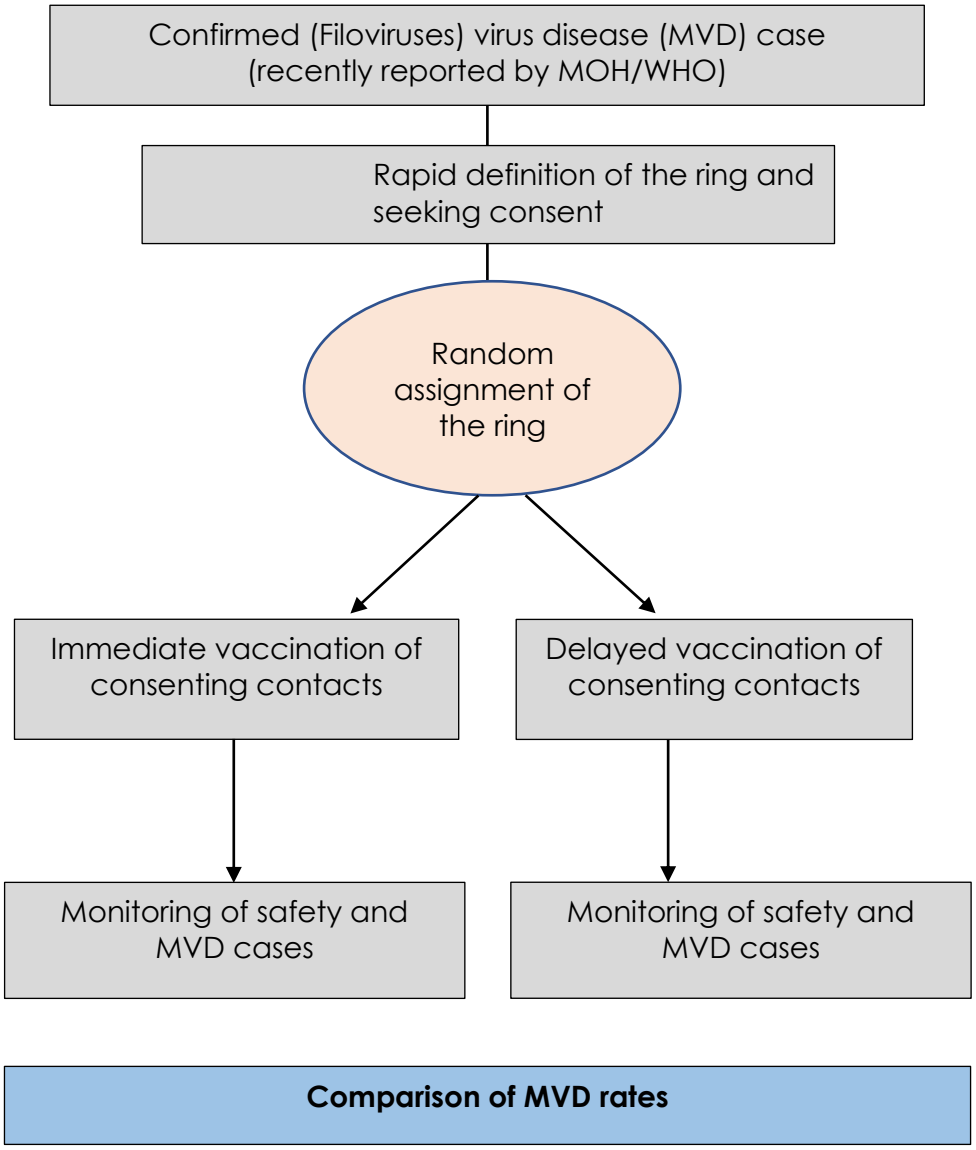
During outbreaks

In brief:

- Within 1-2 days of notification of a filovirus disease confirmed case and before other trial-related activities are initiated, local social mobilization experts will visit the community where the case occurred to seek their consent for the trial team to approach the broader community. SOP ME-03-05.
- The trial team will seek all recent contacts of the newly confirmed index case, including those briefly absent at the time the initial list of contacts is made. SOP ME-01.
- The list will include as recent contacts those who, within the previous 21 days, lived in the same household, or visited or were visited by the index case at or after the onset of symptoms, or who, without using adequate personal protective equipment, provided the index case with care, or were in close physical contact with the patient's body, body fluids, linen, or clothes, or prepared the body for, or were exposed to the body, at a funeral ceremony.
- A separate team will explain the study to all listed and eligible contacts and invite them to provide their written informed consent using a printed information sheet. SOP ME -07.
- The eligible contacts who consent constitute the "ring" (or "cluster") of people who will be included in the trial. SOP ME -01.
- After the last eligible contact has consented or not, the entire ring of consenting contacts will be allocated randomly either to be offered vaccination immediately or 21 days later. At this point, all members of the ring are informed of the allocation outcome. After randomization, no new people can join the ring or be included in the trial or offered vaccination at any time by the trial (unless they subsequently are identified as a member of a different ring). SOP ME -08.
- At the appointed time a vaccination team will arrive and offer vaccination to all ring members. Qualified and protocol-trained nurses will vaccinate the participants at enrolment according to their randomization arm and as per SOPs ME- 08-09.
- During the Phase 1 and 2 in the context of outbreaks, We will then draw up to four 9 ml tubes of blood for the safety and immunogenicity studies. SOP ME -24-28. Samples will be tested by RT-PCR to ensure that they are negative for Filovirus before further processing. Samples will be processed to obtain serum, plasma and peripheral blood mononuclear cells (PMBCs) and will be cryopreserved in liquid nitrogen or at -80°C. Humoral immunity parameters will be evaluated using virus neutralization assays, ELISA assays to measure filovirus-specific IgM and IgG, and ELISPOT assays using overlapping peptide libraries as well as whole antigen to assess filovirus-specific T cell responses. Outside of the indicated time-point schedule remaining blood samples from the safety of diagnostic tests collected on days 0/1 and 3 post-vaccination will be retained for future use to be decided by consensus among vaccine sponsors and developers. Haematology and Chemistry labs will be monitored in the subset of participants who consented to the immunogenicity assays estimated to be about 100 per candidate vaccine and delayed comparator (see table below).
- Identification and confirmation of filovirus disease cases will be done independently of the study team throughout the outbreak and beyond the follow-up period of the trial as part of the national surveillance. Typically, this will involve daily follow-up for the first 21 days. SOP ME -02.

- During phase 1 and 2, participants will be followed up on day 1(the day of vaccination) through day 7 and on days 14, 21, 28, and 56 for all solicited adverse events. Thereafter, follow-up will be on days 90, 180, and 365. SOP ME- 15-17.
- During phase 3, each safety follow-up study visit at the participant's home (0, 7, 14 and 21 days after vaccination, same follow-up will be conducted in both groups), another team will ask those in the ring about any relevant symptoms or signs and any other changes in the patient's health since the last visit. Any adverse effects must be monitored until they are resolved or stabilized. SOP ME -15-17.
- Confirmed cases arising in ring members are included as primary outcomes in the main analysis of vaccine efficacy. Safety and suspected or probable filovirus disease and death from confirmed filovirus disease are included as secondary outcomes. SOP ME -02.
- An independent quality assurance team will continuously monitor the study records. In addition, an independent Data and Safety Monitoring Board will keep the accumulating results under continuous review. SOP ME -17.
- To facilitate the study no paperwork is required, and enrolment and randomisation are done via a cloud-based GCP-compliant computer system. SOP ME -21.

Design of the trial during outbreaks



4. Study objectives

During the inter-epidemic period		
Objectives	**Outcomes**	**Statistical analysis**
Phase 1 and 2: *For candidate vaccines for which the Technical Advisory Committee on Candidate Vaccines Prioritization recommends*		
Primary objectives		
To determine the reactogenicity and safety of candidate filovirus vaccine(s) among healthy volunteers.	We will assess safety by describing the proportion of vaccine recipients who experience adverse events (clinical and laboratory) by severity and causality assessment.	AEs will be summarized with counts, percentages, and exact 95% CIs will be provided.
To determine the immunogenicity of the candidate filovirus vaccine(s).	We will assess immunogenicity by measuring vaccine specific antibody titres, neutralization activity and cell mediated immune responses at pre-defined follow-up visits	Rates and magnitude of vaccine-induced responses
Secondary Objectives		
To determine the durability of filovirus-specific induced immune responses following vaccination. To identify factors influencing vaccine-induced immune responses among trial participants.	We will assess immunogenicity by measuring vaccine specific antibody titres, neutralization activity and cell mediated immune responses at pre-defined follow up visits.	This will be defined in the SAP.
To determine the immune cross reactivity induced by filovirus vaccine candidates .	We will assess immunogenicity by measuring antibody titers and cross-neutralization activity against other filoviruses	This will be defined in the SAP.
Exploratory Objectives		
To determine the effect of filovirus vaccines on host gene expression. To determine the T and B cell specific responses and immune profiling in response to vaccination. To determine the effect of fiilovirus vaccines on the host metabolome. To determine the effect of filovirus vaccines on host innate immune responses	Additional immune response assays will be performed, including T and B cell responses with cell-based immunological assays. We will assess the innate responses with multiplex immunoglobulin analysis, transcriptomic profiles and other assays.	This will be defined in the SAP.

