World Health Organization

SOLIDARITY PARTNERS

Platform Adaptive Randomised Trial for NEw and Repurposed Filovirus treatmentS

CORE Trial Protocol

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R&DBlueprint
Powering research to prevent epidemics

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13 Abbreviations

AE	Adverse event
AESI	Adverse Event of Special Interest
eCRF	Electronic case record form
FVD	Filovirus Disease
GCP	Good clinical practice
ICH	International Conference on Harmonisation
IRR	Infusion Related Reaction
LLOQ	Lower limit of quantitation
MOH	Ministry of Health
SAE	Serious Adverse Event
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
SSAR	Suspected Serious Adverse Reaction
WHO	World Health Organization

14 Filovirus nomenclature and abbreviations used[1]

Disease	First subcategory	Second subcategory	Caused by
Filovirus disease	Ebola disease (ED)	Ebola virus disease (EVD)	Ebola Zaire virus (EBOV)
		Sudan virus disease (SVD)	Sudan virus (SUDV)
		Bundibugyo virus disease (BVD)	Bundibugyo virus (BDBV)
		Other specified Ebola disease	e.g. Tai Forest virus
		Ebola disease, virus unspecified	
	Marburg disease (MD)	Marburg virus disease	Marburg virus (MARV) or Ravn virus (RAVV)
		Other specified Marburg disease	
		Marburg disease, virus unspecified	

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1 TRIAL SYNOPSIS

Type of study	Phase III adaptive platform randomised clinical trial of therapeutics
Clinical trial registration number	(pending)
Co-Sponsor(s)	World Health Organization Ministries of Health as outlined in country specific appendices
Central Coordinating Office	University of Oxford, United Kingdom

Background: *Filoviridae* is a family of single-stranded RNA viruses, some of which cause severe diseases in humans. The most well-known filovirus diseases, Ebola disease and Marburg disease, have a high mortality rate. Outbreaks are devastating to affected communities and can have significant social and economic ramifications for affected countries. Despite this, advancement of evidence-based treatment has been slow because outbreaks are relatively rare, and their timing and exact location difficult to predict.

Aim: The primary aim is to identify the effect of a range of interventions on all-cause mortality at 28 days in patients admitted to a healthcare facility with filovirus disease.

Design: This trial signifies a commitment from the World Health Organization (WHO) and partners to prepare and pre-position a platform trial of treatments for any filovirus disease.

A platform trial is a clinical trial that can study multiple different interventions at the same time and add, assess, and remove new interventions as time goes on, without having to specify the new interventions at the start.* Compared to a more traditional clinical trial design (is this drug better than usual care?), a platform trial can be thought of as disease focussed (what is the best treatment for this disease?).
As well as being able to add new interventions as time goes on, platform trials also have the flexibility to update the control, or 'usual care' group as the study progresses. This is useful for when, for example, the platform trial shows a drug it's testing to be much more effective that 'usual care', then that drug can be used to benefit patients right away and become part of the new 'usual care' against which all new drugs are tested in the trial, creating a potential cycle of improvement in patient care.

Since some treatments might work across a variety of different filovirus diseases (e.g. host directed therapies such as immunomodulatory drugs or drug that stabilise the vascular endothelium) a trial that allows enrolment of patients with any type of filovirus disease would be beneficial – a 'pan-filovirus' protocol. A pan-filovirus protocol is also favoured since it allows a single protocol to be pre-approved and implemented for any filovirus outbreak.

* See: https://www.phctrials.ox.ac.uk/platform-trials-an-explainer

The rationale for a pan-filovirus adaptive platform trial is, therefore, that:

i. A research response that depends on the design, approval, and implementation of a new clinical trial for each outbreak is usually too slow to enrol within the timeframe of a single filovirus epidemic;
ii. Enrolment across different outbreaks to a unified protocol increases the likelihood of a trial that is sufficiently powered to conclusively demonstrate a benefit or lack of benefit on mortality ;
iii. New promising interventions may emerge over time, and their efficient evaluation would benefit from an adaptive platform trial approach;
iv. Certain interventions may be applicable to more than one filovirus strain and therefore may be evaluated in a pan-filovirus protocol.

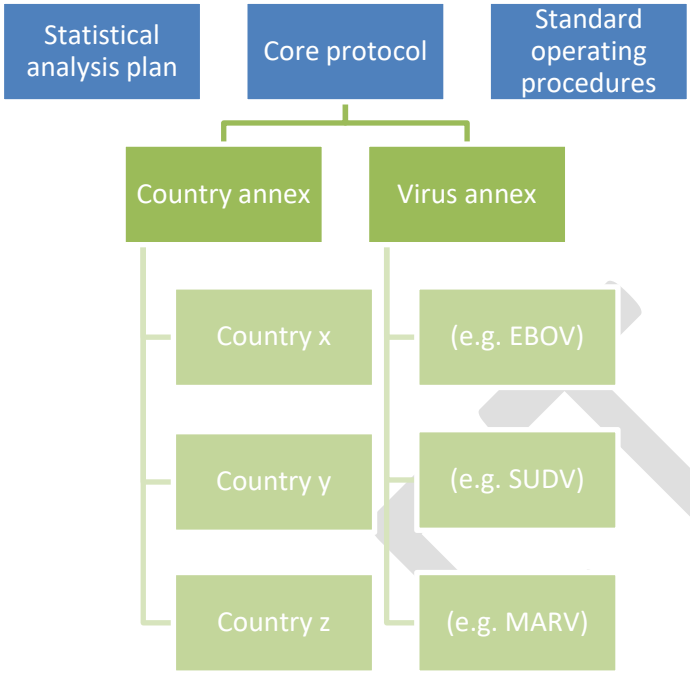
This protocol describes a multi-country, multi-outbreak randomised adaptive platform trial of potential treatments for filovirus disease (FVD). This includes Ebola disease, Marburg disease, and unspecified and emergent filovirus diseases[1]. The treatment comparisons included are determined by expert consultations convened by WHO[2]. If clear evidence of efficacy, futility, or a safety signal are not achieved for any of the comparisons during a given outbreak, the protocol permits the continuation of relevant arms of the trial in future filovirus outbreaks until a clear result is achieved[2].

Protocol structure (see figure 1 below): The trial design permits continued operations even when:

i. Promising new treatments are developed and are ready to be tested;
ii. Treatments no longer require evaluation in a trial because they have been shown to be effective or ineffective or unsafe;
iii. New countries wish to join the trial with their own regulatory requirements;
iv. Outbreaks of different filoviruses occur with different treatment options;
v. New filoviruses emerge.

