CLINICAL TRIAL PROTOCOL

CORE Protocol

Simple, large-scale, multi-country individually randomized placebo-controlled trial

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

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This protocol is a comprehensive framework document incorporating the structural design elements of the WHO CORE Protocol, adapted to the specific context of Rift Valley Fever vaccine trials. Implementation will require coordination across multiple stakeholder organizations, regulatory approvals, and further development of vaccine-specific and site-specific operational procedures.

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1. GENERAL INFORMATION

1.1 Sponsor and Co-Sponsors

Type of study	Phase 2 and 3 randomized study
Registration of the study	[To be completed]
Study product(s)	[Vaccine candidate(s) to be specified]
Vaccine developer(s)	[To be completed]
Co-Sponsor(s)	[To be completed]
Representative of the Co-Sponsor(s)	[To be completed]

1.2 Trial Investigator Information

Principal investigator(s) (PI)	[To be completed]
Sub investigators (as defined in ICH guidelines)	[To be completed]
Trial Manager/coordinator	[To be completed]
External monitors	Contract Research (Name)

1.3 Trial Investigator Information

Study site	Areas with elevated risk of RVF infection and/or confirmed cases of RVF disease
Eligible Population	[Specify occupational/geographic group]
Estimated Enrollment	[Number]

1.4 Study Synopsis

STUDY TITLE	**CORE protocol: Randomized Rift Valley Fever (RVF) vaccine trial in humans in multiple sites**
Primary STUDY OBJECTIVE(S)	To estimate the efficacy of an RVF vaccine in humans
STUDY DESIGN	Humans individually randomized to a single vaccine chosen for evaluation or control (in a 1:1 ratio) stratified by risk (including study sites)
POPULATION	Humans at elevated risk of RVF infection Livestock handlers, abattoir workers, herders, and others with frequent animal contact are recognized as the most affected population and are a high-priority sampling group. The Senegal epidemic is notably affecting young people (ages 15–30) and males, making them a key consideration for the trial's target population. Stratification by risk level. Not only to the high-risk workers.
INTERVENTION	One or more experimental vaccines
COMPARATOR	Placebo (or active comparator) Active comparator will increase community acceptance.
RANDOMIZATION	**Individual randomization** to vaccine or control (placebo or active control) Allocation ratio 1:1 Stratified by risk group (which may include location)
PRIMARY OUTCOME	Vaccine efficacy in humans for preventing laboratory-confirmed RVF disease (using a combination of RT-PCR testing and IgM testing for case confirmation)
SECONDARY OUTCOMES	**Vaccine efficacy in preventing severe disease -** Severe disease can be defined as permanent vision loss, requiring hospitalization, progression to organ failure/complications, or death. For hospitalized patients, the CFR can be high in some places so would need to see what proportion of cases are being hospitalized. Can also measure viral clearance kinetics in a subgroup (this could help provide more information to plan for therapeutic trial). Infection Rate: Detection of serological evidence of RVFV infection regardless of clinical symptoms, requiring DIVA (Differentiating Infected from Vaccinated Animals) testing

	Vaccine safety - evaluate the safety and tolerability of the RVF vaccine candidate in healthy adult volunteers, including assessment of solicited local and systemic adverse events for 7 days post-vaccination, unsolicited adverse events for 28 days, and serious adverse events throughout the study duration.
	Immunogenicity data - Immunological Endpoints o Neutralizing Antibody Responses: Geometric mean antibody titers (GMT) measured at multiple timepoints (Days 0, 7, 14, 28, 84, 112, 365, and 18 months) o IgG Antibody Responses: Geometric mean antibody titers for IgG antibodies against RVFV glycoproteins (Gn/Gc) measured by ELISA o Cellular Immune Responses: IFN-γ responses to RVFV Gn and Gc glycoproteins measured by ELISpot assay (Spot Forming Units per 10^6 PBMCs) Multi-functional T cell responses measured by flow cytometry
	Duration of Immunity: Assessment of antibody persistence and durability of immune responses, particularly in prime-boost vaccination regimens
EXPLORATORY OUTCOMES	**Immunological Correlates of Risk**: Identification of immune markers that correlate with protection or increased susceptibility to RVFV infection
	Surrogate Markers of Protection: Development of immunological surrogates that can predict vaccine efficacy without requiring clinical endpoints.
	Minimal Protective Titer: Determination of the minimum neutralizing antibody titer required for protection (studies suggest titers ≥1:5-1:20 may be protective) **Baseline Seropositivity Impact**: Assessment of how prior RVFV exposure affects vaccine safety and efficacy
	Pregnancy Safety: Safety evaluation in pregnant women, particularly important given spontaneous abortion risks associated with both natural RVFV infection and some veterinary vaccines
	One Health Approach: In outbreak settings, prospective observational evaluation of how animal vaccination influences human disease

FOLLOW-UP	To be determined; probably one year. Study may continue for longer if sufficient number of endpoints are not obtained.
STATISTICAL ANALYSIS	Planned statistical tests: Survival models will be used to estimate vaccine efficacy and effectiveness. Primary analysis: Simple Cox model and Kaplan-Meier curves. Safety data: Simple comparisons using t-tests or small sample equivalents. Study power and Interim analysis: The trial will continue (potentially across outbreaks) until sufficient data are obtained to perform efficacy analysis. After 20 cases, a 20% lower bound on efficacy would be met with a point estimate of 70%, and a vaccine with true efficacy of 85% would have ~80% power to meet a 20% lower bound. Interim analysis: Any interim analysis will use group sequential analysis with O'Brien-Fleming stopping rules.
ETHICAL CONSIDERATIONS	**Informed consent process.** There will be informed consent before participants are vaccinated with vaccine or placebo **Ethics committee approval.** There will be full approval from the various ethics committees involved
SAFETY MONITORING (e.g., Data Safety Monitoring Board).	Trial oversight will be provided by a single Steering Committee (SC) and a single data safety and monitoring board (DSMB). Adaptive aspects of the study, to the extent not predefined in the protocol, will be governed by the SC, which will not have access to unblinded study data. The role of the DSMB will be to apply pre- (and SC-) defined benefit and lack of benefit criteria to the vaccines, and to address potential safety issues as well as data integrity issues. Once one or more vaccines meet specified success criteria, new efficacy/lack of benefit criteria will be introduced.