During the outbreak		
Objectives	**Outcomes**	**Statistical analysis** (general principles outlined here, final analysis plan will be described in the SAP)
Phase 1 and 2: ***For candidate vaccines for which the Technical Advisory Group on Candidate Vaccines Prioritization recommends***		
Primary objectives		
To determine the reactogenicity and safety of candidate filovirus vaccine(s) among healthy volunteers.	We will assess safety by describing the proportion of vaccine recipients who experience adverse events (clinical and laboratory) by severity and causality assessment.	AEs will be summarized with counts, percentages, and exact 95% CIs will be provided.
To determine the immunogenicity of the candidate filovirus vaccine(s).	We will assess immunogenicity by measuring vaccine specific antibody titres, neutralization activity and cell mediated immune responses at pre-defined follow-up visits	Rates and magnitude of vaccine-induced responses
Secondary Objectives		
To determine the durability of filovirus-specific induced immune responses following vaccination. To determine the factors associated with optimal vaccine-induced immune responses among trial participants.	We will assess immunogenicity by measuring vaccine specific antibody titres, neutralization activity and cell mediated immune responses at pre-defined follow up visits.	This will be defined in the SAP.
To determine the putative cross reactivity & protection exerted by the filovirus vaccine candidates.	We will assess immunogenicity by measuring antibody titers and neutralization activity.	This will be defined in the SAP.
Exploratory Objectives		
To determine the effect of filovirus vaccines on host gene expression. To determine the T and B cell specific responses and immune profiling in response to vaccination. To determine the effect of filovirus vaccines on the host metabolome. To determine the effect of filovirus vaccines on host innate immune responses	We will assess T and B cell responses with cell-based immunological assays. We will assess the innate responses with multiplex immunoglobulin analysis, transcriptomic profiles and other assays.	This will be defined in the SAP.
Phase 3: ***To assess the effect of a candidate vaccine in protecting against laboratory-confirmed (Filoviruses) disease.***		
Primary objectives		
The primary analysis will be of laboratory-confirmed filovirus disease (from samples taken either while living, or within 48 hours of death). During outbreaks, all ring participants (including those included in phase I and phase II substudies) will contribute to efficacy analysis.	New cases of filovirus disease in the ring are ascertained through independent active surveillance visits by the surveillance contact tracing teams and case detection reports through the national filovirus disease surveillance system. Estimate of vaccine efficacy.	The primary analysis (per-protocol) will be of laboratory-confirmed filovirus disease cases with symptom onset 10 to 29 days after randomization. The omission of days 0-9 allows time for the vaccination to take effect, and reduces the chance of including cases who got infected prior to the vaccination (given a typical 2-21 days incubation period for (Filoviruses) ebolavirus[8]). Numbers of definite cases and of probable cases in days 0-9, 10-29 and after day 29 since

During the outbreak		
Objectives	**Outcomes**	**Statistical analysis** (general principles outlined here, final analysis plan will be described in the SAP)
		randomization will each be tabulated separately, distinguishing between fatal and non-fatal cases and noting any cases that were excluded from the primary per-protocol analyses (thereby making available modified *intent-to-treat* analyses of outcome by allocated treatment of all randomized ring members). Numbers of individual cases by day since randomization will be plotted by Kaplan-Meier methods. Fisher's exact test for vaccine efficacy significance. Negative binomial for confidence intervals for vaccine efficacy.
Secondary objectives		
The main secondary objective is to assess the safety of the vaccine by monitoring weekly for 21 days any adverse reactions to vaccination and any other serious adverse events. Probable filovirus disease and death from confirmed filovirus disease are included as secondary outcomes. Other secondary objectives include monitoring cases of suspected filovirus disease that were not confirmed and did not cause death, studying how the risk of developing filovirus disease depends on various risk factors, and seeing whether the outcomes of any pregnancies are affected.	We will assess safety by describing the proportion of vaccine recipients who experience adverse events (clinical and laboratory) by severity and causality assessment. Each candidate vaccine will be compared to delayed comparator. Stratified estimates of vaccine efficacy for each of the secondary outcomes	Possible safety events post-vaccination will be described, and tabulated by severity and time since vaccination, causality assessment as will eventual pregnancy outcomes. To be described in the SAP.
Exploratory objectives		
Although efforts will be made to determine whether ring vaccination helps control disease spread beyond the vaccinated contacts, there may be too few cases to answer this directly.	Estimate of overall vaccine effectiveness on the ring level. Stratified analysis of different types of individuals in rings.	To be defined in the SAP.

Definitions of FVD

All sites will use WHO standardized case definitions and surveillance procedures. Samples will be tested at WHO reference labs.

Definition of Confirmed FVD[6]

- Any probable or suspected case (see definitions below) for which a blood sample has been taken and has been confirmed positive in the laboratory for FVD, or
- Any person deceased due to probable FVD from whom a post-mortem sample was taken within 48 hours of death and confirmed positive in the laboratory for FVD.

Definition Probable FVD death[6]

- Any person who died suddenly, or with "suspected FVD" and had a recent epidemiological link to a confirmed case but was not tested and did not have laboratory confirmation of the disease. See SOP ME- 02.

Definition Suspected FVD death[6]

- Any person who had sudden onset of high fever and had had recent contact with a probable or confirmed case of filovirus virus disease (FVD) or a dead or sick animal OR any person with sudden onset of high fever and at least three of the following symptoms: headache, vomiting, anorexia/loss of appetite, diarrhea, lethargy, stomach pain, aching muscles or joints, difficulty swallowing, breathing difficulties, or hiccups; OR any person with unexplained bleeding. SOP ME -02.

5. Study population

The trial will be conducted in any area at risk of (Filoviruses) virus disease.

6. Study visits

During inter-epidemic period

	Who?	Before Day 0	Day 0	Day 0 or 1	Day 7 +/-2	Day 14 +/-2	Day 21 +/-2	Day 28 +/-2	Day 56 +/-2	Day 90 +/-2	Day 180 +/-2	Day 365 +/-2
1. Engage community	CE	X										
2. List names of potentially eligible volunteers	RD		X									
3. Check eligibility	E+C		X									
4. Invite informed consent	E+C		X									
5. Vaccinate	V			X								
6. Monitor any immediate adverse reactions	V			X								
7. Monitor vaccine safety (AEs, SAEs, SUSARs)Ø	FU			X	X	X	X	x	X	X	X	X
8. Collect samples immunogenicity	FU			X	X	X	X	x	X	X	X	X

Ø Samples for safety collection on Days 1 and 3 post-vaccination on Phase 1 volunteers

List of teams

Lab: Designated surveillance laboratory
CE: Community engagement team
RD: Ring definition team
E+C: Eligibility and informed consent team
Call center: Call center that informs on randomization outcome
V: Vaccination team
FU: Follow up team
CT: Outbreak response contact tracing teams (independent from trial teams)

During outbreaks

IMMEDIATE VACCINATION RINGS

	Who?	Before Day 0	Day 0	Day 0 or 1	Day 7 +/-2	Day 14 +/-2	Day 21 +/-2	Day 28 +/-2	Day 56 +/-2	Day 90 +/-2	Day 180 +/-2	Day 365 +/-2
9. Confirm filovirus disease index case	Lab	X										
10. Engage community	CE	X										
11. List names of contacts	RD		X									
12. Check contact eligibility	E+C		X									
13. Invite informed consent	E+C		X									
14. Randomize to immediate or delayed vaccination	Call center		X									
15. Vaccinate	V			X								
16. Monitor any immediate adverse reactions	V			X								
17. Additional monitoring for any filovirus disease cases in the listed contacts	FU				X	X	X					
Phase 1 and 2												
18. Monitor vaccine safety (AEs, SAEs, SUSARs)Ø	FU			X	X	X	X	x	X	X	X	X
19. Collect samples immunogenicity	FU			X	X	X	X	x	X	X	X	X
Phase 3 -												
20. Monitor vaccine safety (AEs, SAEs, SUSARs)	FU				X	X	X					
Independent contact tracing by the MOH/WHO teams	CT	Daily visits to the contacts by non-trial MOH surveillance teams to identify filovirus disease cases										

Ø Samples for safety collection on Days 0 1 and 3 post- vaccination on Phase 1 volunteers

List of teams

Lab: Designated surveillance laboratory
CE: Community engagement team
RD: Ring definition team
E+C: Eligibility and informed consent team
Call center: Call center that informs on randomization outcome
V: Vaccination team
FU: Follow up team
CT: Outbreak response contact tracing teams (independent from trial teams)