This core protocol details the key requirements of the trial irrespective of the location or cause of an outbreak but is supplemented by appendices that describe more detailed information for an outbreak in a particular regulatory jurisdiction (Country appendices), or for a particular virus (Virus appendices). The country appendices name national investigators and partner institutions. They specifically detail adaptations to comply with local regulatory requirements. These are usually governance requirements, ethics considerations (such as proxy or minor consent processes) and changes to reporting timelines. The virus appendices provide details of the treatments to be evaluated for a particular filovirus, and any data collection additions.
The protocol sits alongside a detailed statistical analysis plan that will provide a pre-specified plan for assessing treatment safety and efficacy. Standard operating procedures provide site-level detail on how to interpret and implement the protocol.

Figure 1: Protocol structure



Eligibility and randomisation: This is a randomised controlled trial for patients receiving inpatient care for laboratory-confirmed acute filovirus disease. In a factorial design, eligible patients are randomly allocated (1:1) in one or more comparisons.

- Monoclonal antibodies:
  - Targeted monoclonal antibody/cocktail* vs no additional treatment
- Virus-directed therapy:
  - Antiviral therapy* vs no additional treatment
- Host-directed therapy:
  - Host-directed therapy* vs. no additional treatment

**defined in Virus-specific annexes.*

If one of the treatments is not available at the site (or is contraindicated for a given patient) randomisation may be between fewer arms. In addition, all participants will receive usual standard of care according to WHO guidelines[3], and approved treatments when they exist.

Study outcomes: The primary outcome will be 28-day mortality and the secondary outcome will be time to viral clearance (filovirus RNA <LLOQ). Follow-up will be stopped at the earliest of death, discharge from inpatient care, or 28 days after randomisation. Sub-group analyses will be conducted for groups defined by the following baseline features: Filovirus strain (ED, MD, *MARV,RVV, EBOV, BDV, SUDV*), age, cycle-threshold (Ct) value using quantitative

RT-PCR, days since symptom onset, *Filovirus* vaccination status, randomisation to other trial treatments.

Simplicity of procedures: To facilitate collaboration, to support treatment units seeing a large number of patients, and to minimise risks to healthcare worker safety, trial-specific procedures are streamlined and data collection is focused. Informed consent is proportionate to any additional risks involved in participation in the trial by comparison with the risks of usual care alone. Key follow-up information is recorded at a single timepoint.

Data to be recorded: At randomisation, information will be collected on participant age, sex, major co-morbidities, pregnancy status (in women of child-bearing age), filovirus RT-PCR time of collection and result, symptom onset date, date of admission, disease severity, any contraindications to the study treatments, filovirus vaccination status, and the name of the facility enrolling the patient. Information collected on a single follow-up form will be death (with date and probable cause), hospitalisation status (with date of discharge, if appropriate), filovirus RT-PCR Ct values, treatments provided, and renal and liver function test results. In addition to study outcomes (e.g. mortality), Adverse Events will be recorded if they fall into one of the following groups:

a. Adverse Events of Special Interest (AESIs; e.g. infusion-related reactions).
b. Serious Adverse Events that are not considered to be due to the underlying *Filovirus* infection.
c. Serious (per standard regulatory definition) that are considered with reasonable probability to be related to one of the study medications (i.e. Suspected Serious Adverse Reactions, which includes Suspected Unexpected Serious Reactions [SUSARs]).

Pregnancy and foetal outcomes will also be recorded.

Numbers to be randomised: The larger the number randomised the more accurate and informative the results will be and, over time, the more potential treatments can be assessed. In general, each comparison should be sufficiently large to provide good power (e.g. 90% power at 2P=0.01) to detect a proportional reduction in mortality of at least one third. The sample size required will be dependent on the mortality seen in patients enrolled in the trial (which will be dependent on the specific disease, and which may be lower in trial participants than the wider population hospitalised with Ebola or Marburg Disease, and which may evolve over time as treatment and supportive management evolves). The Trial Steering Committee, blind to information about the effects of ongoing treatment comparisons, will monitor blinded event rates and adjust the required sample size for each comparison as data from the trial accrue.

The study is co-sponsored by WHO and the Ministry of Health in each participating country. It is overseen by a Trial Steering Committee convened by the World Health Organization and a Data Monitoring Committee.

Protocol Review: The trial will be carried out in accordance with the Principles of the International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the Principles for Good Randomised Trials developed by the Good Clinical Trials Collaborative.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the WHO Ethical Review Committee and, in each country where the protocol will be implemented, the relevant human research ethics and regulatory agencies. 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 WHO and country Ethics Review Committees before the changes are implemented to the study (unless they constitute an urgent safety measure). In addition, all changes to the consent forms will be approved by these committees.

2 BACKGROUND AND RATIONALE

2.1 Setting

Filoviridae have caused significant outbreaks in recent years, including Ebola Virus Disease in west Africa (2013-2016), Sudan Virus Disease in Uganda (2022) and Marburg Virus Disease in Equatorial Guinea and Tanzania (2023). These diseases have a high case fatality, with similarities in pathogenesis and somewhat overlapping clinical syndromes.

Ebola Disease is a complex multi-system illness that begins following an incubation period of 2-21 days. Illness usually begins with non-specific symptoms including fever, fatigue, and gastrointestinal distress. As the disease progresses, it is complicated by worsening gastrointestinal losses, shock, multi-organ failure, and sometimes haemorrhage. The pathogenesis of Ebola Disease is reviewed comprehensively elsewhere [4–6]. The virus disseminates broadly in body tissues and increasing viral load is a predictor of severe disease and death[7]. Severe disease is associated with coagulopathy[8], disruption of endothelial function[5] and a strong inflammatory response[9–12]. Estimates of the case-fatality rate are variable depending on the outbreak, but for *SUDV* infection range between 36-65%[13], and is usually between 50-70% for *EBOV* outbreaks.

