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Outline of major design considerations for candidate vaccines trial CORE protocol

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Key trial features

This is a phase 1/2/3 study to evaluate the safety, tolerability, immunogenicity, and efficacy of **X** candidate vaccines against filovirus disease in healthy individuals at risk of filovirus disease.

It has two main components:

1. **During the inter-epidemic period:** Safety and Immunogenicity (phases 1 and 2)
2. **During outbreaks:** Safety and efficacy (phase 3) and for certain candidate vaccines (phases 1 and 2)

Key trial features

The trial is designed to move seamlessly through the phases and even collect data through several phases simultaneously.

- Allows seamless collection of data, including with vaccines that don't yet have phase 1 data
- Allows all trial participants (and vaccine doses) to contribute to the efficacy assessment
- Contributes to the assessment during future outbreaks

Immunogenicity and safety assessments in at-risk populations

- Will help with future prioritizations
- May support an understanding of protective mechanisms
- May support the identification of immune markers that predict protection

Seamless progression from phase 1 to Phase 3

During the inter-epidemic period

During the outbreak

Phases 1 and 2
Individual randomization among vaccines (no placebo)

For candidate vaccines for which the independent Working Group on Vaccine Prioritization recommends

1. **Phase 1.** Enrolment of first 100 (including HCWs/FLWs in affected areas and contacts of previous cases), subject to continuous DMC review

2. **Phase 2.** Enrolment of up to 1000 HCWs/FLWs in affected areas.

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Seamless progression from phase 1 to Phase 3

During the inter-epidemic period ***During the outbreak***

Phases 1 and 2 Individual randomization among vaccines (no placebo) For candidate vaccines for which the independent Working Group on Vaccine Prioritization recommends	→	**Phase 3** Cluster-randomized (immediate versus delayed) For candidate vaccines for which the independent Working Group on Vaccine Prioritization recommends.
1. **Phase 1**. Enrolment of first 100 (including HCWs/FLWs in affected areas and contacts of previous cases) 2. **Phase 2**. Enrolment of up to 1000 HCWs/FLWs in affected areas.		1. Enrolment of participants (contacts of FVD cases including HCWs/FLWs) 2. Analysis as defined in the Statistical Analysis plan

Seamless progression from phase 1 to Phase 3

During the inter-epidemic period ***During the outbreak***

Phases 1 and 2 Individual randomization among vaccines (no placebo) For candidate vaccines for which the independent Working Group on Vaccine Prioritization recommends	→	**Phase 1 and 2** Cluster-randomized (immediate versus delayed) For candidate vaccines for which the independent Working Group on Vaccine Prioritization recommends in order to collect additional safety information before unduly many volunteers are recruited.	**Phase 3** Cluster-randomized (immediate versus delayed) For candidate vaccines for which the independent Working Group on Vaccine Prioritization recommends.
1. **Phase 1.** Enrolment of first 100 (including HCWs/FLWs in affected areas and contacts of previous cases) 2. **Phase 2.** Enrolment of up to 1000 HCWs/FLWs in affected areas.		1. **Phase 1**-Enrolment of up to 200 (100 per arm) participants (contacts of FVD cases including HCWs/FLWs) 2. Safety analysis of Phase 1 data by DSMC (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 participants (contacts of FVD cases including HCWs/FLWs) 2. Analysis as defined in the Statistical Analysis plan

During the inter-epidemic period

Objectives	Outcomes	Statistical analysis
Phase 1 and 2: For candidate vaccines for which the independent Working Group on Vaccine Prioritization recommends		
Primary objectives		
To determine the **reactogenicity** and **safety** of candidate FV 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 FV 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

During the inter-epidemic period

Objectives	Outcomes	Statistical analysis
Phase 1 and 2: For candidate vaccines for which the independent Working Group on Vaccine Prioritization recommends		
Secondary Objectives		
To determine the **durability of FV-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 FV vaccine candidates against other filoviruses.	We will assess immunogenicity by measuring antibody titers and neutralization activity against EBOV, SUDV and BUDV.	This will be defined in the SAP.
Exploratory Objectives		
To determine the effect of FV 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 FV vaccines on the host metabolome. To determine the effect of FV 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 IgG and other assays.	This will be defined in the SAP.