DELAYED VACCINATION RINGS

	Which team?	Before Day 0	Day 0	Day 21 +/-2	Day 28 +/-2	Day 35 +/-2	Day 42 +/-2	Day 49 +/- 2	Day 56 +/-2	Day 111 +/-2	Day 201 +/-2	Day 386 +/-2
1. Confirm filovirus disease index case	Lab	X										
2. Engage community	CE	X										
3. List names of contacts	RD		X									
4. Check contact eligibility	E+C		X									
5. Invite informed consent	E+C		X									
6. Randomize to immediate or delayed vaccination	Call center		X									
7. Vaccinate	V			X								
8. Monitor any immediate adverse reactions	V			X								
9. Additional monitoring for any filovirus disease cases in the listed contacts	FU				X	X	X					
Phase 1 and 2												
10. Monitor vaccine safety (AEs, SAEs, SUSARs)Ø	FU		X Ø	X	X	X	X	x	X	X	X	X
11. Collect samples immunogenicity	FU		X	X	X	X	X	x	X	X	X	X
Phase 3												
12. Monitor vaccine safety (AEs, SAEs, SUSARs)	FU				X	X	X					
Independent contact tracing by the MOH/WHO teams	CT	Daily visits to the contacts by non-trial MOH surveillance teams to identify filovirus disease cases										

Ø Samples for safety collection on Days 0/1 and 3 post-vaccination on Phase 1 volunteers

List of teams

Lab: Designated surveillance laboratory
CE: Community engagement team
RD: Ring definition team
E+C: Eligibility and informed consent team
Call center: Call center that informs on randomization outcome
V: Vaccination team
FU: Follow up team
CT: Outbreak response contact tracing teams (independent from trial teams)

7. Study procedures

1. *Confirm filovirus disease cases (if the study is being conducted during an outbreak)*

All newly diagnosed and laboratory-confirmed filovirus disease cases (see section F.1 above) will be included as a new index case. If the laboratory-confirmed filovirus disease case is a contact included in a previously randomized ring, it will be also included as endpoint. New cases of filovirus disease are ascertained through independent contact tracing visits by the MOH/WHO surveillance teams. Independently of the trial, the surveillance teams list all contacts of each confirmed case and will visit them daily for 21 days from case confirmation to identify any suspected cases of filovirus disease. This surveillance of contacts occurs throughout the outbreak and beyond the follow-up period of the trial (i.e. up to 42 days after the last case of filovirus disease is confirmed in this outbreak). Filovirus disease cases are confirmed by the designated surveillance laboratories, using WHO-recommended test procedures[7]. SOP ME -02.

To avoid the trial placing additional demands on outbreak control teams, there will be dedicated trial teams to support and work closely with the filovirus disease contact tracing and surveillance teams. The ***ring definition team*** must obtain a copy of the case investigation form and of the contact tracing lists from the surveillance team. SOP ME -01.

The trial team will record filovirus disease cases (either index cases for a new ring or incident filovirus disease cases among the ring members -endpoints-) as follows (SOP ME- 02):

- Reviewing daily surveillance line listing of cases and of laboratory results
- Engaging with the MOH/WHO disease surveillance teams to receive information on any suspected, probable and confirmed filovirus disease
- Attending the daily response coordination meetings where newly laboratory-confirmed cases are reported.
- In addition, during each follow-up study visit at the participant's home (0, 3, 7, 14 and 21 days after vaccination), the study group will ask those in the ring about any relevant symptoms or signs that might indicate the onset of filovirus disease. Suspect cases identified during these visits will be immediately referred to the closest filovirus disease treatment unit for diagnosis and clinical management as appropriate. The results of the laboratory testing will be monitored.

In addition, **the trial team** will obtain daily the laboratory results of any suspected, probable, or confirmed cases of filovirus disease among enrolled contacts. This will be complemented by the information obtained during the scheduled trial visits. If 60% or more of the contacts of a new filovirus disease case emerging among the members of a ring have been enrolled before in a previous ring, a new ring will not be defined. (See SOP ME -02)

2. *Engage community*

Engage the community as soon as possible (if during the inter-epidemic period) or within 1–2 days of notification of a filovirus disease confirmed case and before other trial related activities are initiated, local social mobilisation experts (***the social mobilization team)*** visit the community where the ring location is (community where the case resides). SOP ME -03-05.

- They seek their consent for the trial team to approach them, through community leaders

and representatives as appropriate, and explain the trial's objectives and the implications of potential participation.

- The available tools for Good Participatory Practices during clinical trials are being adapted to the context in each country (SOP ME-s 5-7).

3. List all potentially eligible participants

During the inter-epidemic period, the trial team will seek all HCWs/FLWs in affected areas and contacts of previous cases, including those briefly absent at the time the list is made.

During outbreaks, if consent is granted by the community to proceed with the vaccine trial activities, a member of the ***social mobilization team*** and ***the ring definition team*** visits the community to seek contacts. SOP ME -01.

The **ring definition team** will work closely with the contact tracing and surveillance teams to identify all contacts SOP ME -01.

- This team will work to list all recent contacts of the cases in the place of residence of the case and in each and every location visited by the case since the onset of symptoms.
- This team will also determine if this filovirus disease index case is a member of a previously defined vaccination ring and document that.
- If 60% or more of the contacts of the new case have been enrolled before in a previously defined ring, a new ring will not be defined. Each participant is eligible to be in only one ring.

4. Check participants eligibility

Once all potentially eligible are listed, ***assess their eligibility*** by interviewing each person to evaluate their eligibility. SOP ME -06.

Inclusion criteria

<u>During the inter-epidemic period</u>

- Male or female, healthy, health care worker/contact of previous case or residing in an area with reported cases in the past
- At least 18 years of age or older at the time of randomization. NB - that the age of majority may vary by country, and that country regulations will supercede the core protocol.
- Capable of giving signed informed consent.
- Pregnant women will be permitted to participate only in Phase 2 and only after DART studies have been completed and reviewed by regulatory authorities. Any pregnancies will be followed up until delivery.

<u>During outbreaks:</u>

- Male or female contact of a newly confirmed filovirus disease index case
- At least 6 years of age or older at the time of randomization.
- Capable of giving signed informed consent/assent/have parent(s)/legal guardian capable of giving signed informed consent as defined in the SOP ME-07; noting that this may vary by country and country regulations and those will supersede the core protocol SOPs.
- Women of childbearing age will be informed regarding the lack of data on the safety of this vaccine in pregnant and lactating women and will be given the opportunity to participate if they wish to do so. Any pregnancies will be followed up until delivery.

The DSMB will monitor safety and will be asked to provide advice on the inclusion of young children as data on safety is accumulated and when doses become available. The protocol will be then amended accordingly.

Exclusion criteria (for both)

- History of filovirus disease (self-reported or laboratory confirmed).
- History of administration of other experimental treatments in the last 28 days.
- Previous vaccination against (Filoviruses).
- History of anaphylaxis from a vaccine or component of a vaccine.
- Serious bed-confining illness requiring hospitalization at the time of vaccination.

During outbreaks, if a participant does not meet the inclusion criteria, he/she will receive recommendations on infection prevention and control. Participants must meet inclusion/exclusion criteria for the vaccine to be included in the trial. A list is also established of all contacts who are either non-eligible or eligible but not enrolled in the trial. Reasons for non-enrolment will be recorded. (See SOP ME- 07). As noted above, if 60% or more of the contacts of a new filovirus disease case emerging among the members of a ring have been enrolled before in a previous ring, a new ring will not be defined.

5. Invite informed consent

The eligibility and consent team will explain the study and invite written informed consent from all eligible contacts. The study website has printable volunteer information in English and translated in local languages. An electronic image of the signature page is kept, and a copy of the printed information and original consent stay with the volunteer or legal representative.

During the Phase 1 and 2, the ICF will clearly indicate the lack or limited data on the safety of the candidate vaccines included and include consent for sample collection.

All will receive information on infection prevention and control. In addition, the trial team will liaise with the authority(ies) in the community of the vaccination ring in order to reinforce the messages on prevention and control in the community during an outbreak.
The review of eligibility, the completion of the informed consent and the communication of recommendations on the control and prevention of the infection will take about 1-3 hours per ring SOP ME -07.

Group information to all eligible contacts

A meeting will be held by **the eligibility and consent team** during which the study objectives and the informed consent process will be explained to all eligible participants. They will be given a patient information sheet and asked to read the entire consent form and/or receive a complete verbal explanation in a language they understand. Each participant will be given the opportunity to ask questions and request clarifications SOP ME -07.

Individual information and informed consent

Subsequently, each eligible participant will be individually asked by **the eligibility and consent team** if they understand all the parts of the form, and they will be invited to give their consent SOP ME -07:

- They will then be given the opportunity to ask questions to the team before deciding.
- For each participant deciding to be included in the trial, the informed consent, given in writing, and for illiterate orally and in the presence of an independent witness will be documented.

- The team will ask children to express their consent/assent before they can participate in the trial. The assent will mean that they accept to take part in the study. They can also state their disagreement or refuse to participate. The parents or guardians will give their informed consent for their child(ren) to be enrolled in the clinical trial.
- A copy of the signed informed consent form and the Patient Information Sheet SOP ME -07. will be given to each participant.
- During the outbreaks, as the contact is being entered into the trial, neither the contact nor the investigator will know to which group (immediate or delayed) vaccine will be allocated.
- Once consent has been obtained, the participants are included in the study. There are no other opportunities to consent or be included in the study.