Marburg Disease is less well characterised than Ebola Disease because there have been fewer cases and no large outbreaks in almost two decades. Following an incubation of 3-21 days[14], a non-specific febrile illness develops abruptly, followed by symptoms which may include conjunctival injection, rash, and abnormal bleeding. Gastrointestinal symptoms are described[15], but might be less prominent than for Ebola Disease. In comparison, bleeding manifestations might be more frequent[16]. Complications include renal and liver failure and pancreatitis[15,17,18]. Patients die following the onset of shock and multi-organ failure. Coagulopathy, endothelial leak, and an excessive inflammatory response occur and contribute to tissue damage[14,19]. As with other filoviruses, infection occurs following mucosal or broken-skin contact and the virus first infects macrophages and dendritic cells before infecting the organs[19]. There is significant variation in case fatality rates reported for Marburg (ranging from 23-88%), with the two largest outbreaks to date with mortality above 80%[20].

2.2 Treatment Options

The association between high levels of viraemia and Filovirus Disease severity suggests that therapies that target viral replication may benefit patients, and the association with pro-inflammatory mediators and death suggests a possible role for host-directed immunomodulatory treatment.

This protocol allows reliable assessment of the effects of multiple different treatments on major outcomes in Filovirus Disease.

The treatment domains to be assessed in the protocol are:

- Monoclonal antibody/ies [specific to each virus].
- Antiviral [all patients] .

- Host-directed therapy: [all patients].

Further details about these treatments and the reasons for including them are provided in virus specific annexes.

All patients will also receive standard of care consistent with WHO guidelines[3], and national guidelines where these exist. This includes (but is not limited to) rehydration, analgesia and other symptom relief, nutrition, and psychosocial care. Participants might have the option to receive an experimental or licensed vaccine, and this would not interfere with their potential enrolment in this trial.

Where approved treatments exist, patients can receive these without interference with their potential enrolment in this trial. For *EBOV* infections, the monoclonal antibody products REGN-EB3 and mAb114 are strongly recommended by WHO[21] and approved by the US-FDA[22,23], based on the results of a previous clinical trial[24], but there are no approved or recommended host-directed therapies. There are currently no approved anti-viral or host-directed treatments for *SUDV* or *MARV* or other *Filoviridae.*

2.2.1 Modifications to the number of treatment comparisons:

In this adaptive platform trial, the Trial Steering Committee (TSC) may elect to add new treatment comparisons as evidence emerges that other candidate therapeutics or supportive care strategies should be evaluated. In this situation, randomisation may be between more comparisons. Conversely, the Trial Steering Committee may decide to stop some comparisons if there is no longer important uncertainty about the effects of a treatment.

In some patient populations, not all trial comparisons will be appropriate (e.g. due to contraindications or other co-morbidities); in some treatment centres, not all treatments will be available (e.g. due to cold storage requirements or delays to drug production); and at some times, not all treatment comparisons will be active (e.g. due to lack of relevant approvals and contractual agreements). In any of these situations, randomisation will only be between available and suitable treatments.

2.3 Design Considerations

The trial is designed to minimise the burden on clinical staff. Eligibility criteria are therefore simple and trial processes (including paperwork) are minimised.

The protocol is deliberately flexible so that it is suitable for a wide range of settings, allowing:

- A broad range of patients to be enrolled in large numbers.
- Randomisation between only those treatment comparisons that are both available at the clinical service *and* not contraindicated for a given patient.
- Treatment comparisons to be added or removed according to the emerging evidence.
- Continuation of the trial across multiple outbreaks, if necessary (and where regulatory approval is in place) until a clear result is achieved.
- Additional sub-studies to be added (see section 9.7) if appropriate (but inclusion into these will not be a requirement for participation).

2.3.1 Evolving standard of care

Over time, effective treatments may become available and ineffective treatments and practices may be abandoned, typically as the result of reliable information from randomised human efficacy trials (including from this study). In this protocol, all patients will receive usual standard of care. Thus, randomisation will remain relevant to the current clinical situation and the incremental effects of study treatments (on top of what is usual) will be appropriately assessed.

3 DESIGN

3.1 Study aims

This is an open-label, adaptive, randomised platform clinical trial to evaluate the impact of potential treatments on mortality in patients with filovirus disease.

3.2 Eligibility

Patients are eligible for the study if all of the following are true:

(i) Admitted to a hospital or treatment unit for treatment of filovirus disease.
(ii) Positive filovirus RT-PCR (or neonate aged seven days or younger born to a woman with acute laboratory confirmed Filovirus Disease).
(iii) No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if enrolled in the trial (e.g. known allergy to a study drug).
(iv) Not known to have been enrolled in this protocol previously.

In addition, if the attending clinician believes that a patient should definitely not receive one of the active drug treatments (see virus specific annexes for contraindications) or that the patient should definitely be receiving one of the active treatments (e.g. corticosteroids for a licensed indication) or they have already received a treatment in that class during their course of illness, then they will not be eligible for randomisation in that comparison. Co-enrolment in other studies and trials is not an exclusion criterion (unless there is a risk to the validity of either trial, or if co-enrolment increases risk to participants).

3.2.1 Pregnancy and breastfeeding

There is a high maternal mortality in pregnant women with Ebola Disease[25], and foetal survival is rare. There are only three known cases of Marburg Disease in pregnant women. All women died, and the only neonate delivered died shortly after birth[26]. Therefore, pregnant women will be eligib le for enrolment in the trial. Expert obstetric and teratology advice will be provided to the Trial Steering Committee prior to the inclusion of a new treatment in the protocol.

WHO recommends breastfeeding should be stopped in a lactating woman with Ebola Disease[18]. There may be rare circumstances (e.g. a concordantly infected child younger than six months old without a safe feeding substitute[27]) where a woman with a *Filovirus* infection continues to breastfeed. These decisions will be made independent of the trial. In the circumstance that a woman continues breastfeeding she would remain eligible for enrolment with any dose modifications specified in virus specific annexes.

3.2.2 Children

Mortality is higher in children compared to adults with Ebola Disease, but the association between age and death is not certain for Marburg Disease. Children of all ages are eligible for enrolment. Modifications for children are described in virus specific annexes.

3.2.3 Vaccination

Patients will be eligible for enrolment irrespective of whether they have been vaccinated for a filovirus, including the use of experimental vaccines, and vaccines used as post-exposure prophylaxis. Vaccination status, including date and name of vaccine, will be recorded for all patients.

3.3 Randomisation

Randomisation will be between the following treatment domains in a factorial manner.

Table 1. Randomisation domains.