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with the International Conference on Harmonisation Good Clinical Practice (ICH GCP) Guideline E6(R3)

- The Declaration of Helsinki and its amendments
- Applicable national and international regulatory requirements
- UNESCO Universal Declaration on Bioethics and Human Rights
- WHO Guidelines on Good Participatory Practices

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

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

No participant enrolment will commence until written approval is obtained from all required ethics committees and regulatory authorities.

Any amendment to the protocol will require review and approval by the relevant Ethics Committee(s) and National Drug Authority before the changes are implemented in the study.

Signature Principal Investigator

ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
CEPI	Coalition for Epidemic Preparedness Innovations
CI	Confidence Interval
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
eCRF	Electronic case record form
ELISA	Enzyme Linked Immunosorbent Assay
ELISPOT	Enzyme Linked Immunospot Assay
FRNT80	Focus Reduction Neutralization Test (80% endpoint)
GCP	Good Clinical Practice
GMT	Geometric Mean Titer
HR	Hazard ratio
HCW	Healthcare worker
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IgG	Immunoglobulin type G
IgM	Immunoglobulin type M
MOH	Ministry of Health
PBMC	Peripheral blood mononuclear cell
RVF	Rift Valley Fever
RVFV	Rift Valley Fever virus
RT-PCR	Real-time polymerase chain reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Scientific Committee
WHO	World Health Organization

2. BACKGROUND INFORMATION

2.1 Epidemiology of RVF

Rift Valley Fever (RVF) is a zoonotic viral disease caused by Rift Valley Fever virus (RVFV), a negative-sense, single-stranded RNA virus in the genus Phlebovirus within the family *Phenuiviridae*. The virus is transmitted to humans through contact with infected animals (livestock, wildlife) and their products, as well as through mosquito vectors during epizootics. Human outbreaks are characterized by sudden, explosive increases in cases during periods of unusually high rainfall and breeding of Aedes mosquito vectors.

Recent outbreaks have demonstrated the public health significance of RVF. During outbreak periods, attack rates are highest among individuals with occupational exposure to infected animals, including livestock handlers, abattoir workers, herders, and veterinarians. Age-specific attack rates have shown that young people (ages 15-30 years) are particularly affected, with male predominance in occupational exposure groups. Case fatality rates in confirmed infections have ranged from 0.5% to 2% in most outbreaks but can reach higher levels in hospitalized cases with severe disease.

2.1.1 Global Distribution

- Primarily endemic in sub-Saharan Africa and Arabian Peninsula
- Recent outbreaks demonstrate expanded geographic range
- Intermittent outbreaks associated with heavy rainfall and mosquito breeding

2.1.2 Human Disease Burden

- Attack rates highest among occupational contacts with infected animals
- Case fatality rates typically 0.5-2% in general population
- Higher mortality (10-15%) reported in hospitalized cases
- Significant morbidity including prolonged convalescence, haemorrhagic manifestations, and neurological complications

2.1.3 High-Risk Populations

- Livestock handlers, abattoir workers, herders: occupational exposure increases risk
- Healthcare and front-line workers in affected areas: secondary transmission risk
- Young males aged 15-30 years: disproportionately affected during outbreaks (based on Senegal 2014-2025 outbreak data)

2.1.4 Epidemiology of RVF in Each Country

[Country-specific epidemiological information to be provided in country annexes]

2.2 Clinical Presentation

Typical Illness (~80-90% of symptomatic infections):
- Sudden onset of fever (>38°C) with severe headache
- Myalgia and arthralgia lasting 3-7 days
- Chills, malaise, and fatigue
- Nausea and vomiting
- Symptoms typically resolve without complications within 1-2 weeks

Severe Disease (1-10% of infected individuals):*
- Haemorrhagic fever manifestations
- Hepatitis with jaundice
- Renal dysfunction
- Shock and multi-organ failure

Neurological Complications (0.5-1% of cases):
- Meningoencephalitis with altered mental status
- Retinitis and visual loss
- Seizures

Pregnancy-Associated Complications:
- Spontaneous abortion/miscarriage in first and second trimester
- Foetal death in utero
- No clear evidence of teratogenic effects with surviving pregnancies

2.3 Need for a Study of the Safety, Immunogenicity, and Efficacy of Vaccination

There is an urgent need to test the safety, immunogenicity, and efficacy of candidate vaccines that have been developed against RVF. Limited data exist on whether experimental vaccines will provide benefit to people at risk of or recently exposed to RVF. Since there is no established correlate of protection in humans (i.e., laboratory studies alone cannot reliably predict efficacy in individuals at risk of RVF infection), efficacy trials are urgently needed in the context of current RVF transmission patterns.

This protocol is designed to generate robust evidence on vaccine safety, immunogenicity, and efficacy through a coordinated international trial platform that can be rapidly activated in response to outbreak detection and

can combine data across multiple outbreaks to achieve adequate sample sizes for reliable conclusions.

3. Investigational Products

3.1 Vaccine Candidates

Vaccine Candidate 1:

- Working Name/Scientific Name: [TO BE COMPLETED]
- Vaccine Type: [Live attenuated/Inactivated/Viral vector/mRNA/Subunit/Other]
- Manufacturer: [TO BE COMPLETED]
- Formulation: [TO BE COMPLETED]
- Dosing: [Route, dose volume, administration procedure]
- Proposed Schedule: [Prime/Boost timing]
- Known Safety Profile: [Summary of nonclinical and clinical data]
- Storage conditions

Vaccine Candidates 2, 3 (if applicable):

[TO BE COMPLETED - same format as above]

3.2 Comparator

Placebo or Active Comparator:

- Description: [TO BE COMPLETED]
- Justification: Placebo or active comparator used; active comparator may increase community acceptance

4. TRIAL OBJECTIVES AND PURPOSE

This is a phase 2/3 study to evaluate the safety, tolerability, immunogenicity, and efficacy of candidate vaccines against RVF disease in healthy individuals at risk of RVF disease (e.g. occupational contacts such as livestock handlers, abattoir workers, herders, and healthcare workers, as well as people in clusters of recently confirmed cases).

This study has two main components:

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

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

4.1 Objectives During Inter-Epidemic and Outbreak Periods (Phase 2)

4.1.1 Primary Objectives

Objective 1: To determine the reactogenicity and safety of candidate RVF vaccine(s) among healthy volunteers.
Primary Safety Endpoints (Phase 2):

- Outcome: We will assess safety by describing the proportion of vaccine recipients who experience adverse events (clinical and laboratory) by severity and causality assessment.
  - Proportion experiencing solicited local adverse events within 7 days, graded by severity
  - Proportion experiencing solicited systemic adverse events within 7 days, graded by severity
  - Serious adverse events throughout study duration
- Statistical analysis: Adverse events will be summarized with counts, percentages, and exact 95% confidence intervals.