Study visits during the inter-epidemic period, Phase1/2

QA TEAM MONITORING
CLOUD-BASED GCP-COMPLIANT SYSTEM

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

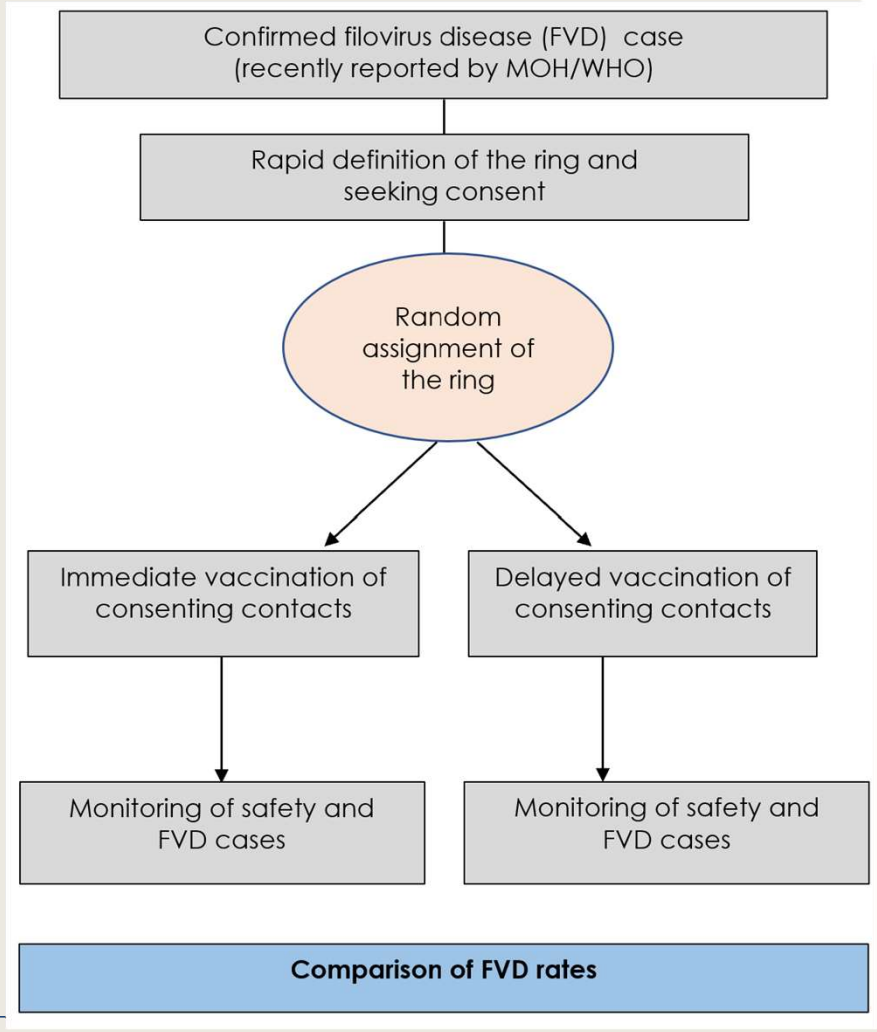
Ø Samples for safety collection on Days 1 and 3 post-vaccination on Phase 1 volunteers

During outbreaks
Phase 3

Cluster-randomized (immediate versus delayed)

To assess the effect of a candidate vaccine in protecting against laboratory-confirmed filovirus disease.

For candidate vaccines for which the independent Working Group on Vaccine Prioritization recommends.



