

# Platform trial design for preventive vaccines against Marburg virus

Ira Longini

University of Florida

Consultant to WHO R&D Blueprint



World Health  
Organization



**R&D**Blueprint

Powering research  
to prevent epidemics

# Inspiration for trial design (lessons learned)

- WHO Ebola ring VSV vaccine trial in Guinea, 2015
  - Successful and rapid determination of the VE during and epidemic
  - rVSV-ZEBOV vaccine is now licensed and is used against Ebola Zaire (Ervebo)
- WHO Solidarity Trial Vaccines (STV) for COVID-19
  - An international, multi center, multi vaccine, adaptive, shared placebo, event driven, individually randomized controlled clinical trial that aims to evaluate the efficacy and safety of promising new COVID-19 vaccines

# Basic trial design

- International, randomized clinical trial platform designed to rapidly evaluate the efficacy and safety of promising new candidate vaccines selected by an independent vaccine prioritization advisory group composed of leading scientists and experts
- Rapidly identify vaccines with worth-while efficacy using an adaptive design
- Vaccines and placebos (or delayed comparator) will be individually and/or cluster randomized depending on trial operation conditions
  - Populations at risk
  - Transmission clusters

# A platform trial design for preventive vaccines against Marburg virus and other emerging infectious disease threats

Clinical Trials

2022, Vol. 19(6) 647–654

© The Author(s) 2022



Article reuse guidelines:

[sagepub.com/journals-permissions](https://sagepub.com/journals-permissions)

DOI: 10.1177/17407745221110880

[journals.sagepub.com/home/ctj](https://journals.sagepub.com/home/ctj)



Ira M Longini<sup>1</sup> , Yang Yang<sup>1</sup>, Thomas R Fleming<sup>2</sup> ,  
César Muñoz-Fontela<sup>3,4</sup>, Rui Wang<sup>5,6</sup>, Susan S Ellenberg<sup>7</sup> ,  
George Qian<sup>8</sup>, M Elizabeth Halloran<sup>2,9</sup>, Martha Nason<sup>10</sup>,  
Victor De Gruttola<sup>6</sup> , Sabue Mulangu<sup>11</sup>, Yunda Huang<sup>8</sup>,  
Christl A Donnelly<sup>12,13</sup> and Ana-Maria Henao Restrepo<sup>14</sup>

## Abstract

**Background:** The threat of a possible Marburg virus disease outbreak in Central and Western Africa is growing. While no Marburg virus vaccines are currently available for use, several candidates are in the pipeline. Building on knowledge and experiences in the designs of vaccine efficacy trials against other pathogens, including SARS-CoV-2, we develop designs of randomized Phase 3 vaccine efficacy trials for Marburg virus vaccines.

# Marburg Vaccine Trial Core Protocol Working Group

## Met about 10 times, July – September, 2022

Nancy Sullivan (NIH) Chair

Abdourahamane Diallo (WHO/Africa)

Alhassane Toure (WHO/Africa)

Sabue Mulangu (U Kinshasa, DRC)

Martha Nason (NIH)

Amy Finan (Sabin)

Ian Crozier (NIH)

John Beigel (NIH)

Galina Yamshchikov (NIH)

Winnie Janssens

Ira Longini (U Florida)

Yunda Huang (Fred Hutch)

Ana Maria Heano Restrepo (WHO)

William Fischer (U North Carolina)

Draft pro



# Solidarity Trial Vaccines

An international randomised trial of candidate vaccines against Marburg

10 August 2022

Version 0.2  
CONFIDENTIAL

© World Health Organization 2021. All rights reserved.

This is a draft. The content of this document is not final, and the text may be subject to revisions before publication. The document may not be reviewed, abstracted, quoted, reproduced, transmitted, distributed, translated or adapted, in part or in whole, in any form or by any means without the permission of the World Health Organization. The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted; the names of proprietary products are distinguished by initial capital letters.