Domain	Filovirus x (e.g. SUDV)	Filovirus y ((e.g. EBOV)	Filovirus z (e.g. SUDV)
Randomisation 1 (monoclonal antibody/ies)*	Virus specific monoclonal antibody vs no additional treatment (1:1)	Virus specific monoclonal antibody vs no additional treatment* (1:1)	Virus specific monoclonal antibody vs no additional treatment (1:1)
Randomisation 2 (antiviral)	Antiviral vs no additional treatment (1:1)		
Randomisation 3 (host-directed)	Host directed therapy vs no additional treatment (1:1)		

* Where a licensed monoclonal product exists e.g. MAb114 or REGEN-EB3 for EBOV, patients should receive the licensed monoclonal product as part of usual care and would therefore not be randomised into the monoclonal domain. However, in some circumstances randomization in this domain may occur (e.g. to test a different dose vs. the licensed dose).

Randomisation will be done through use of an internet (or, where necessary, telephone) based randomisation service. In an effort to prevent the impact of chance imbalances in key baseline prognostic factors on the study results, randomisation will, wherever possible, be performed with minimisation by such factors. Minimisation factors will be age strata (children, younger adults, older adults), viral load, and outbreak. (Where this is not possible, simple randomisation will be performed.)

If one of the treatments is not available at the site or not suitable for the individual patient they will not be eligible for randomisation in that domain but remain eligible for randomisation in the other domains. For example, if the monoclonal antibody is not available at the site, then a patient may be randomised in the antiviral therapy (antiviral vs. no additional treatment) and host-directed therapy (host-directed therapy vs. no additional treatment) comparisons only.

3.4 Interventions

Details on the specific treatments included for each virus are described in virus specific annexes.

3.5 Study outcomes

3.5.1 Primary outcome

- All-cause mortality at 28 days following randomisation

3.5.2 Secondary outcome

- Time (days) to *Filovirus* RNA <LLOQ (lower limit of quantitation) within 28 days [Viral clearance, using results from study or routine clinical samples, is defined as the first negative *Filovirus* RT-PCR test without a subsequent positive test result or subsequent death. In the unlikely scenario that a patient is discharged home without two successive negative RT-PCR tests, the date of the first negative test or, if there is no negative test result, the date of medical discharge will be used.]

3.5.3 Other outcomes

- Viral load (measured by cycle threshold) on blood samples taken at Day 3, 5, 7 and 10.
- Progression of organ dysfunction, measured on blood samples taken at Day 3, 5, 7, 10.

3.5.4 Safety outcomes

In addition to study outcomes (e.g. mortality), Adverse Events will be recorded if they fall into one of the following groups:

a. Adverse Events of Special Interest (AESIs; e.g. infusion-related reactions).
b. Serious Adverse Events that are not considered to be due to the underlying *Filovirus* infection.
c. Serious (per standard regulatory definition) that are considered with reasonable probability to be related to one of the study medications (i.e. Suspected Serious Adverse Reactions, which includes Suspected Unexpected Serious Reactions [SUSARs]).

Pregnancy and foetal outcomes will also be recorded.

Study outcomes will be assessed based on data recorded up to the time of death, hospital discharge or 28 days after randomisation (whichever occurs first). Pregnant women will be followed up to completion of pregnancy.

4 STATISTICAL ANALYSIS

All analyses for reports, presentations and publications will be prepared by the Statistical Analysis Team. The purpose of this section is to describe the main statistical approaches to be used in the trial. Additional technical details (e.g. cut points for subgroup analyses) will be defined by the Trial Steering Committee and Statistical Analysis Team prior to any unblinding of effects of study treatments and made publicly available (including any subsequent revisions) .

4.1 Main analysis approach

For all each randomised comparison, the outcomes will be made between all participants randomised to the different treatment comparisons, irrespective of whether they received some, none, or all of their allocated treatment (i.e. these comparisons will be based on "intention-to-treat" analyses).
The primary analyses will involve pairwise comparisons between the active 'experimental' and 'reference' arms as follows:

- Effect of monoclonal antibody: monoclonal vs. no additional treatment.
- Effect of antiviral: antiviral vs. no additional treatment.
- Effect of host-directed therapy: host-directed therapy vs no additional treatment.

Logistic regression adjusted for baseline levels of key prognostic factors will be used to estimate the conditional odds of 28-day mortality for each treatment group relative to its control (ie, the 28-day conditional odds ratio) and its 95% confidence interval. A two-tailed P-value <0.05 will be considered as statistically significant. Logistic regression (based on vital status at Day 28, regardless of the time to death within this 28-day range) will be used in preference to Cox regression because the latter might give undue weight to the exact times of death of the very poor-prognosis patients (thereby giving inadequate weight to the death or survival of the better-prognosis patients). However, for illustrative purposes, Kaplan-Meier plots showing the pattern of survival over the first 28 days will also be created, both overall and within prognostic categories. For the primary objective of assessing the effects of each study treatment on 28-day mortality, discharge alive before day 28 will be assumed as survival to day 28 (unless there are additional data confirming otherwise).
For the secondary objective of assessing the effects of each treatment on time to filovirus RNA <LLOQ within 28 days, differences in median days to filovirus RNA <LLOQ will be tested using the Wilcoxon rank-sum test, imputing deaths prior to day 28 as the worst ranks, with earlier deaths having a worse rank than later deaths. The study will collect viremia data at baseline and approximately days 3, 5, 7, 10. Patients who are discharged from inpatient care but without an available *Filovirus* RT-PCR test result will be assumed to have *Filovirus* RNA <LLOQ on their day of discharge (unless in a particular case there is good evidence to the contrary).
For each treatment, the main comparisons will ignore any other treatments that the patient may have been randomised to in a factorial manner. However, subgroup analyses of each treatment effect will include analyses by such factorial treatments.

4.1.1 Management of control groups

Since not all treatments may be available or suitable for all patients, those in the 'no additional treatment' arm will only be included in a given comparison if, at the point of their randomisation, they *could* alternatively have been randomised to the active treatment of interest (i.e. the active treatment was available at the time and it was not indicated or contra-indicated). The same applies to any further treatment comparisons that may be added at a later stage; they will be compared only to those patients recruited concurrently.

4.1.2 Adjustment for baseline characteristics

The main logistic regression analyses described above will adjust for important prognostic markers recorded at baseline (eg, age, RT-PCR Ct value, virus type, and time since symptom onset). This provides a safeguard against the impact that any chance imbalances in their frequencies between randomised groups may have on the randomised comparisons. In addition, even if there were no such imbalances, adjustment for baseline characteristics somewhat increases statistical power by ensuring that, effectively, better-prognosis patients are compared only with each other and that worse-prognosis patients are compared only with each other. Exact details of the prognostic factors adjusted for in the logistic regression analyses will be provided in the SAP prior to any unblinded analyses being done.