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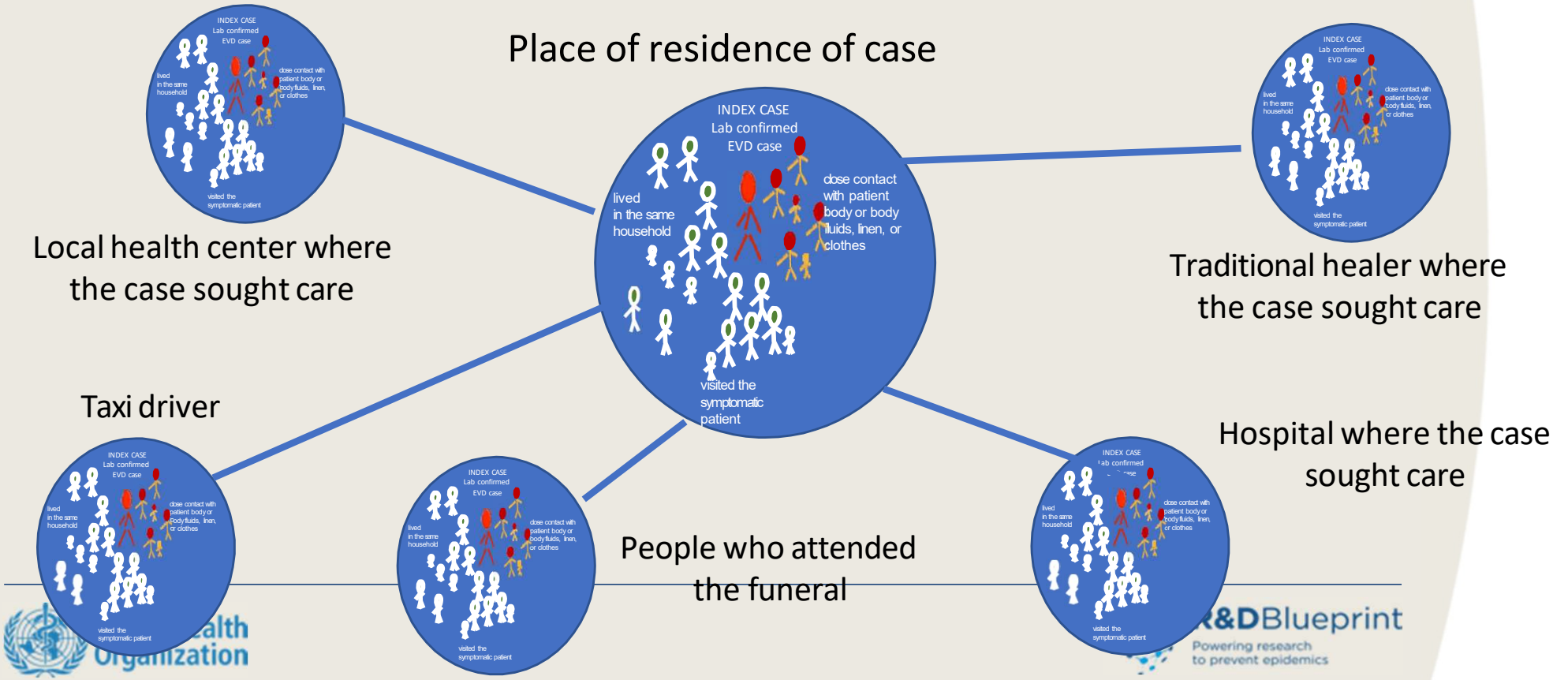
A ring is not a geographic site

A ring includes **all recent contacts** of the cases in the place of residence of the case and in each and every location visited by the FVD case since the onset of symptoms



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During outbreaks

For certain candidate vaccines for which the independent Working Group on Vaccine Prioritization recommends in order to collect additional safety information before unduly many volunteers are recruited.

1. **Phase 1-** Enrolment of up to 200 (100 per arm) participants (contacts of FVD cases including HCWs/FLWs)

   Safety analysis of Phase 1 data by DSMC (7 and 14 days post-vaccination) with formal recommendation on whether to continue to recruit.

2. **Phase 2** - Enrolment continues (up to 1000 contacts)

These participants will also be included in Phase 3 analyses

During the outbreak

Objectives	Outcomes	Statistical analysis (general principles outlined here, final analysis plan will be described in the SAP)
Phase 3: To assess the effect of a candidate vaccine in protecting against laboratory-confirmed filovirus ebolavirus disease.		
Primary objectives		
The primary analysis will Be **efficacy** of laboratory-confirmed FVD (from samples taken either while living, or within 48 hours of death).	New cases of FVD in the ring members. Ascertained through independent active surveillance visits by the surveillance contact tracing teams and case detection reports through the national FVD surveillance system.	The primary analysis (per-protocol) will be of laboratory-confirmed FVD 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 filovirus ebolavirus[8]). 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. Fisher's exact test for vaccine efficacy.