During outbreaks, if a person does not wish to participate in the study, they will receive recommendations regarding infection prevention and control. The study team will document the members of the ring with whom contact has been established, the number of people who refuse to participate, the baseline demographic information (age, sex, but no personal identification information) and the reasons for said refusal. Individuals may choose not to disclose the reason(s) for their non-participation SOP ME -07.

6. Randomize

During the interepidemic period, ***there are no rings or immediate or delayed randomization***. However, participants will be randomized to receive one of the vaccines included in the study. ***The eligibility and consent team*** calls the trial office, which will enters the details of the participant and then obtain a computerized random allocation. The participants will be individually randomized. SOP ME -08.

During outbreaks, after the last **eligible contact** has consented or not, the entire ring of all **the consenting contacts** will be allocated randomly. SOP ME -08. Only at this point, all members of the ring will be informed of the allocation outcome. Hence, foreknowledge of the outcome of the ring allocation if voluntary entry takes place, cannot bias the decision to enter the study and cannot affect the electronic data collection immediately before randomization (see SOP ME- 08).
An independent statistician not otherwise involved in the trial will generate the allocation sequence. The randomization list will be stored in a data management system not accessible to anyone involved as trial participants.

During outbreaks, ***the ring eligibility and consent team*** will call the trial office, which will enter details of the ring and then obtain a computerized random allocation. SOP ME -08. Randomization of participants will be performed for the whole ring and is not performed separately for individuals.

- The rings will be cluster-randomised (1:1) to either immediate vaccination or delayed vaccination (21 days later) of all eligible and consenting contacts in each ring (cluster).
- A designated member of the **eligibility and consent team** will contact the **trial call center** where a designated **randomization team member** with access to internet will use the edc tool to randomize the ring and a random allocation will be generated (by an algorithm that ensures approximate balance in ring sizes between the two vaccination options).
- The basic information on the ring and the outcome of the randomization will be stored in a designated eCRF.
- The outcome of the randomization will be informed to the **team leader orally**. Again, the allocation cannot be revealed to any participant before the informed consent process is

completed for the entire ring. Once randomization occurs, the list of ring members is definitely closed, and no additional members can be added.

7. Vaccinate

Within each ring of people who are eligible and consented prior to randomization, all will be offered vaccination immediately, or 21 days later by **vaccination teams**. SOP ME-09.
After randomization has been completed, no new people can join the ring or be included in the trial or be offered vaccination at any time for any reason by the trial. Vaccination will take place in the location where the volunteers reside at the time of vaccination.

Study vaccine(s)

The following candidate vaccines have been initially selected to be included in the trial. Other candidate vaccines may be added to the trial as soon as they become available and meet inclusion criteria. A complete list of all vaccines in the trial will be presented as an appendix in the following format:

Candidate vaccines to be evaluated in the ring vaccination trial

Type of vaccine	Vaccine developer	Viruses targeted	No. of doses	Immunogenicity & safety in humans?	Efficacy against FV inanimals?[1]

[1]*All vaccines that can protect animals against a ~~potentially~~ lethal dose of the Filovirus.*

Candidate vaccines are described in the Investigators Brochures.

Administration of the vaccine

The procedures for the vaccination visit will follow the developers' recommended vaccination procedures as described in SOP ME-09 and in the Pharmacy manual.

Vaccine Characteristics, Stability, Labelling, Preparation, Handling, Storage and Accountability

At WHO's request and instructions developers will ship study vaccines to participating sites from global vaccine repositories. All other supplies will be provided by the participating site with support from the Co-Sponsors. The participating sites' principal investigator is responsible for study vaccine disposition and accountability and meeting all regulatory obligations. SOP ME -10.

Concurrent treatment interventions

All interventions approved and required for the purposes of the treatment of a disease or for a specific health condition of a registered participant are authorized. Prohibited interventions consist of vaccination with another (Filoviruses) ebolavirus candidate vaccine.

8. Monitor immediate adverse reactions

After vaccination, participants will be observed on site for 30 minutes to monitor any immediate adverse events following the vaccination.

A physician equipped with emergency medication and resuscitation equipment will be available in case of anaphylactic shock, SAE or SUSAR. SOP ME -15 and17. In addition, during these 30 minutes:

- Participants will be informed of the study evaluation calendar and the subsequent visits as part of the study.
- Participants will also receive a card and will be invited to communicate with the research team if they experience any concerning symptoms before the next scheduled study visit.

9. Sampling for immunogenicity studies (Phase 1 and 2)

- Samples in the immediate rings during outbreaks, or post-vaccination in inter-epidemic periods are taken as described in the tables above. SOP ME -24-28.

All samples from case primary contacts are potentially infectious and hence a detailed biosafety protocol has been developed for the study. All participants will be given a medical examination which will involve checking of temperature and a general health assessment. Blood samples will be collected by a well-trained phlebotomist in appropriate PPE (see SOP ME 24-26 sample collection). Blood tubes will be placed in storage bags, secured in bio containers and transported by a dedicated transport vehicle to a designated laboratory for further processing.

PCR tests will be conducted at all time points using 50 µl of EDTA blood. All blood samples will remain in bio containers at 4 °C until PCR results are available. PCR-negative samples will be further processed as indicated below. PCR-positive samples will be discarded or (if available) processed in a dedicated class III cabinet (Glovebox).

The blood samples will be processed for further chemistry and hematology tests or immunological tests. For sample processing (see SOP ME –26 serum and SOP ME –27 PBMCs and cryopreservation) the materials will be handled within a biosafety Class II cabinet.

Laboratory safety outcome measures will include Haematology assays (hemoglobin, hemoglobin change from baseline, hematocrit percent, mean corpuscular volume (MCV), platelets, and white blood cell (WBC), red blood cell (RBC) and lymphocyte counts), chemistry assays (alanine aminotransferase (ALT), AST, ALP, GGT, total protein, albumin, direct bilirubin, total bilirubin, urea, creatinine, sodium, potassium and chloride), humoral immunity parameters (virus neutralization assays, ELISA assays to measure filovirus-specific IgM and IgG) and ELISPOT assays using overlapping peptide libraries as well as whole antigen to assess filovirus-specific T cell responses.

Outside of the indicated time-point schedule remaining blood samples from the safety of diagnostic tests collected on days 1 and 3 post-vaccination may be utilized for exploratory research (e. g. innate immune responses measured via multiplex ELISA, transcriptomic profiles or other assays). SOP ME -24.

10. Monitor filovirus disease cases (if study is being conducted during outbreaks)

The trial team will record filovirus disease cases (either index cases for a new ring or incident filovirus disease cases among the ring members -endpoints-) as follows (SOP ME -02.):

- Reviewing daily surveillance line listing of cases and of laboratory results
- Engaging with the MOH/WHO disease surveillance teams to receive information on any suspected, probable and confirmed filovirus disease.
- Attending the daily response coordination meetings where newly laboratory confirmed cases are reported.
- In addition, during each follow-up study visit at the participant's home (0, 3, 7, 14 and 21 days after vaccination), the study group will ask those in the ring about any relevant symptoms or signs that might indicate the onset of filovirus disease. Suspect cases identified during these visits will be immediately referred to the closest filovirus disease treatment unit for diagnosis and clinical management as appropriate. The results of the laboratory testing will be monitored (SOP ME- 02).

Participants will be provided instructions in how to contact the trial team, and reminded to contact the trial team if they have symptoms of interest between the schedule visits of the study.

Filovirus disease cases in the delayed rings will be monitored similarly in the pre-vaccination period, without the specified home visits. All identified pre-vaccination filovirus disease cases in the delayed rings will be confirmed at the time of planned vaccination.

11. Monitor solicited and unsolicited AEs, SAEs and SUSARs

During each follow-up visit, **the follow up team** will visit every contact at home and will ask questions about symptoms or signs in order to document the presence adverse events and any other changes in the participants` health since the last visit. All identified adverse effects will be monitored until they are resolved or until stabilization.
During Phase 1 and 2, the follow-up safety visits post-vaccination will be conducted on days 7, 14, 21, 28, 56, 90, 180, and 365. During Phase 3, the follow-up safety visits post-vaccination will be conducted on days 7, 14, 21. SOP ME -16/17.

Detailed safety data collection during Phase 1 and 2 during outbreak and inter-epidemic periods
Additional safety data will be collected on candidate vaccines recommended for the trial during the Phase 1 and 2. This will be reflected in dedicated eCRFs.

For candidate vaccines for which the independent Technical Advisory Committee on Candidate Vaccines Prioritization recommends additional safety information before unduly many volunteers are recruited, the following procedures apply. Before proceeding to the recruitment of a larger number of volunteers, the DSMB will review the safety data seven days and 14 days after vaccination of approximately 200 participants. Safety data will be collected on these participants using the below-mentioned safety monitoring procedures. The decision of the DSMB to continue recruitment will be based on the safety information of these participants.