Objective 2: To determine the immunogenicity of the candidate RVF vaccine(s)

- Outcome: We will assess immunogenicity by measuring vaccine-specific antibody titers, neutralization activity, and cell-mediated immune responses at pre-defined follow-up visits.
  Primary Immunogenicity Endpoints (Phase 2):
  - Geometric mean neutralizing antibody titers (FRNT80) at Days 0, 7, 14, 28, 84, 112, 365, and 18 months
  - Proportion achieving seroconversion

- Geometric mean IgG antibody titers against RVFV glycoproteins (Gn/Gc)
- Cellular immune responses (IFN-Œ≥ by ELISpot, multifunctional T cell responses by flow cytometry

- Statistical analysis: Rates and magnitude of vaccine-induced responses will be calculated.

4.1.2 Secondary Objectives

Objective 3: To determine the durability of RVF-specific induced immune responses following vaccination

- Outcome: We will assess immunogenicity by measuring vaccine-specific antibody titers, neutralization activity, and cell-mediated immune responses at pre-defined follow-up visits.

Objective 4: To identify factors influencing vaccine-induced immune responses among trial participants

- Analysis: This will be defined in the Statistical Analysis Plan (SAP).

Objective 5: To determine the immune cross-reactivity induced by RVF vaccine candidates

- Outcome: We will assess immunogenicity by measuring antibody titers and cross-neutralization activity against other RVF lineages if relevant.

4.1.3 Exploratory Objectives

Objective 6: To determine the effect of RVF vaccines on host gene expression, T and B cell-specific responses, immune profiling, host metabolome, and innate immune responses

- Outcome: Additional immune response assays will be performed, including T and B cell responses with cell-based immunological assays, transcriptomic profiles, and other assays.

4.2 OBJECTIVES DURING OUTBREAKS (Phase 2/3)

4.2.1 Primary Objective

Objective 1: To estimate the efficacy of candidate RVF vaccine(s) in preventing laboratory-confirmed RVF disease during outbreak periods. The primary analysis will be of laboratory-confirmed RVF disease. The end point after the first dose must be measured, even if a booster is used for longevity of response.

- Outcome: New cases of RVF disease are ascertained through independent active surveillance visits and case detection reports through the national RVF disease surveillance system.
- Statistical analysis: The primary analysis (per-protocol) will be of laboratory-confirmed RVF disease cases with symptom onset X to Z days after randomization. The omission of Days X to Y allows time for the vaccination to take effect and reduces the chance of including cases who were infected prior to vaccination (given a typical XXX day incubation period for RVF). Vaccine efficacy will be calculated as:
  $VE = [1 - (IR_{vaccinated}/IR_{unvaccinated})] \times 100\%$,
  where IR represents the incidence rate in each group.
  Fisher's exact test will be used for significance testing, and negative binomial methods will be used for confidence intervals.

4.2.2 Secondary Objectives

Objective 2: To quantify the protective effect of candidate RVF vaccine(s) specifically against severe and life-threatening manifestations of RVF disease during outbreak periods. This objective recognizes that while preventing any RVF infection is ideal, even partial protection against the most serious clinical outcomes (haemorrhagic complications, organ failure, fatal cases) would provide substantial clinical benefit to vaccinated individuals.

- Outcome: This secondary efficacy endpoint will assess whether the vaccine offers differential protection for severe disease compared to mild-to-moderate illness. Severe RVF disease, defined as laboratory-confirmed RVF disease meeting any of the following criteria:
  - Permanent reduction or loss of vision in one or both eyes
  - Hospitalization required for clinical management
  - Development of organ failure or serious complications (haemorrhagic manifestations, hepatic failure, renal failure, respiratory failure, or circulatory shock)
  - Death attributable to RVF disease
  - IgG seroconversion
- Statistical analysis: Separate calculation of vaccine efficacy specifically for severe disease versus non-severe disease. Efficacy against severe disease will be estimated using competing risk analysis methods to appropriately account for cases that develop non-severe disease. For hospitalized patients, the CFR can be high in some places so would need to see what

proportion of cases are being hospitalized. Can also measure viral clearance kinetics in a subgroup.

Objective 3: To continue comprehensive assessment of vaccine safety throughout the outbreak period when trial conditions intensify, disease transmission is active, and epidemiological circumstances differ substantially from inter-epidemic periods (Phase 2). This objective ensures that safety monitoring does not diminish when clinicians focus on disease case management, and that any novel safety concerns emerging during high-transmission periods are rapidly identified. Phase 3 safety assessment also allows evaluation of vaccine safety in the context of concurrent RVF infection in the community—important for understanding whether vaccination influences disease susceptibility in previously exposed individuals and whether pre-existing immunity affects vaccine tolerance.

Solicited Adverse Events (within X days post-vaccination):
- Local adverse events: pain, redness or discoloration, swelling, induration at injection site (graded by size and severity, to be specified)
- Systemic adverse events: fever, chills, fatigue, headache, myalgia, arthralgia, nausea, vomiting (graded by severity impact on daily functioning)

Unsolicited Adverse Events (within XX days post-vaccination):
- Any health problems not specifically listed as solicited adverse events reported by participants

Serious Adverse Events
- Deaths from any cause
- Hospitalization for any reason
- Permanent disability or serious complications
- Any event requiring medical intervention to prevent serious outcome

Objective 4: To evaluate whether vaccine efficacy varies significantly across pre-defined population subgroups and geographic locations, thereby identifying which populations experience maximum vaccine benefit and which may require alternative or supplementary intervention strategies.

4.2.3 Exploratory Optional Objectives

Objective 5: To conduct detailed post-hoc analysis of baseline immune markers collected after vaccination (either pre-outbreak or during the outbreak period) in relationship to which vaccinated and control participants subsequently developed RVF disease during outbreak periods. This exploratory objective aims to identify specific immune characteristics that predict protection from infection ("correlates of protection") and alternatively, characteristics that predict disease susceptibility ("correlates of risk").