During the outbreak

Objectives	Outcomes	Statistical analysis (general principles outlined here, final analysis plan will be described in the SAP)
Phase 3: **To assess the effect of a candidate vaccine in protecting against laboratory-confirmed filovirus ebolavirus disease.**		
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 FVD and **death** from confirmed FVD are included as secondary outcomes. Other secondary objectives include monitoring cases of suspected FVD that were not confirmed and did not cause death, studying how the risk of developing FVD 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 the 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.

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During the outbreak

Objectives	Outcomes	Statistical analysis (general principles outlined here, final analysis plan will be described in the SAP)
Phase 3: **To assess the effect of a candidate vaccine in protecting against laboratory-confirmed filovirus ebolavirus disease.**		
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.	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.	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.

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Study visits during outbreaks, Phase 3

IMMEDIATE VACCINATION RINGS											
	Who?	**Before Day 0**	**Day 0**	**Day 0 or 1**	**Day 7 +/-2**	**Day 14 +/-2**	**Day 21 +/-2**	**Day 56 +/-2**	**Day 90 +/-2**	**Day 180 +/-2**	**Day 360 +/-2**
Confirm FVD index case	Lab	X									
Engage community	CE	X									
List contacts	RD		X								
Check contact eligibility	E+C		X								
Invite informed consent	E+C		X								
Randomize (immediate or delayed arm)	Call center		X								
Vaccinate	V			X							
Monitor any immediate adverse reactions	V			X							
Additional monitoring for any FVD cases in the listed contacts	FU				X	X	X				
Phase 1 and 2											
Monitor vaccine safety (AEs, SAEs, SUSARs)[Ø]	FU			X	X	X	X	X	X	X	X
Collect samples immunogenicity	FU			X	X	X	X	X	X	X	X
Phase 3											
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 FVD cases**									

Study visits during outbreaks, Phase 3

DELAYED VACCINATION RINGS

	Which team?	Before Day 0	Day 0		Day 21 +/-2	Day 28 +/-2	Day 35 +/-2	Day 42 +/-2	Day 56 +/-2
Confirm FVD index case	Lab	**X**							
Engage community	CE	**X**							
List names of contacts	RD		**X**						
Check contact eligibility	E+C		**X**						
Invite informed consent	E+C		**X**						
Randomize to immediate or delayed vaccination	Call center		**X**						
Vaccinate	V				X				
Monitor any immediate adverse reactions	V				X				
Additional monitoring for any FVD cases in the listed contacts	FU					X	X	X	
Phase 1 and 2									
Monitor vaccine safety (AEs, SAEs, SUSARs)ø	FU		**X** ø		X	X	X	X	X
Collect samples immunogenicity	FU		**X**		X	X	X	X	X
Phase 3									
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 FVD cases**							

A note on very approximate sample size (to be determined later)

- Ring vaccination follows the transmission
- Assume attack rate in rings is 1-2% with a lot of variation, ICC = 0.05
- Sample size per arm:
- maybe 100 rings per arm (3,000 people)??? Interim analyses (either one or two looks using Obrien-Fleming α spending criteria)

In 2015 in Guinea, for VSV ERVEBO vaccine, at interim analysis (half-way point):

For the primary analysis, there where 4,394 people in the two arms, a total of 90 rings

- **Vaccine efficacy** = 100%, 95%CI [75% - 100%], p = 0.0036
- **Overall Vaccine effectiveness** = 75%, p = 0.1791

Trial completion, SAP, and regulatory approvals

Decisions about completing the trial will be made by the blinded steering committee, based on an assessment of accumulated endpoints & epidemic trends.