4.1.3 Pre-specified subgroup analyses

Pre-specified subgroup analyses of the effects on the primary and secondary outcome will be conducted for each part of the main randomisation. Tests for heterogeneity (or tests for trend between 3 or more ordered groups) will be conducted to assess whether there is any good evidence that the effects in particular subgroups differ materially from the overall effect seen in all patients combined. The results of subgroup analyses will be interpreted with appropriate caution. In particular, due allowance for the number of such analyses will be made in the interpretation of the results noting that even if a treatment truly works similarly well in all patients, by chance it is highly likely that it will seem not to in some subgroups (and may even appear to be harmful). The following subgroups will be considered:

- Marburg or Ebola disease (and by virus strain e.g. MARV, RAVV, *EBOV, BDV SUDV*).
- Age (children, younger adults, older adults).
- *Filovirus* nucleoprotein cycle-threshold (Ct) value using quantitative RT-PCR from latest test conducted prior to randomisation (high, low).
- Number of days since symptom onset (divided at the approximate median).
- *Filovirus* vaccination status (yes, no, unknown).
- Randomised allocation in other completed factorial comparisons.

Further exploratory subgroup analyses will include:

- Severity of disease at time of randomisation on the basis of one or more of:

(a) Extent of physiological disturbance at the time of enrolment (e.g. qSOFA score[17] in adults (0-1, 2 or more); or PEWS score[28] in children (0-2, 3 or more).
(b) Evidence of organ dysfunction at the time of enrolment (e.g. creatinine > 150 umol/L; aspartate transaminase or alanine transaminase > 5 times the upper limit of normal).

4.1.4 Allowance for multiple comparisons

The mortality results for 1:1 comparisons in the factorial design are uncorrelated with any other results and will therefore be reported without formal adjustment for multiple testing. Throughout, due allowance for the number of analyses (including of secondary and other outcomes and of effects in subgroups) will be made in interpreting the results.

4.2 Sample size estimation

The larger the number randomised, the more accurate and informative the results will be and, over time, the more potential treatments can be assessed. However, it is not possible to make precise sample size estimates in the context of an outbreak where there are many unknowns. The numbers required will be influenced by many factors, including the case fatality and speed of presentation and diagnosis at a clinical facility, changes in usual standard of care, and how much the proportional reduction in mortality differs between better-prognosis and worse-prognosis patients.

Ideally, each comparison should be sufficiently large to provide good power (e.g. 90% power to achieve 2P=0.01) to detect a proportional reduction in mortality of at least one third. This may require randomisation of several hundred patients in each comparison. For example, if mortality in the reference arm was 50%[12,18,19], randomisation of around 520 participants in a single comparison would give more than 90% power at 2P=0.01 to detect a proportional reduction in mortality of one-third and more than 80% power at 2P=0.05 to detect a smaller (but still useful) reduction in mortality of one-quarter. (Note that with 50% mortality in the reference arm, the above mortality *risk* reductions of one-third or one quarter would represent mortality *odds* reductions of, respectively, one-half or two-fifths.)

However, it is possible that any single outbreak might end before the trial has recruited such numbers during that outbreak, or in some instances, that availability of some of the study interventions will limit enrolment. Even these more limited numbers, perhaps from a single outbreak, might still deliver clear results and change clinical practice. Suppose, for example, that 120 patients were randomised between a monoclonal antibody plus usual care vs. usual care alone. The primary analysis of the effects of adding the antibody to usual care would then be based on only 60 vs 60 patients, far fewer than ideally needed. Nevertheless, suppose that the antibody reduced 28-day mortality from 30% to 10% in the better-prognosis half of all patients and from 90% to 70% in the worse-prognosis half (approximately as was seen for patients with high and low RT-PCR Ct values with two successful antibodies to *EBOV* in the PALM trial in eastern DRC). Combining the results from 2x2 analyses within each of these two prognostic strata would then yield clear evidence of benefit at 2P<0.01.

This does not mean that 120 patients is the ideal trial size, but it does indicate that useful information *could* emerge from even quite a small trial and may be achievable in a single outbreak. If this trial, or some parts of it, extends over multiple outbreaks in various locations, it could eventually include substantial numbers and address additional questions[2].

4.2.1 Review and potential to modify sample size

Throughout the trial, the Trial Steering Committee, blind to information about the effects of ongoing treatment comparisons, will monitor event rates (both overall and by groups with different prognoses) to determine whether, in its view, sufficient participants have been randomised in each comparison. For instance, if the blinded mortality rate turns out to be much lower than anticipated in section 4.2, then the TSC may decide to increase the number of patients in order to achieve the desired power to detect a mortality risk reduction of one third. At the end of an outbreak, for each comparison the Trial Steering Committee may elect to: (a) close it and report the unblinded results; or (b) pause it (remaining blind to the results) with a view to re-opening it in the case of a new outbreak[2]. In this context, it is recognised that some potential treatments may only be relevant for MARV, SUDV or EBOV infections (e.g. a particular monoclonal antibody) whilst others may be relevant for a broad range of patients with Filovirus Disease regardless of the particular virus (e.g. host-directed immunomodulatory treatments).

5 DATA MONITORING COMMITTEE (DMC) [NOW SEPARATED]

During the study, interim analyses of all study data will be supplied in strict confidence to the independent DMC. The DMC will request such analyses at a frequency relevant to the emerging data from this and other studies. Further details of the roles and responsibilities of the DMC will be described in a Data Monitoring Committee Charter.

The DMC will independently evaluate these analyses and any other information considered relevant. The DMC will determine if, in their view, the randomised comparisons in the study have provided evidence on mortality that is strong enough (with a range of uncertainty around the results that is narrow enough) to affect national and global treatment strategies.

In such a circumstance, the DMC will inform the Trial Steering Committee who will be responsible for considering any amendments to the protocol and trial comparisons and for plans to make the results available to the public. Unless this happens, the Trial Steering Committee, Principal Investigator(s), study staff, investigators, study participants, funders and other partners including WHO and relevant Ministries of Health and pharmaceutical partners supplying study treatments will remain blind to the interim results until 28 days after the last patient has been randomised for a particular intervention arm (at which point unblinded analyses may be conducted for that comparison).