- Outputs (examples):
  - Identification of specific immune markers or signature combinations most strongly associated with protection
  - Quantification of protective threshold values (e.g., "neutralizing antibody titer >1:xxx associated with X% protection")
  - Assessment of predictive value for use in future vaccine development and validation

- Statistical Approach:
  - Correlation analysis between baseline immune markers and subsequent disease development
  - Receiver operating characteristic (ROC) curve analysis to identify immune marker thresholds predictive of protection
  - Multivariable logistic regression models incorporating multiple immune markers to construct predictive immune signatures
  - Machine learning approaches (if sample size permits) to identify complex immune patterns associated with protection
  - Sensitivity and specificity assessment for candidate surrogates

Objective6: Development of immunological surrogates that can predict vaccine efficacy without requiring clinical endpoints

- Outcome:
- Identification of one or more surrogate immune marker(s) or signatures suitable for use as primary endpoints in future Phase 2 vaccine trials
- Recommendations for surrogate endpoint thresholds predictive of clinical efficacy
- Discussion of surrogate limitations and contexts where clinical trials would still be warranted

- Surrogacy Criteria Assessment:
- Statistical surrogacy: Does the immune marker correlate with clinical outcome?
- Mechanistic plausibility: Is there a logical biological mechanism linking the immune marker to protection?
- Predictive validity: Can the marker be measured reliably and prospectively predict protection in new populations?

Objective 7:

Baseline Seropositivity Impact: Assessment of how prior RVFV exposure affects vaccine safety and efficacy

Objective 8: To prospectively evaluate vaccine safety, tolerability, and outcomes in pregnant women who either become pregnant after vaccination or are discovered to be pregnant during the trial, as pregnancy represents a special population warranting enhanced safety assessment. RVF infection

during pregnancy is associated with high rates of spontaneous abortion, making pregnancy both a contraindication for RVF infection and a population that might benefit from vaccination; however, safety of vaccines in pregnancy must be rigorously established. This exploratory objective documents pregnancy outcomes in vaccinated vs. placebo-vaccinated pregnant participants, providing preliminary safety data to inform future vaccine pregnancy recommendations.

- Comparative Analysis:
- Pregnancy outcome rates in vaccine-vaccinated pregnant women vs. placebo-vaccinated pregnant women
- Assessment of whether vaccination timing (before conception, during pregnancy) influences outcomes differently
- Investigation of any adverse pregnancy outcomes suggesting potential vaccination effects
- Evaluation of safety for potential future vaccine recommendations in pregnancy

Objective 9: In outbreak settings, evaluation of combined human and animal vaccination strategies on human disease prevention.

- Ecological analysis correlating animal vaccination coverage at geographic level with human disease outcomes, especially in the control group
- Stratified analysis of human vaccine efficacy in high vs. low animal vaccination coverage areas
- Assessment of whether animal vaccination coverage modifies human vaccine efficacy
- Investigation of potential synergistic effects (combined strategy superior to human alone)

Objective 10: To identify and characterize asymptomatic or subclinical RVFV infections occurring in trial participants (both vaccinated and control groups) using DIVA (Differentiating Infected from Vaccinated Individuals) testing platforms, thereby revealing the full spectrum of infection outcomes beyond clinically apparent RVF disease. This exploratory objective recognizes that not all RVFV infections result in symptomatic illness is some individuals develop asymptomatic viremia or seroconvert to RVF antibodies without experiencing documented clinical symptoms.

DIVA Logic:

- Test for presence of anti-NSP antibodies (particularly anti-N or anti-NSs protein antibodies)
- If NSP antibodies detected = Natural infection (RVFV virus replicated in individual)
- If NSP antibodies absent = Vaccination only (no viral replication)
- This principle enables clear serological differentiation without requiring virus isolation or other high-biosafety testing.

- Statistical analysis: True Vaccine Efficacy:

VE (all infections) = [1 − ($Rate_{vaccine}$ / $Rate_{placebo}$)] × 100%
Compare to symptomatic-only efficacy to assess whether vaccine protects against asymptomatic infections
All participants classified into one of four categories based on DIVA testing pattern:

Classification	**Anti-N ELISA**	**Anti-NSs ELISA**	**Interpretation**	**Estimated**
Vaccinated Only	Positive	Negative	Vaccination-induced	~60-70% vaccinated
Natural	Positive	Positive	Evidence of	~5-15% (varies
Seronegative	Negative	Negative	No prior infection; no vaccination response	~15-25% vaccinated group
Equivocal/Other	Mixed or weak patterns	Mixed or weak patterns	Requires repeat or additional testing	~1-3%

5. ASSESSMENT OF EFFICACY

(With complete case definitions and adjudication procedures)

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

5.1 Definition of Suspected RVF Disease

Any person with clinical features suggestive of RVF AND had contact with sick or dead animals (sheep, goats, cattle, camels), or their products, in the 15 days prior to onset of symptoms. Clinical features suggestive of RVF include:

- Sudden onset of fever (>38°C) with headache, myalgia and/or arthralgia, and no other identified cause (e.g., malaria)
- Spontaneous miscarriage without other identified aetiologias

Clarification of asymptomatic cases found by diagnostics also need to be considered, as well as determining how co-infection (i.e. malaria) can be identified and considered in clinical cases.

5.2 Additional WHO surveillance definition for early disease

Acute febrile illness (axillary temperature >37.5 °C or oral temperature of >38.0°C) of more than 48 hours duration that does not respond to antibiotic or antimalarial therapy, and is associated with:

- Direct contact with sick or dead animals or their products
- Recent travel (during last week) to, or living in an area where, after heavy rains, livestock die or abort, and where RVF virus activity is suspected/confirmed
- Abrupt onset of any one or more of the following: exhaustion, backache, muscle pains, headache (often severe), discomfort when exposed to light, and nausea/vomiting

5.3 Definition of Probable RVF Disease

WHO outbreak case definition: Any suspected case (as defined above).

Alternative probable case definition from surveillance guidelines:
A suspected case with history of close contact with an RVF affected ruminant (cow, goat and sheep) during the previous 6 days. Close contact includes:

- Slaughtering and butchering (traditional or commercial)
- Disposal of carcasses/foetuses
- Assistance with birthing or other animal husbandry activities resulting in exposure to animal blood and body fluids
- Veterinary procedures
- Consumption of meat and raw (unpasteurized/uncooked) milk

5.4 Definition of Confirmed RVF Disease

Any suspected or probable case with a laboratory positive result, including:

- Detection of virus by RT-PCR
- Positive IgM
- IgG seroconversion (a rise in IgG antibody titers between two consecutive samples taken 2-weeks apart
- Virus isolation

Alternative laboratory confirmation methods:

- ELISA showing the presence of anti-RVFV IgM
- RT-PCR detection of RVF RNA

5.5 Additional Clinical Considerations

Late stages of disease or complications (2-3 weeks after onset):
Patients who have experienced, in the preceding month, a flu-like illness with clinical criteria, who additionally develop:

- CNS manifestations which resemble meningoencephalitis
- Unexplained visual loss
- Unexplained death following sudden onset of acute flu-like illness with haemorrhage, meningoencephalitis, or visual loss during the preceding month

5.6 Discarded Case

Any suspected or probable case with a negative laboratory result (showing no specific antibodies, RNA or specific detectable antigens).[1]

6.STUDY POPULATION

6.1 Target Population

Humans at elevated risk of Rift Valley Fever infection.