During Phase 1 and 2, participants will be followed up on day 1(the day of vaccination) through day 7 and on days 14, 21, 28, and 56 for all solicited adverse events. Thereafter,

follow-up will be on days 90, 180, and 365, Data on adverse events will be collected using a vaccine report card and an adverse events app specifically developed for the trial. Safety labs (Haematology and Chemistry) will be monitored in the subset of participants who consented for the immunogenicity assays estimated to be about 200 per candidate vaccine (immediate and delay arms).

Pregnant or breast-feeding female participants

In order to monitor the safety of the participant and of the unborn child, every pregnancy identified at randomisation/consent or later in a participant who has been vaccinated must be reported within one week of discovery as defined in SOP ME -18. The pregnancy outcome will be documented, including spontaneous or voluntary termination of pregnancy, birth details, the presence or absence of congenital malformations, or any complications for the mother and/or the new-born. The pregnancy outcome will be documented even if the safety period provided for monitoring as part of the trial has ended.

Definition of SAEs and SUSARs

A serious adverse event (SAE) is any adverse occurrence that:

- causes death.
- could be life-threatening: an AE is life-threatening if the participant could have died during the event; this does not include events that could have caused death if they had been more severe.
- results in a significant and long-lasting disability or incapacity: an AE results in a disability or incapacity if the event causes a major disruption in the participant's ability to perform their daily activities. This definition is not intended to include episodes of relatively minor medical importance such as headaches, nausea, vomiting, diarrhoea, flu, injection site reactions, and accidental trauma (e.g., a sprained ankle).
- requires hospitalization or the extension of ongoing hospitalization: as a general rule, "hospitalization" means that the participant was admitted (typically implying a stay of at least 24 hours) by the hospital or emergency room for treatment that would not have been appropriate for a doctor's office or outpatient environment.
- is a birth defect in the child of a participant in the study.
- is an important medical event that may be harmful for the participant or may require an intervention to prevent one of the other outcomes mentioned above deemed to be regarded as serious. Examples of such treatments are intensive treatment in the emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

SAEs will be considered as unexpected if the nature, severity, or consequence of the event is not consistent with the information currently available on the vaccine and, it will be reported as a SUSAR (Suspected Unexpected Serious Adverse Reaction).

Hospitalization for a non-urgent surgical procedure associated with a pre-existing health condition, for which the severity and frequency did not increase after the start of the study, or for routine clinical procedures (including hospitalization for "social" reasons), is not considered a SAE. If there is any doubt as to the necessity of the hospitalization, the AE will be considered serious. A routine clinical procedure is defined as a procedure that may take place during the study and that must not interfere with the administration of the vaccine, or with any of the procedures specific to the current protocol. If any adverse event occurs during an eligibility procedure and meets any of the SAE criteria, this event will be duly documented and reported.

Evaluation of causality

If an event meets the criteria to be deemed as "serious" (see the definition of SAEs), it will be considered by the data and safety monitoring board) to determine all the factors applicable to each SAE. These contributory factors will be documented and reported accordingly. The investigator must make every effort to explain each SAE and evaluate its cause-and-effect relationship, if any, with the administration of the experimental vaccine.

Reporting of SAEs and SUSARs

All SAEs and SUSARs must be investigated and reported by the pharmacovigilance coordinator. SOP ME -17.

The **study pharmacovigilance coordinator** will be responsible for monitoring safety and reporting of SAEs and SUSARs during the study and for preparing the documentation for their reporting by the principal investigator. The table below summarizes the calendar of reporting for SAEs and SUSARs.

SAE and SUSARs report calendar

Reported by	Reported to	What?	Timeframe
Pharmacovigilance coordinator	Principal investigator (or his/her delegate)	Initial report	Within 24 hours for all SAEs
Principal investigator	In each country ethics review committee and national regulatory agency Data and safety monitoring board Vaccine developer WHO ethics review committee WHO trial team	Initial report	Within 24 hours for any SAEs and fatal or life-threatening SUSARs, Within 7 days for other SUSARs
Pharmacovigilance coordinator	Principal investigator (or his/her delegate)	Final report	Within 24 hours after death or event resolution or stabilization
Principal investigator	In each country ethics review committee and national regulatory agency Data and safety monitoring board Vaccine developer WHO ethics review committee	Final report	Within 24 hours after death or event resolution or stabilization
Principal investigator	Data and safety monitoring board	Summary	Monthly report on SAEs & SUSARs

The **principal investigator** will report any SAEs and SUSARs to the each in-country Ethics Review Committee and National Regulatory Authority in accordance with the local law and the requirements. The principal investigator will also report them to the WHO Ethics Review Committee and the trial Data and Safety Monitoring Board and to the developer of the vaccine. Adequate documentation will be provided to the Co-sponsor to ensure that all of them have been duly informed within appropriate time limits.

The pharmacovigilance coordinator must provide an updated summary report every month. This report must summarize the SAEs and SUSARs information and specify the number of cases, the reported SAEs or SUSARs (diagnosis), the date of occurrence, the causality, and the

outcome. This summary will be sent to the members of the Data and Safety Monitoring Board. The Board may also request special summary reports on severe adverse events.

SAEs will be treated in accordance with the current good clinical practices. Medical care, consultation and drug treatment services will be provided by the study team. The participants will also be referred to the local healthcare institution or system and will be treated in accordance with the national health standards.

End-of-study visit

- The day-365 visit post-vaccination for Phases 1 and 2 and day-180 visit for phase 3 are defined as the end-of-study visit (SOP ME -19.) for non-pregnant participants.
- The general health condition of the participant will be recorded, and information on all changes in the participant's profession or residence, or all other important factors that have changed over time, will be collected during this visit.
- The participants will then be informed that no further contact is required as part of the study, but that they must nevertheless inform the study team by phone of all potential serious adverse events or if they may have become infected with (Filoviruses) ebolavirus.

Expenses and allowances

Participants are not expected to travel for study visits, as the visits will be made at their home. However, if they must travel, reasonable travel costs will be reimbursed for all visits, upon submission of receipts, or a mileage allowance will be granted, as appropriate.

8. Statistics

1. Sample size

As the detailed information on transmission dynamics of filoviruses is not available, the decision about when to end the trial will be made by the Trial Scientific Committee without knowledge of previous allocation, based on an assessment of the number of accumulated endpoints and epidemic trends. The final sample size achieved will depend on the number of new index cases accumulating during the study period.

The proposed ring vaccination study involves a population at increased risk of infection as they have recently been in contact with a case of filovirus disease, so it may well provide useful information about the protection of such case contacts quickly, within just a few months.

To judge by experience in the 2015 ring vaccination trial in Guinea, perhaps 5-10% of the rings of contacts around these index cases would be "informative" (i.e., would include at least one case of filovirus disease with the onset of symptoms 10 to 29 days after randomization).

Even if the current outbreak is controlled within just a few months, such a trial could still be usefully informative if at least one of the candidate vaccines has a substantial protective effect – for example, if there were 6 vs 0 "informative" rings (delayed vs immediate vaccination) this result would be 2p=0.03, i.e., a conventionally significant difference between delayed and immediate vaccination.

2. Statistical analysis

According to GCP guidelines it is acceptable to develop a Statistical Analysis Plan (SAP) later on as long as this is done before the data is unblinded or analysed[2]. Given the emergency situation and uncertainty associated with (Filoviruses) virus epidemiology, this option will be implemented. For, it will be possible to write the SAP more precisely and appropriately some weeks after the trial has started. In addition, there is the intent to continue efficacy endpoint accumulation across multiple outbreaks[3]

Phase 1 and 2

Each candidate vaccine will be compared to delayed comparator.
We will assess immunogenicity by measuring vaccine specific antibody titres, neutralization activity at each of the follow up visits starting with day 21 follow up and all other follow up time points and cell mediated immune responses. Rates of seroresponse following vaccination are also of interest.

Phase 3

The primary analysis (per-protocol) will be of laboratory-confirmed filovirus disease cases with symptom onset 10 to 21 days after randomization. The omission of days 0-9 allows time for the vaccination to take effect, and reduces the chance of including cases who got infected prior to the vaccination (given a typical 2-21 days incubation period for (Filoviruses) ebolavirus[8]).

Confirmed cases arising in enrolled ring members during the relevant ascertainment window are included as primary outcomes in the main analysis of vaccine efficacy. We will analyse outcomes at the cluster level rather than the individual level. Thus, the primary analysis will compare the number of rings with at least one case of filovirus disease with onset of symptoms 10 to 29 days after randomization. To judge by experience in the 2015 ring vaccination trial in Guinea, perhaps 5-10% of the rings of contacts around an index case would be "informative" in such analyses (i.e., would include at least one case of filovirus disease with onset of symptoms 10 to 29 days after randomization).

Numbers of definite cases and of probable cases in days 0-9, 10-29 and after day 29 since randomization will each be tabulated separately, distinguishing between fatal and non-fatal cases and noting any cases that were excluded from the primary per-protocol analyses (thereby making available modified *intent-to-treat* analyses of outcome by allocated treatment of all randomized ring members).

Numbers of individual cases by day since randomization will be plotted by Kaplan-Meier methods.