5.1 Early stopping for benefit

The DMC will advise the Trial Steering Committee if, in its view, the randomized comparisons in the study provide “proof beyond reasonable doubt” that one of the study treatments reduces the primary outcome of mortality. In making this determination, the DMC would be expected to consider both the results for the overall population and for important subgroups of patients (see section 4.1.3) Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but in general a benefit of at least 3 standard errors in an interim analysis on the primary outcome would be needed to justify halting the study prematurely for efficacy[29]. If, in the view of the DMC, the evidence is not sufficiently convincing to affect national and global treatment strategies, then it would not be expected to recommend stopping the trial for efficacy. This approach has the practical advantage that the number of interim analyses has a negligible impact on the final significance level at which the primary outcome is tested.

5.2 Blinding

This is an open-label study. However, while the study is in progress, access to tabular results by allocated treatment allocation will not be available to the research team, patients, Ministries of Health, pharmaceutical partners supplying study treatments, or members of the Steering Committee (unless the DMC advises otherwise).

6 STUDY PROCEDURES

6.1 Practical considerations

Detailed information on how to implement trial procedures will be provided in standard operating procedures. Trial operations will be embedded in routine clinical workflow where possible to maintain high levels of familiarity, reduce error, and minimise duplication of effort.
A focused approach to clinical data collection will be used in recognition of the resource-limitation and clinical demand that may occur at some participating sites, the infectious risks to healthcare workers with study procedures, and that the critical research question is whether these treatments improve survival in diseases with high mortality.
Country-specific modifications to this core protocol (e.g. due to differences in age of consent, or proxy consent regulations) are contained in the relevant annexes.

6.2 Identification

Potential participants will be identified from the point that the treating clinician in a participating clinical site is notified of a positive *Filovirus* RT-PCR result by the laboratory. Patients are eligible for enrolment at any point during their acute illness.

6.3 Consent

Informed consent must be obtained for each patient before enrolment into the study. To maximise the opportunity for potential participants to make their own decisions about participation prior to potential clinical deterioration, patients with suspected Filovirus Disease can be approached for consent, although they will not be enrolled in the study until laboratory confirmation of disease.
For children, consent will be sought from their parents or legal guardian. The age where a child is able to consent for themselves will adhere to legislation in the country of trial operation (provided in country-specific annexes). Where possible, children who are 10 years old or more will also be asked for assent.

If an adult patient cannot provide consent, reasonable attempts will be made to reach the next of kin to provide consent by proxy.

Proxy consent must be witnessed but may be obtained over the telephone if a parent/guardian or legally acceptable representative cannot be physically present (e.g. due to treatment unit visiting rules or parental quarantine, isolation, or illness).
Due to the severity of Filovirus Disease, patients who lack capacity to consent due to severe disease, and for whom a relative to act as the legally designated representative is not available, randomisation and consequent treatment will proceed with consent provided by a clinician (independent of the clinician seeking to enrol the patient and not connected with the conduct of the trial) who will act as the legally designated representative (if allowed by local regulations). If a participant subsequently regains capacity prior to discharge, they should be provided with information about the trial, their rights, and how to exercise them. Provision of such information should be documented in the medical record.

Consent will include provision for secondary use of data which includes use by the pharmaceutical partners that supply study treatments, regulators, public health and academic organisations.

6.4 Baseline information

The following information will be recorded. For laboratory tests, the most recent value obtained for routine clinical practice is used, if available.

- Clinical facility (e.g. name of treatment unit) enrolling patient.
- Patient details (e.g. name, date of birth, sex).
- Major comorbidities (e.g. malaria, HIV, tuberculosis, diabetes, malnutrition, previous *Filovirus* infection).
- Date of Filovirus Disease symptom onset.
- Date of admission to treatment facility.
- Latest *Filovirus* test result (date, strain, Ct value).
- Vital signs.
- Focused symptom assessment (bleeding, confusion).
- Biochemistry results (creatinine, ALT and/or AST).
- Malaria test result.
- Pregnancy test result (in women with childbearing potential) with estimated gestational age or trimester.
- Contraindication to each of the study drugs.
- Use of relevant concomitant medication (e.g. antivirals, corticosteroids, antimalarials).
- Vaccination (including date) for *Filovirus.*

6.5 Randomised allocation of treatment

All participants will receive usual standard of care guided WHO recommendations[12] and can receive licensed therapies (where they exist). Randomisation will be undertaken using a web-based service.

6.5.1 Treatments

Treatment and dosing information is provided in relevant annexes. Up to three arms will be active for a given virus.

- Antiviral.
- Monoclonal antibodies.
- Host-directed therapy.

6.6 Administration of allocated treatment

Treatments are provided open-label. Drugs will be prescribed by a clinician delegated by the principal investigator to do so, and administered by appropriately trained clinical staff. Treatments should be administered as soon as possible following randomisation (although

it is recognised that logistic issues may mean that initiation of some treatments may be delayed). The patient's own doctors are free to reduce the infusion rate of the treatment or stop study treatments if they feel it is in the best interests of the patient without the need for the patient to withdraw from the study. Medications can be given to treat potential adverse events (such as antihistamines, and corticosteroids (irrespective of allocation in trial)). Virus-specific annexes will provide details regarding management of resumption of infusion for specific treatments where required.

6.7 Schedule of assessments

Staff safety takes precedence over study assessments. Where assessments are undertaken for clinical need (e.g. RT-PCR), these are not duplicated as a study-specific procedure.

Schedule of assessments

	B	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D+	Death or discharge	D28	Pregnancy outcome
Baseline assessments															
Consent	X														
Name and demographics	X														
Clinical facility	X														
Clinical severity assessment	X														
Vital signs	X														
Malaria result	O[§]														
Pregnancy result [a]	X[§]												X[b]		X
Study assessments															
Survival													X	X	
RT-PCR Ct result	X[§*]	O	O	X	O	X	O	X	O	O	X	O	X	X	
Biochemistry (Cr, ALT and/or AST)	X			X		X		X			X				
Key medications	X												X	X	
Maternal and foetal outcomes	X												X		X

Safety assessments		R	R	R	R	R	R	R	R	R	R	R	R	R	R
Study treatment		R	R	R	R	R	R	R	R	R	R	R			

§ Most recent result prior to enrolment. X: study assessment (clinically collected samples will not be duplicated). O: result recorded when collected for clinical reasons but not collected as a study assessment. R: result collected when applicable. (a) in women of child-bearing age, (b) in women of child-bearing age discharged alive.