6.1.1 Geographic Target

RVF endemic regions in sub-Saharan Africa and Arabian Peninsula, areas of previous RVF outbreak activity

6.1.2 Demographic Target

Healthy adults aged 15-30 years (may be extended based on outbreak epidemiology)

6.1.3 Occupational/Risk Target

- Livestock handlers, herders, and pastoralists
- Abattoir and meat processing workers
- Veterinary and para-veterinary personnel
- Healthcare workers and first-line responders in affected areas
- Individuals residing in clusters of confirmed RVF cases during outbreaks

6.2 Population Justification

RVF outbreaks disproportionately affect individuals with occupational exposure to infected animals. Recent epidemiological data indicate that the disease notably affects young people (ages 15 to 30) and predominantly affects males, making this demographic a key consideration for the trial's target population. The Senegal epidemic demonstrated that livestock handlers, abattoir workers, and herders are recognized as the most affected population and constitute a high-priority sampling group.

6.3 Inclusion Criteria

- Age 15-30 years (to include both female and male participants, and may be extended based on epidemiological data)
- Occupational category: livestock handlers, abattoir workers, herders, veterinarians, HCWs, FLWs, or others with frequent documented animal contact
- Residence or occupation in RVF-endemic regions or areas with active transmission/recent outbreak
- Ability to provide informed consent (or parental/guardian consent for participants <18 years with participant assent)
- Willingness to participate and comply with study procedures
- For women, willingness to undergo a pregnancy test immediately before vaccination
-

6.4 Exclusion Criteria

- Known allergy to vaccine components
- Acute febrile illness at time of enrolment

- Concurrent participation in another vaccine trial
- Previously vaccinated in the month prior to this trial
- Planned immunisation that will take place during the trial
- Immunosuppression or immunodeficiency disorders
- Pregnancy (at baseline; pregnancy during follow-up will be monitored)
- Receipt of other vaccines within 2 weeks prior to study vaccination
- Any condition deemed by the investigator to compromise participant safety or study integrity.

7. STUDY VISITS

[Detailed visit schedule table to follow]
Table. Detailed visits schedule

Visit number	Description	Timing (days)

7.1 Trial-Wide Duration

7.1.1 Phase 2 Enrolment Period: [TO BE DETERMINED]

7.1.2 Phase 3 Enrolment Period: [TO BE DETERMINED] - Initiated within X days of RVF case confirmation and should include a blood draw at this point to determine Phase III baseline.

7.1.3 Overall Trial Duration: Expected X-Y years from first participant enrolment

8. STUDY PROCEDURES

8.1 During the Inter-Epidemic Period

In brief:

1. The study team will seek all (define population group) in relevant areas/clusters and create a list of people at risk including those briefly absent or who moved out or have died at the time the list is made.
2. A separate team will explain the study to all listed and eligible individuals and invite them to provide their written informed consent.
3. The eligible participants who consent will be included in the study until the set sample size is achieved.
4. A vaccination team will offer vaccination to eligible and consenting participants according to their randomization arm.
5. We will draw up to X, z ml tubes of blood for safety and immunogenicity studies. Samples will be tested by RT-PCR to ensure they are negative for RVFV before further processing. Samples will be processed to obtain serum, plasma, and peripheral blood mononuclear cells (PBMCs) and will be cryopreserved in liquid nitrogen or at -80°C. Humoral immunity parameters will be evaluated using virus neutralization assays (FRNT80), ELISA assays to measure RVF-specific IgM and IgG, and ELISPOT assays to assess RVF-specific T cell responses.
6. 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 comparator).
7. Participants will be followed up on Days 0/1 through Day 8 and on Days 14, 21, 28, 56 for all solicited adverse events. Thereafter, follow-up will be on Days 90, 180, and 365.
8. To facilitate the study, no paperwork is required, and enrolment and randomization is done via a cloud-based GCP-compliant computer system.
9. An independent quality assurance team will continuously monitor the study records. An independent Data and Safety Monitoring Board will keep the accumulating results under continuous review.

8.2 During Outbreaks

In brief:

1. Within X days of notification of an RVF 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. Community engagement begins as soon as possible during the inter-epidemic period or within 1-2 days of notification of an RVF disease confirmed case. Local social mobilization experts will visit the community, seeking consent from

community leaders and representatives for the trial team to approach the broader community. They will explain the trial's objectives and implications of participation using adapted tools for Good Participatory Practices. Ideally, forecasting to identify 'at risk' populations will have taken place in order to expedite this.

2. Confirm RVF Disease Cases (if the study is being conducted during an outbreak)

The trial team will seek all people at risk in the area/cluster, including those briefly absent at the time of initial contact listing. The eligibility and informed consent team will verify that all listed individuals potentially meet inclusion/exclusion criteria using a standardized assessment form.

3. The list will include as at risk potentially eligible population those who, within the previous X days:
    - Lived in the same household as the case
    - XXXX
    - XXXXX

Following community consent, the social mobilization team and eligibility team will visit the community to identify people at risk, potentially eligible.

4. The eligible people who consent will be included in the trial. A separate team will explain the study to all listed and eligible individuals using printed information sheets, providing adequate time for questions. For participants <18 years, parental/guardian consent will be obtained with participant assent. Documentation of consent will be obtained with the participant's signature (or thumbprint if literacy is limited) and witness signature

5. Once an eligible person consented, he/she will be allocated randomly either to be offered vaccination or comparator. After the person eligible has consented or declined, the consenting contacts will be allocated randomly to either vaccine or comparator vaccination. (Randomization will be conducted via a cloud-based GCP-compliant computer system.

6. At the appointed time, a vaccination team will arrive and offer vaccination to all volunteers who consented. Qualified and protocol-trained nurses will vaccinate participants at the assigned timepoint according to their randomization arm. Vaccination procedures will follow SOPs including proper injection technique, vaccine handling, and cold chain management.