Possible safety events during the first 3 weeks after vaccination will be described, and tabulated by severity and time since vaccination, as will eventual pregnancy outcomes.

---

[2] *https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-9-statistical-principles-clinical-trials-step-5_en.pdf*
[3] *https://www.nejm.org/doi/10.1056/NEJMsb1905390*

9. Ethical and regulatory aspects

1. *Community engagement*

Engagement within the communities in the zone concerned by the study is critical. At the beginning of the study, a team of social mobilizations and community engagement experts will visit the communities to inform the population of the study area about the study objectives. The available tools for Good Participatory Practices during clinical trials will be adapted to each country context [9,10]. The Principal Investigator and the community engagement team will consult with community representatives before, during, and after the trial, thereby ensuring that the process is participatory, transparent, and constructive.

2. *Ethics approval*

The investigator will ensure that the trial is conducted in accordance with the principles of the Declaration of Helsinki. The investigator will ensure that the trial is conducted in full compliance with the applicable regulations and the ICH guidelines on good clinical practices[11,12].

The protocol, the informed consent form, the patient information sheet, and all promotional material proposed will be submitted to the following ethics committees for ethical review:

- National Ethics Committee for Health Research, national level
- WHO Ethics Review Committee, WHO Geneva

Due to the need to implement the clinical trial rapidly, the applications will be submitted to these committees simultaneously. The investigator will submit all significant amendments to the original approved documents to the aforesaid parties, obtaining approval as necessary.

Once a year, during the clinical trial, or at request, the investigators will send the annual progress report to the appropriate ethics committees. In addition, an end-of-trial notification and a final report will be submitted to the same committees and the Co-sponsors.

3. *Approval by the national regulatory authorities*

Regulatory approval will be obtained from the National Regulatory Authority of each country. The approval of the regulatory authorities will involve the following guidelines and standards:

- The requirements defined by the National Regulatory Authority of each country and by the Ministry of Health for approval of the clinical trial.
- The most recent version of the GCP guidelines of the ICH.

4. *Privacy and confidentiality of the participants*

The trial staff will ensure that the anonymity of the participants is preserved. The participants will only be identified by initials, ID number, age, and sex on the eCRF (at enrolment only), and subsequently, by ID number.

- All data will be stored securely, and only the trial staff and authorized personnel may consult them. The trial will make the data anonymous as soon as practically possible.
- The investigator file and the associated source documents will be retained for at least five years after completion of the study. The patient identification codes will be retained for at least 15 years after completion of the study. The written authorizations of all sponsors will be obtained before destroying the files.
- All documents referring to the study will be stored in a locked cabinet at the study site. The filing cabinets containing the trial data and the participant information will be locked, and

only the persons authorized by the sponsor and by the regulatory authorities may access them. The participant's personal data will remain confidential, and the personal information of all participants will be protected to the extent permitted by law. Only the staff involved in the study and the local and international regulatory agencies may consult these files. The investigator will keep the investigator files, the patient identification list and the selection / recruitment log (including the first and last name, age, and address).

10. Decision by a volunteer or legal representative to withdraw from follow-up

Volunteers will be informed at study entry of their right to withdraw at any time during follow-up without any adverse consequence and without giving any reason. Withdrawal from the vaccine group that was randomly allocated at study entry need not imply withdrawal from information on outcome being reported to the WHO at the end of the follow-up period. Cases that occur before the withdrawal date will be counted. But, if the volunteer (or a legal representative of the volunteer) decides to withdraw and that no further data will be sent to the WHO study office, then only the date of withdrawal will be reported; no further information will be given, unless an adverse drug reaction report is legally required. (See SOP ME- 20).

11. Administrative aspects

1. Registration of the study

Before beginning, the study will be registered in the Pan African Clinical Trial Registry selected.pactr.org, which is indexed by the International Clinical Trials Registry Platform selected.who.int/ictrp/en/.

2. Amendments to the protocol

The sponsor will modify the study protocol if necessary to ensure that the clinical investigations are always conducted in accordance with the appropriate and up-to-date protocols. The amendments will be submitted to the regulatory authorities and ethics committees for approval. Developers will be notified of the pending amendment and of its approval and provided with the final amendment language, as provided in the signed letter of agreement. The amendments requiring modifications will be defined in accordance with the guidelines of the national regulatory authority (Annex 2).

3. Insurance

The degree of liability of the sponsor is defined by the GCPs of the ICH.
Volunteer participants will be insured, in accordance with the applicable laws and regulations, against all financial loss due to bodily injury and/or other damages resulting from this study. WHO has established a global clinical trials liability insurance (for individuals suffering serious adverse reactions arising from the use of the investigational vaccines as part of this trial) that will cover all investigators, developers and stakeholders that participate in the trial.

12. Study Organization

This study is a collaboration between the Ministry of Health in each country and local and international partners (see Annex 3). National investigators will lead the trial. The experience and expertise brought to the study by the national researchers and partners will accelerate

the implementation of the study and will facilitate rapid analysis of data and reporting of the results. The trial is funded by various organizations and partners. The vaccines will be provided by the manufacturer, and additional support will be provided by the participating institutions.

The trial Co-Sponsors of this study are the National Ministry of Health and the World Health Organization. The study candidate vaccines will be available at no cost from the study Sponsors, but the study does not cover any other aspect of patient care. The independence of this study from any actual or perceived financial influence, such as from pharmaceutical companies or their consultants, is critical. Therefore, any conflicts of interest in its design, conduct, analysis, interpretation or publication, will be disclosed and managed by the WHO and the national Co-Sponsor.

13. Data management and retention of records

1. Data oversight

A data management center will be set up on the study site. Data collection will take place on tablets in the field using standard electronic Case Report Forms (eCRFs). The data management center will be in constant communication with the central coordinator or the local principal investigators to report problems with the data (e.g., questions on the forms, queries / modifications on forms).

2. Trial master file and investigator site file

The investigators must keep the appropriate medical records and research records in relation to this trial in an electronic file, in accordance with the GCPs of the ICH [11,12] and with the regulatory and institutional requirements for the protection of participant confidentiality. The principal investigator, the co-investigator, and the clinical research nurses will have access to the records. The investigators will allow authorized representatives of the sponsor(s) and the regulatory agencies to examine (and if the applicable law requires, to copy) the clinical records for purposes of quality assurance, audit, and evaluation of the tolerance and progress of the study. The sponsor will provide each developer with the trial master file of their respective vaccine as specified in the signed agreement.

3. Record-keeping

The trial master file and the investigator's master file, in particular a copy of the signed informed consent forms, as well as all the source documentation, must be retained by the investigator (and another copy must be retained by the sponsor), who will ensure that they are archived for twenty years in a safe location, with the other study documents, such as the signed informed consent forms, the protocol, the investigator brochure, and all amendments to the protocol. A contract research organization will support the establishment and maintenance of the trial master file and the investigator's master file.

4. Data management

The trial will use electronic case reporting forms. These eCRFs are built into a system that let researchers and clinical staff enter data directly into the system in the field. Castor complies with all applicable laws and regulations, including ICH Good Clinical Practice (GCP), 21 CFR Part 11, EU Annex 11, General Data Protection Regulation (GDPR), HIPAA (US), ISO 9001 and ISO 27001. Data will be stored in a data repository on WHO data server. The Data manager will

create a set of standard data access descriptor/view files, which will be used in the generation of analysis datasets.

5. Source records and study record retention

Source data are/will be all electronic (eCRF). The collection of data using eCRFs is described in SOP ME- 21. In this trial, the following documents have been identified as "source-documents":

- (Filoviruses) virus cases investigation sheet, WHO
- (Filoviruses) virus laboratories results
- (Filoviruses) virus contacts tracing sheet, WHO
- Form for the inventory of contacts for filovirus disease cases (Linear list), WHO
- Contact monitoring form, WHO
- Case report form (CRF)

Study-related records, product accountability records, and informed consent records will be maintained for at least 5 years after the trial ends. If, before or during that period, this study is used in a licensing application for any purpose, then the records will be kept for at least 5 years after that application is approved or rejected. No records will be destroyed without the written consent of the WHO, acting in its role as co-sponsor of the trial. The sponsor and regulatory agencies will have the right to conduct confidential audits of such records (but should be mindful of the workload facing participating hospitals and the infection control requirements during this outbreak).

14. Quality assurance and control

1. Training to ensure trial quality

Before any participants are recruited, coordination meetings will be held with the research team during which the justification and objectives of the study will be explained. In addition, GCP training will be provided to the clinical study team.

The objective will be to ensure that the clinical study team of the trial is properly prepared and trained and that it understands the details of the study, its design, and the strategy for the administration of the vaccine proposed under the study before the clinical study is implemented.

Investigators involved in the Guinea Ring Trial will support the implementation of the trial, particularly in the initial preparatory phases, to facilitate the identification of contacts, community education and information and follow-up of trial participants.

2. Monitoring protocol compliance

Monitoring to ensure trial volunteers are protected and the trial data are timely and complete will be conducted mainly by central data checks. In addition, in each country The Co-Sponsors will identify local monitors to help local site staff resolve any problems, and to provide training focused on any specific local needs. Monitoring will be implemented in compliance with international regulations.