**R&DBlueprint**  
Powering research  
to prevent epidemics

## Solidarity Trial Vaccines

An international randomised trial of candidate vaccines against Marburg

### Table of Contents

Table of Contents	2
Acknowledgements	3
DECLARATION OF INVESTIGATOR	4
Summary	7
Goal and Objectives of the trial	1
INDIVIDUALLY AND CLUSTER RANDOMIZED DESIGNS	10
Features and Advantages	13
Primary Efficacy Endpoint and its Evaluation	13
Lack of benefit criteria for the primary efficacy endpoint	14
Hybrid design	14
Secondary and Supportive Endpoints and their Evaluation	15
Safety	16
Participating sites	17
Participating populations	17
Inclusion and exclusion criteria	18
Inclusion criteria	18
Exclusion criteria	18
Randomization	19
Blinding	20
Study vaccines and study vaccination schedules	21
Vaccine characteristics, stability, labelling, preparation, handling, storage and accountability	21
Follow-up	22
Schedule of visits	22
Vaccine discontinuation (which does not imply withdrawal from follow-up)	23
Decision by a volunteer or legal representative to withdraw from follow-up	24
Study sample size	24
Reporting of Results	27
Study governance	27
Co-Sponsors	27

Version 0.1 – 30 June 2022

2/31



**World Health Organization**



**R&DBlueprint**  
Powering research  
to prevent epidemics

# Primary Efficacy Endpoint

- To evaluate the effect of selected vaccines on the **rate of virologically confirmed Marburg virus disease**, regardless of severity.
- Vaccine safety

# **Secondary Endpoints (partial list)**

- **Protection against infection based on serology and PCR**
- **Immune correlates of risk and protection**
- **Protection against fatal disease**



# Marburg vaccines trial (blending across designs)

## 1.a: Individually randomized in high-risk populations

Individual randomization to vaccine or comparator in areas of high exposure to Marburg virus

The vaccine and comparator will be delivered according to a vaccination schedule

All vaccines selected for trial are eligible for testing at all sites

## 1.b.: Individually randomized within transmission clusters

Individual randomization to vaccine or comparator within clusters of infection transmission

Clusters are ring vaccination

Transmission units such as households, compounds, or other types of contact units

A single vaccine is tested in each ring or cluster, but multiple vaccines tested across rings or clusters

## 2: Cluster randomized

Clusters themselves are randomized to receive vaccine or comparator

Clusters are ring vaccination  
Transmission units such as households, compounds, or other types of contact structures

A single vaccine is tested in each ring or cluster, but multiple vaccines tested across rings or clusters

Long-term accumulation of data where transmission may occur

Rapid accumulation of data during outbreaks

# Statistical analysis for Marburg virus vaccine trial

- Primary endpoint: Laboratory confirmed Marburg virus disease
- Primary hypothesis test:

$$H_0: VE \leq 30\% \quad \text{vs} \quad H_1: VE > 30\%,$$

where VE is defined as  $VE = 1 - \lambda_1/\lambda_0$ .

- $\lambda_1$  is the hazard rate for MVD for vaccine recipients
  - $\lambda_0$  is the hazard rate for MVD for comparator recipients
- 
- One sided  $\alpha = 0.025$ , power = 0.90, 1% cumulative AR in comparator arm

# Rough sample size summary

- For individual randomization
  - **150** cases of MVD across these two arms (vaccine and comparator), maximum of about **20,000** participants per arm (or **200** clusters per arm).
  - Two interim analyses at **50 (67 clusters per arm)** and **100 (133 clusters per arm)** cases using O'Brien-Fleming boundaries for early termination.

# Way Forward

- Goal is to initiate trial rapidly (within days) once first vaccines are selected
- Select the feasible trial design options and extract from the overall protocol
  - Such designs could be sequentially implemented across time and outbreaks if necessary
- For an emergency outbreak situation, probably cluster randomization (option 2) comparing immediate to delayed vaccination of rings is the most implementable design

# Monitoring efficacy

- Each candidate vaccine will be monitored for early evidence of benefit or lack of benefit using prespecified monitoring guidelines and boundaries that may lead to halting further randomization of participants into a vaccine arm.
- Early monitoring for benefit is critical for obtaining and reporting data that could support rapid deployment of efficacious vaccines.
- Reject vaccines with  $VE \leq 30\%$  and find vaccines with  $VE > 50\%$

# Trial governance

- Trial oversight will be provided by a **single Steering Committee (SC)** and a **single data monitoring committee (DMC)**.
- 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 DMC 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.

# Thank you