7. Monitor Immediate Adverse Reactions. Participants will be observed for at least 30 minutes post-vaccination for immediate adverse reactions. Any immediate reactions will be documented on the adverse event reporting form and managed appropriately.

8. Monitor RVF Disease Cases (if study conducted during outbreaks). Confirmed cases arising in trial participants are included as primary outcomes in the main analysis of vaccine efficacy. Identification and confirmation of RVF disease cases will be done independently of the study team throughout the outbreak and beyond the follow-up period as part of national surveillance. Typically, this will involve daily follow-up for the first 28 days. All newly diagnosed and laboratory-confirmed RVF disease cases will be included as a new index case. New cases of RVF disease are ascertained through independent RVF surveillance teams. RVF disease cases are confirmed by designated surveillance laboratories using WHO-recommended test procedures. The trial team will record RVF disease cases as follows:
    - Reviewing daily surveillance line listing of cases and laboratory results
    - Engaging with MOH/WHO disease surveillance teams to receive information on suspected, probable, and confirmed RVF disease
    - Attending daily response coordination meetings where newly laboratory-confirmed cases are reported
    - Obtaining daily laboratory results of any suspected, probable, or confirmed cases among enrolled contacts
    - During each follow-up study visit, asking those in the trial about any relevant symptoms that might indicate RVF disease onset; suspect cases will be immediately referred to the closest RVF treatment unit

9. Sampling for Immunogenicity Studies (Phase 2)

In adults, up to three, 9ml in EDTA tubes and two 7.5ml vacutainer tubes of blood will be drawn at pre-defined timepoints. For children between 6 and 12 years old, this maximum will be reduced in accordance with guidelines (Becann-McBride, K, Phlebotomy Handbook – Blood collection Essentials, 7th Edition)

Samples will be:
Additional exploratory assays as defined in the SAP
Circulating antigen-specific immunoglobulins (various assays eg ELISA, MSD, Luminex or other)
Antibody neutralisation assays

ELISPOT cellular immunity assays to specific antigens and/or peptides

Exploratory assay. These assays may include analysis of serum biomarkers such as pro-inflammatory cytokines and chemokines, metabolites, B and T cell epitope mapping, viral genomics, immune dominance analysis, evaluation of B and T cell clonal expansion in response to vaccination and immune phenotype of RVF-specific T cells.

Assays designed to calibrate readouts into International Units or other standard unit in the absence of an international standard.

Haematology and clinical chemistry patient variables will be monitored in approximately 100 participants per vaccine candidate and comparator arm. 10.Monitor Solicited and Unsolicited AEs, SAEs, and Unsolicited AEs, SAEs, and SUSARs. Participants will be followed up on Days 0/1 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. During Phase 3, each safety follow-up study visit at the participant's home (Days 0, 7, 14, and 21 post-vaccination, will include assessment of any relevant symptoms or signs and any changes in the participant's health since the last visit.

11.An independent quality assurance team will continuously monitor the study records. An independent Data and Safety Monitoring Board will keep the accumulating results under continuous review.

Adverse Event Monitoring Schedule- DRAFT

Solicited adverse events	Monitored for 7 days post-vaccination	Days 0, 3, 7
Unsolicited adverse events	Monitored for 28 days post-vaccination	Days X,Y,Z
Serious Adverse Events	Monitored throughout the study duration	

Adverse Event Assessment

- Participants will be provided with diary cards to record solicited local and systemic adverse events for 7 days post-vaccination
- Clinical assessment of injection site reactions will be performed by study staff at defined timepoints
- Telephone follow-up or in-person visits will assess unsolicited AEs at Days 7, 14, and 28
- SAEs will be reported within 24 hours of identification to the Data Safety Monitoring Board and relevant regulatory authorities
- All AEs will be assessed for causality using standardized algorithms
- Pregnancy outcomes will be monitored and documented

8.3 Treatment and Interventions

(to be included, with the consideration that there may be more than one vaccine to be taken into account with the possibility of inclusion in platform analysis of trials)

9. STATISTICS

9.1 Sample Size

The study is designed to continue (potentially across outbreaks) until sufficient clinical endpoint data are accumulated to perform an adequate efficacy analysis.

9.1.1 Sample Size Justification

The number of participants enrolled will be determined based on:

- Estimated attack rates in the target population during the study period
- Geographic and temporal variation in RVF transmission
- Expected enrolment rates across multiple sites
- Adaptive adjustment based on interim clinical endpoint accumulation

The target enrolment will be prospectively defined based on attack rate assumptions; however, enrolment may be extended if clinical endpoint accumulation is slower than anticipated.

9.2 Bias Minimization Measures

9.2.1 Randomization and Allocation Concealment

- Computer-generated random sequence
- Allocation ratio 1:1
- Stratified randomization by site and risk category
- Secure, GCP-compliant cloud-based randomization system
- Electronic allocation concealment through secure web portal
- Treatment assignment revealed only at point of vaccination

9.2.2 Blinding Procedures

- Participants blinded: identical vaccine/placebo appearance
- Study staff blinded: do not know treatment assignment
- Data managers blinded until database lock
- Biostatistician blinded until analysis plan finalized
- Vaccine labels display only participant ID and randomization number
- All case report forms show only randomization number

Unblinding Circumstances:

- Medical emergency requiring treatment knowledge
- Authorized by unblinding committee with documentation

9.2.3 Outcome Assessment Blinding

- RVF disease case confirmation by independent diagnostic team
- Laboratory confirmation at WHO facilities with specimen identifiers only
- Case adjudication committee blinded to treatment assignment

9.3 Statistical Analysis

9.3.1 Interim Efficacy Target

With 20 confirmed RVF disease cases distributed between vaccine and control arms (approximately 10 per arm), a 20% lower bound on the 95% confidence interval of vaccine efficacy would be met with a point estimate of 70% or higher.

9.3.2 Final Power

A vaccine with true efficacy of 85% would have approximately 80% statistical power to meet a 20% lower bound on efficacy at the time of final analysis.