A Contract Research Organization will monitor the trial activities in the field. Their focus will be on factors that are critical to quality (i.e., to volunteers' safety and the reliability of the trial

findings). Remedial actions would therefore focus on issues with the potential to have a material impact on these issues.

The Contract Research Organization will conduct monitoring of the integrity and quality of the data collected in the eCRFs. This will include electronic completeness and quality checks for all records, raising of queries, completeness of documentation related to SAEs and SUSARs

3. Protocol deviations and violations

The study will be conducted in accordance with the principles of International Conference on Harmonisation Guidelines for Good Clinical Research Practice (ICH-GCP) and relevant local, national and international regulations.

Any serious breach of GCP will be handled in accordance with regulatory requirements and classified as protocol deviations or violations. (SOP ME -22.) If this happens, this should be reported within 24 hours on the study website eCRF. The DSMB chair will be informed and will then decide whether this constitutes a major protocol deviation that warrants forwarding promptly to the relevant national coordinator, ethics committee, and respective developer.

4. Inspections

The investigators and institutions involved in the study must ensure that the regulatory authorities can perform the controls, audits, and inspections concerning the implementation of the study. This includes the official inspections of documents, facilities, files, and all other resources that the regulatory authorities consider associated with the clinical trial and likely to be found at the trial site or on the premises of the sponsor and/or contract research organizations, or in any other establishment deemed appropriate by the regulatory authorities. In the event a health authority requests an inspection of the above-mentioned records, WHO will notify the vaccine developer thereof as soon as reasonably possible after becoming aware of such request.

Any inspection agreed to by WHO will be without prejudice to WHO's privileges and immunities. WHO will consult with the vaccine developer before any such inspection and provide the vaccine developer with the results thereof when WHO receives them.

WHO will consult with the vaccine developer on any response to the health authority. In the event that a health authority inspects the vaccine developer in relation to the Trial, WHO will, at the vaccine developer's request and without prejudice to WHO's privileges and immunities, provide reasonable support to the vaccine developer in responding to questions from the health authority concerned, i.e. insofar as such questions relate to WHO activities or WHO records.

15. Data sharing and publications

After the trial has ended and its results have been reported, anonymized data sharing will occur as per the Policy Statement on Data Sharing by the World Health Organization[13].
The protocol and the final data sets will be available on the dedicated site at the WHO website after the study results are published.

This international collaboration is co-ordinated through the World Health Organisation, which is also a sponsor of the trial. Any wholly reliable findings will be disseminated rapidly by the WHO.

There will be group authorship recognizing the contribution of all national and local investigators and guided by the International Committee of Medical Journal Editors (ICMJE) recommendations.

Although the writing committee will consist of the executive group and the trial secretariat, authorship will include all steering committee members and local collaborators whose team, in the view of the national principal investigator, contributed substantially towards the trial. The results of the study will be presented at conferences held in each country and each of the partner countries, as well as at international conferences.

Developers will be kept informed about timelines to report and publish data in accordance with the signed agreement with each sponsor.

16. References

1. Ebola ça Suffit Ring Vaccination Trial Consortium. The ring vaccination trial: a novel cluster randomised controlled trial design to evaluate vaccine efficacy and effectiveness during outbreaks, with special reference to Ebola. BMJ. 2015 Jul 27;351:h3740. doi: 10.1136/bmj.h3740.
2. Henao-Restrepo AM, Longini IM, Egger M, et al. Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial. Lancet. 2015 Aug 29;386(9996):857-66. doi: 10.1016/S0140-6736(15)61117-5.
3. Henao-Restrepo A-M, Camacho A, Longini IM, et al.: Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!). The Lancet 389, 505-18 (2017)
4. Foege WH, Millar JD, Henderson DA. Smallpox eradication in West and Central Africa. Bull World Health Organ. 1975;52(2):209-22. PMID: 1083309; PMCID: PMC2366358.
5. Henderson DA. Principles and lessons from the smallpox eradication programme. Bull World Health Organ. 1987;65(4):535-46. PMID: 3319270; PMCID: PMC2491023.
6. World Health Organization. Case definition recommendations for Ebola or (Filoviruses) virus diseases. 8 August 2014. https://www.who.int/publications/i/item/WHO-EVD-CaseDef-14.1. Accessed on October 3, 2022.
7. World Health Organization. Diagnostic tests evaluated through the WHO emergency use assessment and listing process. https://www.who.int/teams/regulation-prequalification. Accessed on October 3, 2022.
8. Van Kerkhove MD, Bento AI, Mills HL, Ferguson NM, et al. A review of epidemiological parameters from Ebola outbreaks to inform early public health decision-making. Sci Data. 2015 May 26;2:150019. doi: 10.1038/sdata.2015.19.
9. World Health Organization. Good Participatory Practice (GPP) with trial populations for the Solidarity Trial Vaccines (STV). & September 2021. https://www.who.int/publications/m/item/good-participatory-practice-(gpp)-with-trial-populations-for-the-solidarity-trial-vaccines-(stv). Accessed on October 3, 2022.
10. World Health Organization. Good Participatory Practice for trials of (re-)emerging pathogens (GPP-EP): Guidelines Good participatory practice guidelines for trials of emerging (and re-emerging) pathogens that are likely to cause severe outbreaks in the near future and for which few or no medical countermeasures exist (GPP-EP). 6 December 2016. https://www.who.int/publications/m/item/good-participatory-practice-guidelines-for-trials-of-emerging-(and-re-emerging)-pathogens-that-are-. likely-to-cause-severe-outbreaks-in-the-near-future-and-for-which-few-or-no-medical-countermeasures-exist-(gpp-ep). Accessed on October 3, 2022.
11. ICH Guideline E6 on good clinical practice - Draft ICH E6 principles 24 June, 202.1 EMA/CHMP/ICH/337843/2021. https://www.ema.europa.eu/documents/scientific-guideline/ich-guideline-e6-good-clinical-practice-draft-ich-e6-principles_en.pdf. Accessed on October 3, 2022.
12. ICH harmonised guideline-Integrated addendum to ICH E6(R1): Guideline for good clinical practice E6(R2) Current Step 4 version. 9 November 2016 https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf. Accessed on October 3, 2022.
13. World Health Organization. New WHO policy requires sharing of all research data. 16 September 2022. https://www.who.int/news/item/16-09-2022-new-who-policy-requires-sharing-of-all-research-data. Accessed on October 3, 2022.

17. Annexes

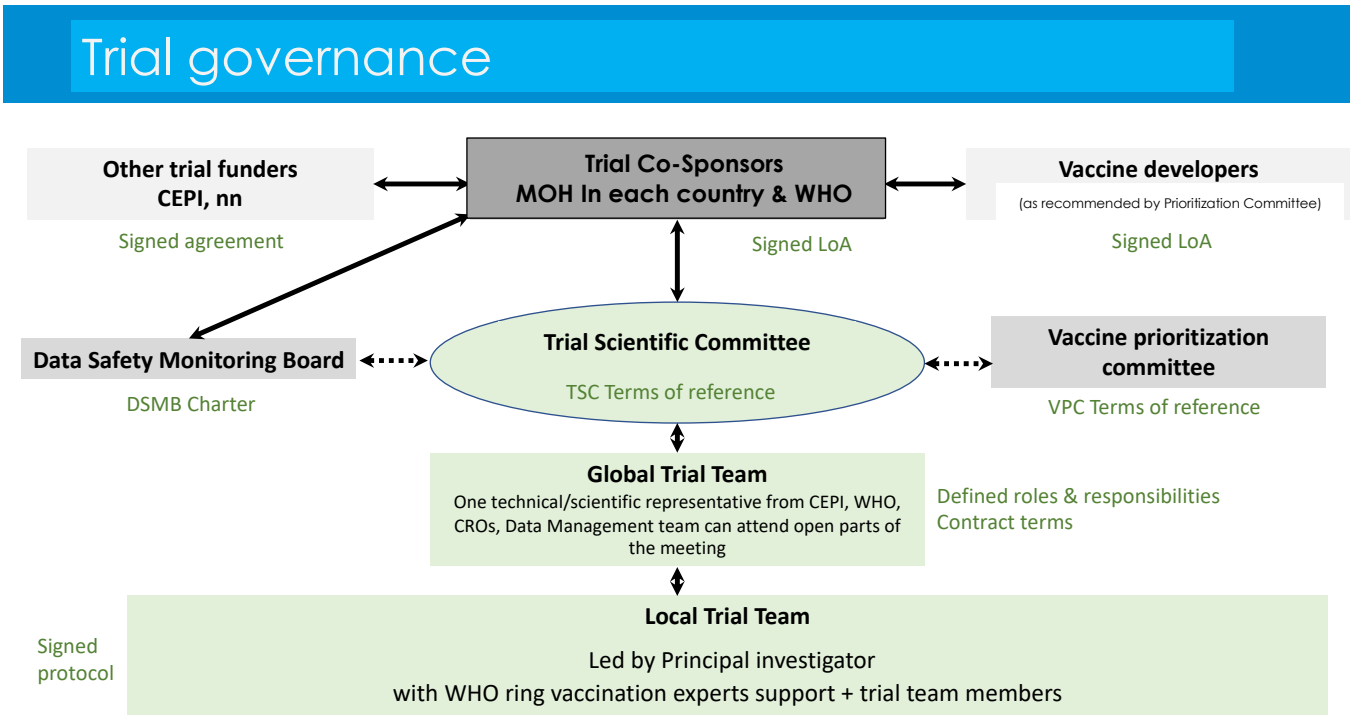
Annex 1. Standard operating procedures and electronic case record