6.8 Monitoring of patients

Detailed guidance on procedures for monitoring patients during and after infusions will be provided in trial standard operating procedures. In particular, patients should be monitored during infusions sufficient for early recognition and treatment of anaphylaxis or other infusion-related reactions, with emergency drugs (e.g. adrenaline, antihistamine) readily available.

6.9 Collecting follow-up information

The following information will be ascertained at the time of death or discharge or at 28 days after randomisation (whichever is sooner):

- Vital status (alive / dead, with date and cause of death, if appropriate).
- Hospitalisation status (inpatient / discharged, with date of discharge, if appropriate).
- Results of *Filovirus* RT-PCR tests performed as part of routine clinical practice (date of tests, positive / negative and Ct value).
- Use of supportive treatment if available (e.g. blood products, non-invasive or invasive mechanical ventilation, renal replacement therapy).
- Use of any treatments included in this protocol (including drugs in the same class) or other purported treatments for Filovirus Disease.
- Participation in other randomised trials of interventions (vaccines or treatments) for Filovirus Disease.
- Result of repeat pregnancy test in women of child-bearing age.

Follow-up information is to be collected on all study participants who have not withdrawn consent to follow up, irrespective of whether or not they complete the scheduled course of allocated study treatment. If the trial team become aware of any deaths from direct or indirect late effects of *Filovirus* infection after Day 28 these should be recorded.

6.9.1 Duration of follow-up

All randomised participants are to be followed up until death, discharge from hospital or 28 days after randomisation (whichever is sooner). Attempts may be made to contact patients post-discharge to confirm vital status at day 28 but failure to do so will not be considered a protocol deviation.

6.9.1.1 Follow up of pregnant participants

Additional data will be collected for women who are pregnant at the time of enrolment into the trial. Reasonable efforts will be made to follow-up pregnant women until the conclusion of their pregnancy to identify pregnancy outcomes, congenital anomalies and neonatal complications. This will be undertaken through structured telephone interviews with the mothers or their healthcare providers. Any maternal, neonatal or infant outcomes that constitute a potential SSAR will be reported to the Country Principal Investigator and managed in accordance with protocol. Offspring of pregnant participants and neonates should be referred to national programmes for longitudinal follow up where these programmes exist.

6.10 Withdrawal of consent

A decision by a participant that they no longer wish to continue receiving study treatment should not be considered to be a withdrawal of consent for follow-up. However, participants are free to withdraw consent for some or all aspects of the study at any time if they wish to do so. In accordance with regulatory guidance, de-identified data that have already been collected and incorporated in the study database will continue to be used (and any identifiable data will be destroyed). For participants who lack capacity, if their legal representative withdraws consent for treatment or methods of follow-up then these activities would cease. Withdrawal of consent will not affect supportive care provided at the clinical site, or participation or benefit from other programmes or research.

7 DATA AND SAFETY MONITORING

In addition to study outcomes (e.g. mortality), Adverse Events will be recorded if they fall into one of the following groups:

1. Adverse Events of Special Interest (AESIs; e.g. infusion-related reactions).
2. Serious Adverse Events that are not considered to be due to the underlying *Filovirus* infection.
3. Serious (per standard regulatory definition) that are considered with reasonable probability to be related to one of the study medications (i.e. Suspected Serious Adverse Reactions, which includes Suspected Unexpected Serious Reactions [SUSARs]).

Pregnancy and foetal outcomes will also be recorded wherever possible to the end of the pregnancy.

Other adverse events will not be collected because of the severity of the underlying disease (including a high risk of mortality) and to avoid an excessive burden on staff working in a high-risk clinical environment. In this context, the occurrence of non-serious adverse events is of limited importance to regulatory and clinical decisions. All Adverse Events that meet one of the criteria above should be reported on the case report form.

7.1 Adverse Events of Special Interest

AESIs will be reported on the case report form whether serious or not. They will include Infusion-Related Reactions (IRRs). An IRR is defined as an adverse reaction to an infusion of a study drug that occurs during or within one hour after completion of an infusion. These will be classified according to severity:

- Mild: no specific treatment required.
- Moderate: treatment with antihistamines or steroids required.
- Severe: treatment with adrenaline required, including anaphylaxis.

Further AESIs will be specified as necessary in the disease-specific annexes.

7.2 Serious Adverse Events that are not considered to be due to the underlying *Filovirus* infection

In critically ill patients, a very large proportion of patients will suffer an SAE that is unrelated to the drug being evaluated[30]. Recording SAEs that are a part of the natural history of the disease or are captured through primary or secondary endpoints does not add to reliable evaluation of the safety and efficacy of a drug. In fact, recording such data is more likely to reduce the likelihood of a reliable assessment since it will distract from the accurate and complete collection of more important data. In this trial the SAE of death is recorded through the primary endpoint. New or worsening events that meet the definition of an SAE and are considered by the site investigator to be unlikely to be related to underlying filovirus disease will be reported on the case report form.

7.3 Suspected Serious Adverse Reactions

The focus is on those events that, based on a single case, are highly likely to be related to the study medication. Examples include anaphylaxis, cytokine release syndrome, Stevens Johnson Syndrome, or bone marrow failure, where there is no other plausible explanation.

Any Serious Adverse Event† that is believed with a reasonable probability to be due to one of the study treatments will be considered a Suspected Serious Adverse Reaction (SSAR). In making this assessment, there should be consideration of the probability of an alternative cause (for example, Filovirus Disease itself), the timing of the event with respect to study treatment, the response to withdrawal of the study treatment, and (where appropriate) the response to subsequent re-challenge.

All SSARs will be reported on the case report form as soon as possible and in addition notified to the Central Coordinating Office by the site investigator (or delegated staff) on the same day by telephone so that the details required for potential expedited reporting can be collected and confirmed.

7.3.1 Central assessment and onward reporting of SUSARs

The CCO with the national Principal Investigator are responsible for expedited review of reports of SSARs received. An assessment will be made of whether the event is “expected” or not (assessed against the relevant Summary of Product Characteristics or Investigator Brochure). Any SSARs that are not expected would be considered a Suspected Unexpected Serious Adverse Reaction (SUSAR).
All confirmed SUSARs will be reported to the Chair of the DMC and to relevant regulatory authorities, ethics committees, and investigators in an expedited manner in accordance with local regulatory requirements. In addition the DMC will receive all SSARs (whether expected or not) at the time of their regular meetings.