9.3.3 Primary Analysis

Method: Survival analysis using Cox proportional hazards regression models with a clear time horizon
Endpoints: Time from vaccination to laboratory-confirmed RVF disease
Primary Analysis:

- Kaplan-Meier curves will be constructed for each treatment arm
- Vaccine efficacy (VE) will be estimated as: VE = [1 - HR(Vaccine/Control)] X 100%, where HR is the hazard ratio from the Cox model
- 95% confidence intervals will be calculated for the point estimate of VE

Model Specification:

- Cox model will include treatment group as the primary predictor
- Stratification variables (site, risk group) will be included in the model
- Interactions between treatment and key covariates will be explored in secondary analyses

9.3.4 Secondary Analyses

Efficacy against severe RVF disease

- Cox proportional hazards models will estimate efficacy against severe disease
- Competing risk analysis will account for non-severe disease cases

Stratified efficacy analysis:
Efficacy will be estimated separately by:

- Risk category (livestock handlers, abattoir workers, herders, HCWs/FLWs, other)
- Age group (15-22 years, 23-30 years, >30 years if applicable)
- Gender
- Baseline RVF serostatus
- Geographic site

Subgroup interactions:

- Tests for homogeneity of treatment effects across subgroups
- If significant interactions identified, subgroup-specific efficacy estimates will be reported

Safety Analysis

Adverse event analysis:

- Incidence rates of solicited local and systemic AEs compared between vaccine and control arms using chi-square tests or Fisher's exact tests
- For continuous safety measures, two-sample t-tests or Mann-Whitney U tests
- SAEs summarized descriptively with causality assessment

Safety analysis populations:

- Safety analyses performed on the as-treated population
- Safety database locked independently prior to efficacy analysis

Immunogenicity Analysis

Antibody titers:

- Geometric mean titers (GMT) calculated for each timepoint and treatment arm
- GMT ratios (vaccine/control) and 95% CIs presented
- Seroconversion rates and time to peak response estimated

Cellular immunity:

- Mean spot forming units (SFU) per 10^6 PBMCs calculated for IFN-Œ≥ and other cytokine measures
- Comparisons between vaccine and control arms using appropriate statistical tests

Immunogenicity subset:

- A randomly selected subset of enrolled participants (target 20-30% of cohort) will undergo detailed immunological assessment
- This subset will be representative of the overall population by site, risk group, and gender.

9.4 Interim Analysis Plan

- Any interim efficacy analyses will be conducted using group sequential analysis methodology with O'Brien-Fleming stopping rules
- Interim analyses may be triggered by:
- Accumulation of 20, 40 or 60 confirmed clinical endpoints
- Safety concerns identified by the Data Safety Monitoring Board
- Protocol amendments or operational reasons

9.5 Stopping rules

- Pre-specified efficacy stopping boundaries
- Pre-specified futility stopping boundaries
- Safety stopping rules defined by the Data Safety Monitoring Board

10. ETHICAL AND REGULATORY ASPECTS

10.1 Ethics Approval

Full ethics committee approval will be obtained from all participating institutions prior to participant enrolment. Approval will also be obtained from regulatory authorities in each country as required. These approvals will include permissions for blood draw, storage and analysis as stated above. Continuing review: The study will be submitted for annual continuing review. All protocol amendments will be submitted for ethics review prior to implementation.

10.2 Approval by National Regulatory Authorities

In each country where the protocol will be implemented, approval will be obtained from relevant human research ethics and regulatory agencies prior to study initiation.

10.3 Privacy and Confidentiality of Participants

All participant data will be managed with strict confidentiality protections

- Participants will be assigned unique study identification numbers
- Personal identifying information will be stored separately from study data with appropriate access controls
- Data transmitted between sites or stored on computers will be encrypted
- Study reports will present only de-identified data

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

Participants retain the right to withdraw from the study at any time without providing a reason or experiencing any penalty or loss of benefits. Participants who become pregnant may continue in the study but will be monitored for pregnancy-specific outcomes.

11. DISCONTINUATION AND WITHDRAWAL

11.1 Discontinuation from Investigational Product

Criteria for Discontinuing Vaccine

11.1.1 Serious Adverse Events

- SAE possibly, probably, or definitely related to vaccine
- Unacceptable severity or risk
- Participant preference after experiencing serious event

11.1.2 Participant Withdrawal of Consent

- Explicit withdrawal of informed consent
- Participant request to not receive vaccine dose

11.1.3 Protocol Deviations

- Previously unrecognized exclusion criteria post-enrolment
- Development of contraindication to vaccine

11.1.4 Other Reasons

- Pregnancy diagnosed after enrolment
- Development of immunosuppressive condition
- Loss of ability to comply with procedures

11.1.5 Data Collection After Discontinuation

- Safety follow-up continues per protocol
- Immunogenicity blood draws continue unless refused
- Efficacy assessment continues for RVF disease outcomes

11.2 Withdrawal from Trial

Criteria for Trial Withdrawal

11.2.1 Participant Withdrawal of Consent

- Explicit request to withdraw from all study activities
- Documented in writing when possible

11.2.2 Death

- Death from any cause
- Circumstance investigated and documented

11.2.3 Loss to Follow-up

- After 3 consecutive unsuccessful contact attempts
- Despite intensive tracking procedures
- Documented in trial record

11.2.4 Relocation

- Participant relocates permanently outside trial area
- Unable to continue study participation

11.3 Participant Replacement

- Participants withdrawn due to eligibility violations replaced
- Participants withdrawn due to vaccine-related SAE may be replaced after DSMB review.

12. COMMUNITY ENGAGEMENT

Community engagement will be conducted using adapted tools for Good Participatory Practices during clinical trials, tailored to the local context in each country.

xxxxxxxx

13. ADMINISTRATIVE ASPECTS

13.1 Registration of the Study

The study will be registered with [Clinical Trials Registry] prior to participant enrolment.

13.2 Amendments to the Protocol

13.2.1 Substantial Amendments

Any substantial changes to study objectives, design, population, intervention, or outcomes will be documented as formal protocol amendments. Amendments will be reviewed and approved by the Trial Scientific Committee and ethics committees prior to implementation. Amendments will require participant re-consent if they materially affect participant safety or rights.

13.2.2 Non-Substantial Administrative Changes

Minor administrative or procedural changes may be documented as study notes and do not require formal amendments or ethics approval.

13.3 Financing

XXXXX

13.4 Insurance

Insurance arrangements and compensation for study-related injuries will be established in accordance with local regulations and ethics requirements.

14. STUDY ORGANIZATION

14.1 Trial Governance Framework

[See Annex 3: Trial governance structure with roles and responsibilities of all parties]

14.2 Trial Co-Sponsors

XXXXXX and Ministry of Health in each country
The roles and responsibilities of Co-sponsors are defined by generic Letters of Agreement (LoA) between Co-sponsors.