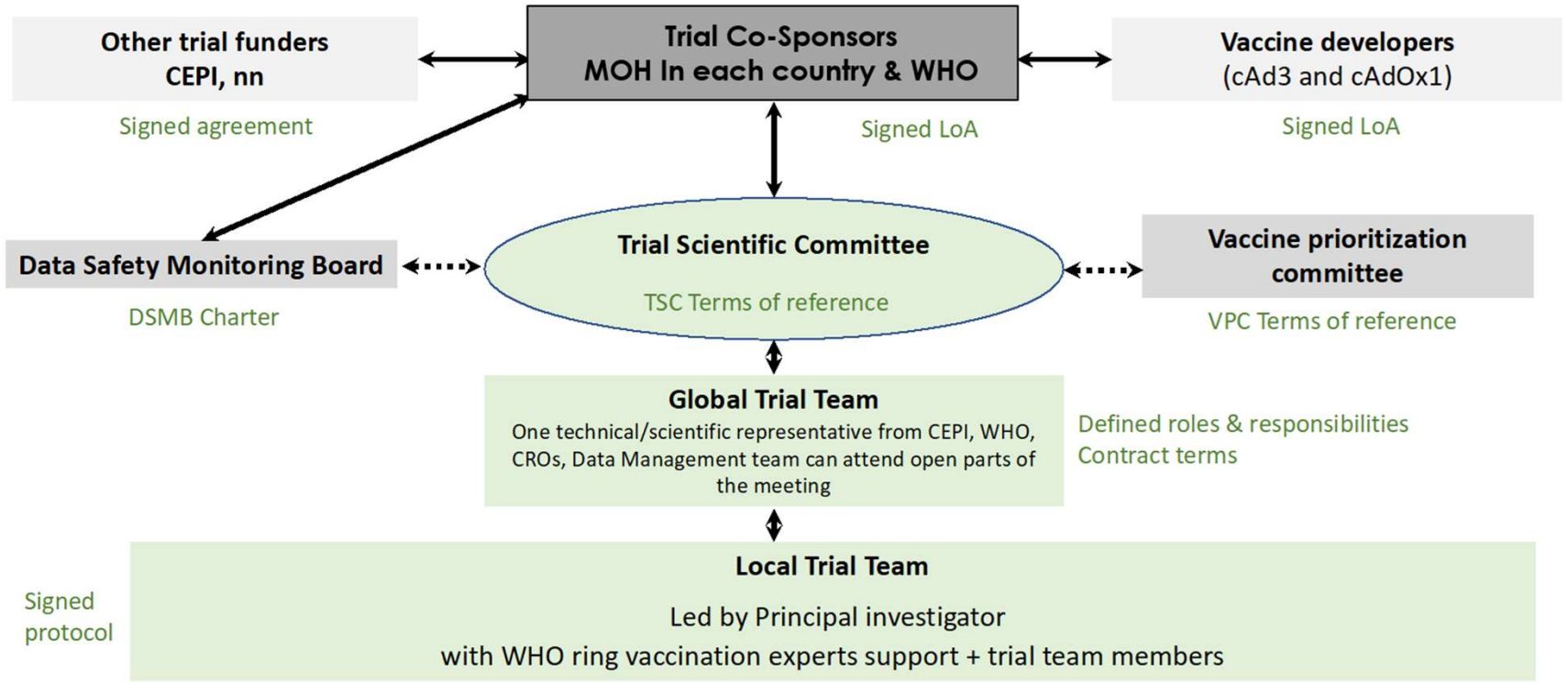
To allow rapid initiation of the study and adaptation to the outbreak, SAP details will be provided later (but before unblinding)

The intent is to continue efficacy endpoint accumulation across multiple outbreaks to increase the likelihood of obtaining valid data about vaccine efficacy

The trial will be conducted in compliance with ICH GCP guidelines

Regulatory approvals will be obtained from local NRA, based on requirements defined by NRA & MOH

Trial governance



In summary

This is a phase 1/2/3 study to evaluate the safety, tolerability, immunogenicity, and efficacy of **X** candidate vaccines against filovirus disease in healthy individuals at risk of filovirus disease.