Trial activity	SOP ME-number	eCRFs or other data collection tools
List all contacts in a ring	SOP ME- 01	Ring definition list
Definition of index case for a ring and primary endpoint	SOP ME- 02	Primary endpoint form
WHO Tool on Good Participatory Practices during trial	SOP ME- 03	
Solidarity Trial Vaccines crisis communication planning guide	SOP ME- 04	
Good Participatory Practice (GPP) with trial populations for the Solidarity Trial Vaccines	SOP ME- 05	
Assessment of eligibility	SOP ME- 06	Ring participants form
Informed consent and Patient Information Sheet	SOP ME- 07	Informed consent documentation form
Randomization to immediate or delayed vaccination	SOP ME- 08	Outcome of randomization form
Vaccination procedures	SOP ME- 09	Vaccination form Pharmacy manual
Country reception with cold chain requirements	SOP ME- 10	Cold chain monitoring spreadsheets
Storage, packing, and distribution with cold chain requirements & Transport to secondary storage with cold chain requirements	SOP ME- 11	Cold chain monitoring spreadsheets
Disposal and waste management	SOP ME- 12	Cold chain monitoring spreadsheets
Setup and maintenance of cold chain infrastructure	SOP ME- 13	Cold chain monitoring spreadsheets
Cold Chain (CC) decommissioning	SOP ME- 14	Cold chain monitoring spreadsheets
Monitor immediate adverse reactions	SOP ME- 15	Adverse events reporting form Trial vaccination card
Monitor Adverse Events	SOP ME- 16	Adverse events reporting form
Monitor SAEs and SUSARs/ Reporting of SAEs and SUSARs	SOP ME- 17	SAE and SUSARs reporting form
Monitoring pregnancy outcomes	SOP ME- 18	Pregnancy outcome reporting form
End of study visit	SOP ME- 19	End of study visit form
Participants discontinuation or withdrawal from study	SOP ME- 20	Participants discontinuation or withdrawal form
Collection of data using eCRF	SOP ME- 21	
Protocol deviation and protocol violations	SOP ME- 22	Protocol deviation and protocol violations forms
Infection Prevention and Control (IPC)	SOP ME-23	
General for the Solidarity trial core protocol primary immunogenicity endpoints	SOP ME-24	
Blood Collection	SOP ME-25	
Serum Collection	SOP ME-26	
PBMC and plasma collection and cryopreservation	SOP ME-27	
Sample Storage	SOP ME-28	

Annex 2. History of protocol amendments

Date	Version	Brief description of amendments	Rationale

Annex 3. Trial governance framework



Trial Co-Sponsors

The roles and responsibilities of the Co-sponsors are defined by generic Letters of Agreement (LoA) between WHO and them. These LoAs follow the generic agreements that WHO has used over the years and that govern its relationships and its role in the context of research projects.

WHO will coordinate the randomization and data management in a centralized database run by a CRO not accessible to WHO staff or the trial team, to which all trial sites will contribute data. WHO agrees to ensure that its designate will store and maintain the records for the Trial in accordance with ICH Good Clinical Practice. If at any point, WHO no longer wishes to retain the records from the Trial, then the vaccine developer must be given the option to have the records stored at the vaccine developer's expense, and on terms that are acceptable to WHO and in accordance with ICH Good Clinical Practice. If the records for the Trial are stored at the vaccine developer's expense, the vaccine developer will apply the foregoing *mutatis mutandis* in respect of WHO.

Vaccine developers

Similar to co-sponsors, the roles and responsibilities of the vaccine developers are defined by a LoA between WHO and them. WHO will engage and set up collaborations with the vaccine developers via a signed LoA and interact with them as defined in the LoA. These LoAs follow the generic agreements that WHO has used over the years and that govern its relationships and its role in the context of research projects. The vaccine developer warrants and represents that the candidate vaccine has been manufactured in accordance with current Good Manufacturing Practices (cGMP), to the extent that each standard of cGMP is or can be applicable; and complies with the label requirements set forth by the trial Sponsor(s) and provided to the developers.

The vaccine developer furthermore warrants and represents that the vaccine developer is lawfully entitled to enter into this trial and provide the candidate vaccine free of charge to WHO for the purpose of the trial; and to the best of the vaccine developer knowledge, as of the date of signature of the LoA with WHO, neither the supply to WHO nor the importation, use and administration of the Vaccine in the countries where the trial takes place infringes the valid patent rights of any third party.

As part of the generic WHO LoA terms, the developers agree to transparency in reporting trial results and will provide sufficient data to support inclusion of their vaccine in the trial and the required number of doses of their vaccine and corresponding delayed comparator to WHO. The LoA also defines that if the vaccine is safe and efficacious, the developer commits to make the vaccine available in sufficient amounts and at an affordable price to the public health sector of the developing countries.

If these trials results support efficacy claims, vaccine developers will be responsible for interacting with regulators responsible for approving the use for emergency authorization or licensure. Developers may withdraw their vaccine from further randomization, but not from follow-up. Developers will not be expected to make a financial contribution to the trial.

Trial Scientific Committee (TSC)

This is an independent scientific committee established to review scientific elements important for the design, conduct and analysis of the trial. The TSC will provide advice to the study Co-Sponsor(s) and the Global trial team on issues regarding trial design, conduct and analysis. It will provide formal recommendations on the direction of the trial:

- Reviewing the progress of the trial
- Reviewing initiation of enrolment at new sites
- Reviewing appropriateness of sites for evaluation of specific candidate vaccines
- Considering recommendations provided by the independent DSMB
- Ensuring that reports emerging from the trial are scientifically valid
- Making recommendations on trial conduct or adaptive design elements to the WHO and the MOH s co-Sponsors of the trial
- In conjunction with Trial co-Leads, the TSC will liaise with the Sponsor and donor coordination group, technical advisory committee on candidate vaccines prioritization committee, and Trial Team as appropriate.

The TSC will ensure that the conduct of the trial in each site is harmonized with respect to important aspects such as data collection, laboratory tests, and implementation of vaccination. Adaptive aspects of the study, to the extent not predefined in the protocol, will be governed by the TSC, which will not have access to unblinded study data.

Invited trial team members can attend only the open sessions of the TSC.

Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board is a group of independent experts external to the trial assessing the progress, safety data and critical efficacy endpoints of the trial.

In order to do so, the DSMB may review unblinded study information during the conduct of the trial. Based on its review the DSMB provides the Co- Sponsors with recommendations regarding study modification, continuation, or termination.

The DSMB will keep the emerging evidence provided by the independent statistical center on safety and on efficacy under continuous review.

The DSMB will be responsible for providing information to the Sponsor and the trial co-Leads, when required to be reported to regulators (normally restricted to serious, unexpected, suspected adverse reactions). This information will also be given to developers to be shared by them with regulators and to update the product-specific Investigator's Brochure.

The DSMB will provide recommendations regarding continuation or termination of randomization to vaccine arms or of the entire trial, either due to persuasive evidence of benefit or lack of benefit, or unacceptable safety issues. In assessing the acceptability of the safety profile of each vaccine regimen, the DSMB will consider the totality of information regarding benefits and risks.

To enhance trial integrity, the DSMB may also formulate recommendations to the TSC. These may relate, for example, to participant recruitment rates and eligibility, improving adherence to protocol-specified regimens, participant retention, and the timeliness of data capture and adjudication of trial endpoints. The Data and Safety Monitoring Committee (DSMB) will meet frequently, and any results will be communicated to the Co-Sponsors within 1 week of a DSMB of any decision in relation to a stopping rule.

The DSMB will be advisory to the TSC, who will be responsible for promptly reviewing the DSMB recommendations, discussing them with the DSMB only if necessary for clarification, discussing them with the study sponsor(s), and making decisions about their implementation.

Invited members of the trial team can attend only the open sessions of the DSMB.

Technical Advisory Committee on Candidate Vaccines Prioritization

The Technical Advisory Committee on Candidate Vaccines Prioritization aims to provide guidance as well as to prioritize vaccine platform approaches and/or candidates to be considered for further development and potentially consider for late-stage evaluation in the context of the Solidarity Trial Vaccines.
The objectives of this group are:

1. To review the current pipeline of candidate vaccines
2. To review the current pipeline of candidate vaccines and discuss their value in protecting against (Filoviruses) ebolavirus disease.
3. To make preliminary recommendations on whether the development of candidate vaccines should be prioritized for the Trial.

Invited experts can attend only the open sessions of the Working Group.