14.3 Vaccine Developers

Vaccine developers' roles and responsibilities are defined by LoA with WHO.
Vaccine developers warrant that:

- The candidate vaccine has been manufactured in accordance with current Good Manufacturing Practices (cGMP)
- They are lawfully entitled to enter the trial and provide the vaccine free of charge
- The vaccine does not infringe valid patent rights of third parties

Developers commit to:

- Transparency in reporting trial results
- Providing sufficient data for vaccine inclusion
- Making the vaccine available in sufficient amounts at affordable prices in developing countries if safe and efficacious

Developers may withdraw their vaccine from further randomization but not from follow-up and will not be expected to make financial contributions.

14.2 Trial Scientific Committee (TSC)

An independent scientific committee established to review scientific elements important to the trial's design, conduct, and analysis. The TSC will:

- Review trial progress
- Provide formal recommendations on trial direction
- Review initiation of enrollment at new sites
- Advise on protocol modifications

14.3 Data Safety Monitoring Board (DSMB)

An independent committee established to review unblinded efficacy and safety data. The DSMB will:

- Review accumulated efficacy and safety data on a regular schedule
- Assess vaccine safety and efficacy based on pre-defined criteria

- Formulate recommendations to the TSC regarding trial continuation, modification, or cessation
- Monitor data integrity and completeness
- Detect and report data quality issues
- Have authority to recommend trial cessation based on:
- Overwhelming evidence of vaccine efficacy
- Evidence of inadequate efficacy
- Unacceptable safety concerns
- Data integrity compromises
- Feasibility or ethical concerns

15. DATA MANAGEMENT AND RETENTION OF RECORDS

15.1 Data Oversight

The Sponsor(s) will coordinate the randomization and data management in a centralized database run by a Contract Research Organization not accessible to Sponsor(s) staff or the trial team. All trial sites will contribute data to this centralized system.

15.2 Trial Master File and Investigator Site File

Trial Master Files will be maintained by the Trial Sponsor containing:
- Protocol and amendments
- Ethics and regulatory approvals
- Curriculum vitae of key personnel
- Delegation logs
- Safety reports
- DSMB and TSC correspondence

Investigator Site Files will be maintained at each study site containing:
- Study documentation
- Informed consent forms
- Case report forms
- Safety reports
- Communication with ethics committees and regulators

Record-Keeping

All records will be stored in accordance with ICH Good Clinical Practice guidelines and local regulatory requirements. Records will be retained for a minimum of 6 years after study completion or as required by local regulations.

15.3 Data Management

Data will be collected using electronic case report forms (eCRFs) via a cloud-based GCP-compliant computer system. Data quality checks will be built into the system to ensure accuracy and completeness. All data queries will be resolved prior to database lock.

15.4 Source Records and Study Record Retention

Source documentation will be maintained at study sites and will be available for monitoring and audit. Personal identifying information will be stored separately from study data with appropriate security measures.

16. QUALITY ASSURANCE AND CONTROL

16.1 Training to Ensure Trial Quality

All study personnel will receive training on:

- Protocol procedures and requirements
- Good Clinical Practice principles
- Case definitions for RVF disease
- Informed consent procedures
- Data collection procedures
- Safety monitoring and reporting
- Infection prevention and control measures
- Use of electronic data collection systems

Training will be documented and records maintained in the Trial Master File and Investigator Site Files.

16.2 Monitoring Protocol Compliance

An independent quality assurance team will continuously monitor:

- Protocol adherence at study sites
- Completeness of case report forms
- Accuracy of data entry
- Informed consent documentation
- Safety reporting procedures
- Laboratory procedures and quality

Monitoring visits will be conducted at regular intervals with findings documented and communicated to study sites.

16.3 Protocol Deviations and Violations

Any deviations from or violations of the protocol will be:

- Documented using standardized protocol deviation forms
- Reported to the Trial Scientific Committee
- Evaluated for impact on participant safety and data integrity
- Managed according to predefined procedures

16.4 Inspections

The study will be subject to inspection by:

- Ethics committees and regulatory authorities
- Independent auditors
- External monitors appointed by WHO or Co-sponsors
- Quality assurance teams

All inspection findings will be documented and appropriate corrective actions implemented.

17. DATA SHARING AND PUBLICATIONS

17.1 Publication Policy

17.1.1 Ownership
Study data and results are owned by the Co-sponsors and participating institutions. Publications will be prepared to present trial results to the scientific and medical community.

17.1.2 Authorship
Publications will be prepared by designated writing committees comprising investigators and biostatisticians. Authorship will follow International Committee of Medical Journal Editors (ICMJE) guidelines. Significant contributors will be acknowledged.

17.1.3 Publication Timing
Primary results will be submitted for publication following completion of the primary analysis and Data Safety Monitoring Board review. Secondary and exploratory analyses may be published in subsequent manuscripts.

17.1.4 Review Process
All manuscripts will be reviewed by the Trial Scientific Committee prior to submission for publication to ensure accuracy, appropriate interpretation, and alignment with trial governance.

17.1.5 Transparency
Trial documents and findings will be made freely available on the WHO R+D Blueprint website to ensure transparency and accessibility to the scientific community and public health authorities.

17.2 Data Sharing

17.2.1 De-identification
Individual participant data will be de-identified for secondary analyses or sharing with external researchers according to HIPAA Safe Harbor or equivalent standards.

17.2.2 Data Sharing Agreements
Data sharing will be governed by written data-sharing agreements specifying:
- Permitted uses of the data
- Publication policies
- Confidentiality obligations
- Intellectual property considerations

REFERENCES

1. World Health Organization. Rift Valley Fever. [WHO Fact Sheet]

2. WHO R&D Blueprint. Prioritized Diseases. [Available at: https://www.who.int/teams/blueprint/]

3. International Conference on Harmonisation. ICH Guideline E6 on Good Clinical Practice.

4. [Additional references to be completed based on current literature]

ANNEXES

Annex 1: Standard Operating Procedures and Electronic Case Record Forms

Trial Activity	SOP Number	eCRFs or Other Data Collection Tools

Annex 2: History of Protocol Amendments

Date Version Brief Description of Amendments Rationale

Annex 3: Trial Governance Framework

[Governance structure diagram to include:]

- Trial Co-Sponsors (in each country)
- Vaccine Developers
- Trial Scientific Committee
- Data Safety Monitoring Board
- Site-specific governance committees
- Roles and responsibilities matrix