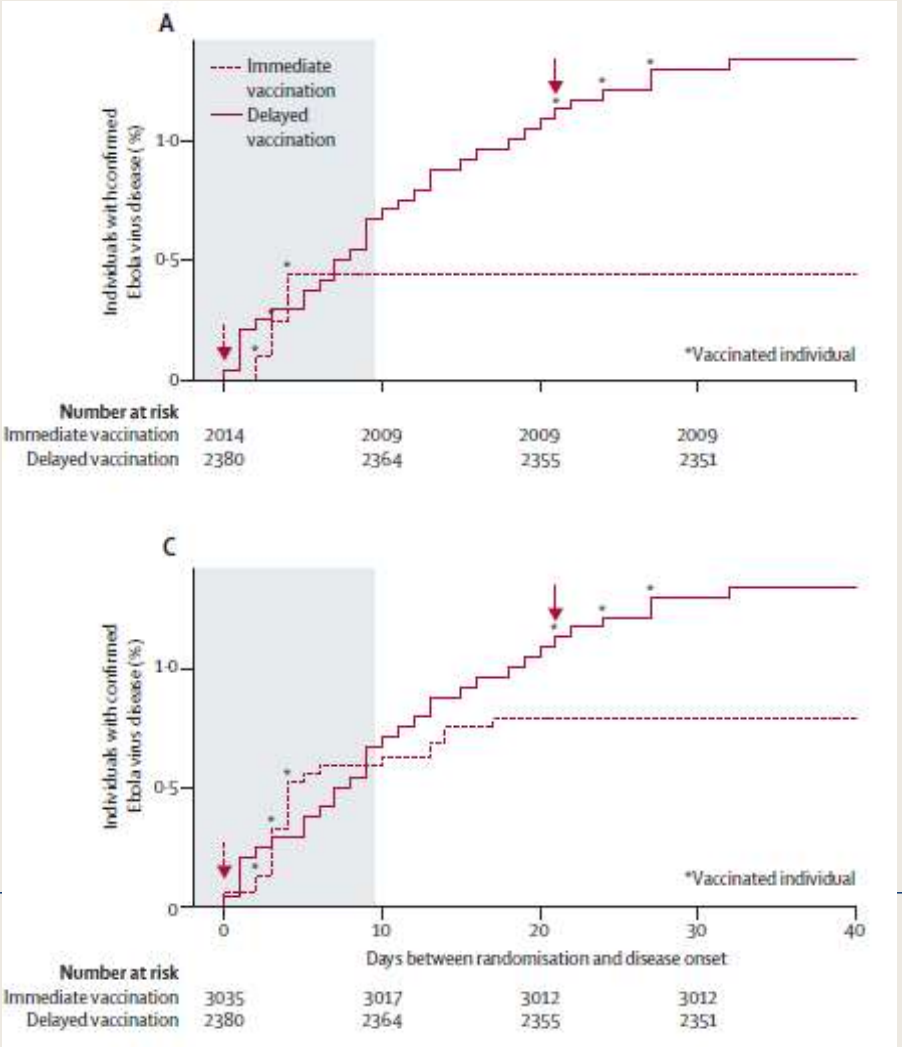
It has two main components:

1. **During the inter-epidemic period:** Safety and Immunogenicity (phases 1 and 2)
2. **During outbreaks:** Safety and efficacy (phase 3) and for certain candidate vaccines (phases 1 and 2)

The trial is designed to move seamlessly through the phases and even collect data through several phases simultaneously.

THANK YOU

Cumulative risk, estimates, statistics



Primary outcome:
Vaccine efficacy = 100%
95%CI [75% - 100%]
p = 0.0036

Secondary outcome:
Overall Vaccine effectiveness = 75%
95%CI [– 7% - 94%]
p = 0.1791

Source: Henao-Restrepo, Longini, Egger, Dean, *et al.* *Lancet* (2015)

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Statistical approach: Cluster-randomized trial

Vaccine efficacy: $\widehat{VE} = 1 - \widehat{\lambda_1}/\widehat{\lambda_0} = 1 - \hat{\theta}$

$\widehat{\lambda_1}$ = the estimated hazard of confirmed illness in the vaccinated

$\widehat{\lambda_0}$ = the estimated hazard confirmed illness in the unvaccinated

Model will be a mixed-effects, time-dependent, Cox regression model with a random effect (frailty) when there is clustering, or small sample equivalent using cumlative incidence (logist reg).

Hypothesis test: Reject vaccine with VE< 30%, find vaccine with VE ≥ 50%

Statistical approach

- Adaptive α spending boundaries (O'Brien-Fleming)
- Trial would be event driven until target cases and positive rings met
  - Core protocol where trial would continue across locations and outbreaks until target endpoints met

Statistical approach

- Assuming ring attack rate of 1-2% and ICC = 0.05, we would probably need about 100 rings (5,000 total participants) per arm, with an interim look at about 50 rings per arm
  - More exact calculations can be carried out once properties of vaccine and design are known

Filovirus context

Vaccines that are effective against Ebola Zaire are not expected to work against Sudan, Marburg or other filoviruses

Several plausible investigational vaccine candidates are based on widely evaluated platforms, but we don't know if any of them will work in humans

- Safety data exists with each platform
- Limited experience in humans with these specific vaccines
- Limited vaccine doses

The trajectory of outbreaks is uncertain