7.4 Pregnancy and foetal outcome.

Pregnant women who are enrolled in the trial will be followed until conclusion of the pregnancy. Pregnancy outcomes will be recorded in the case report form system.

† Serious Adverse Events are defined as those adverse events that result in death; are life-threatening; require in-patient hospitalisation or prolongation of existing hospitalisation; result in persistent or significant disability or incapacity; result in congenital anomaly or birth defect; or are important medical events in the opinion of the responsible investigator (that is, not life-threatening or resulting in hospitalisation, but may jeopardise the participant or require intervention to prevent one or other of the outcomes listed above).

8 QUALITY MANAGEMENT

8.1 Quality By Design Principles

This study is designed and is to be conducted in accordance with the Principles for Good Randomised Trials developed by the Good Clinical Trials Collaborative[31], the ICH Principles of Good Clinical Practice, and the recommendations and guidelines issued by relevant regulatory agencies. The design, conduct and analysis of this trial is focussed on issues that might have a material impact on the wellbeing and safety of study participants (patients with Filovirus Disease) and the reliability of the results that would inform the care for future patients.

The critical factors that influence the ability to deliver these quality objectives are:

- To minimise the burden on busy clinicians working in an overstretched clinical service during a major outbreak.
- To ensure that suitable patients have access to the trial medication without impacting or delaying other aspects of their emergency or supportive care, or the care of other patients in the clinical environment.
- To provide information on the study to patients and clinicians in a timely and readily digestible fashion but without impacting adversely on other aspects of the trial or the patient's care.
- To minimise additional risk to health and safety of study staff.

In assessing any risks to patient safety and well-being, a key principle is that of proportionality. Risks associated with participation in the trial must be considered in the context of usual care. At present, there are no proven treatments for *SUDV or MARV* and mortality for patients with *Filovirus* infections is high.

8.2 Training and monitoring

In accordance with the Quality by Design principles (see section 8.1), the focus will be on those factors that are critical to quality (i.e. the safety of the participants and the reliability of the trial results). Remedial actions would focus on issues with the potential to have a substantial impact on the safety of the study participants or the reliability of the results.

Any serious breach of the Principles of ICH-GCP in the conduct of the clinical trial will be handled in accordance with regulatory requirements. Prior to initiation of the study at each Local Clinical Centre (usually a *Filovirus* Treatment Facility or hospital) (LCC), the national Principal Investigator will confirm that the LCC has adequate facilities and resources to carry out the study. LCC site investigators and study staff will be provided with training materials.

A site initiation monitoring visit will be planned for each site, with the format dependent on operational considerations. The central coordinating office (CCO) or national Principal Investigator may arrange monitoring visits to LCCs as considered appropriate based on speed of recruitment, perceived training needs and the results of central statistical monitoring of study data. The purpose of such visits will be to ensure that the study is being conducted in accordance with the protocol, to help LCC staff to resolve any local problems,

and to provide extra training focussed on specific needs. There will be routine frequent communication between sites and the CCO.
No routine source data verification will take place – source data collected in the red-zone will be destroyed in line with infection prevention guidelines. Verified copies will be collected and stored.

8.3 Data management

Treatment centre staff will use the study IT applications for study management and to record participant data (including case report forms) in accordance with the protocol. Data will be held in central databases located on secure cloud servers. In some circumstances (e.g. where there is difficulty accessing the internet or necessary IT equipment), paper case report forms may be required with subsequent data entry. Randomisation will always be done electronically (the outcome may be transmitted between site and trial managers by phone [e.g when internet connection is intermittent] or electronically). Although data entry should be mindful of the desire to maintain integrity and audit trails, in the circumstances of a *Filovirus* outbreak the priority is on the timely entry of data that is sufficient to support reliable analysis and interpretation about treatment effects. CCO staff will be responsible for provision of the relevant web-based applications and for generation of data extracts for analyses.

All data access will be controlled by unique usernames and passwords, and any changes to data will require the user to enter their username and password as an electronic signature in accordance with regulatory requirements. Staff will have access restricted to the functionality and data that are appropriate for their role in the study.

8.4 Laboratory assays

Paediatric samples will be reduced in volume according to standard procedures. Standard care samples will be prioritised over research samples if volume reduction is required. Ability to take samples is dependent on staff availability, the availability of suitable laboratory facilities and caseload. Research samples may therefore be reduced or missed if needed to maintain care standards and staff safety, and to reflect the assays that can be performed by the laboratory attached to a treatment facility.
Samples will not be duplicated if they are collected on the same day for clinical reasons.

***Filovirus* testing:** *Filovirus* RT-PCR are performed per local clinical laboratory protocols as part of standard care. The virus species tested will be dependent on the species responsible for outbreak at the time of testing. The results of these tests (quantitative result and assay used) will be recorded at baseline and each day subsequently (see section 6.8). Samples obtained for PCR are typically ≤4 ml whole blood in an EDTA tube. Finger or heal-pricks of blood on a dry swab are sometimes obtained when venepuncture is not possible.
Malaria testing: Malaria diagnostic tests are performed on the triage blood sample as part of standard care. The result will be recorded at baseline.

Pregnancy testing: For women of childbearing age (15-49 years) a βHCG test is performed on the triage blood sample as standard of care. Urine testing is also acceptable. The result will be recorded at baseline. A further test will occur at discharge or day 28 (which ever comes earliest) as a study specific sample.
Biochemistry: Creatinine, AST, and ALT will be collected at baseline and days 3,5,7,10 per local clinical laboratory protocols.

8.5 Source documents and archiving

Source documents for the study constitute the case report forms and records held in the study main database. When documentation is paper-based, source data collected at the patient bedside (e.g. consent forms) will not be removed due to infection control requirements, and will be destroyed. Copies of these documents will be made (e.g. using digital photography) prior to destruction, and these copies will be retained. The ability to store documents at local sites will be limited by infection control requirements and operational challenges (e.g. temporary opening during a local outbreak). Study documents will be retained for the duration directed by national legislation from the completion of the study by the principal investigator in secure physical or electronic storage. The sponsor, regulatory agencies and any organisation that donates study treatment will have the right to conduct confidential audits of relevant records in the CCO and LCCs. However, such audit activities should be mindful of (a) the workload facing participating clinical sites, (b) the infection control requirements during a *Filovirus* outbreak, and (c) the temporary nature of many clinical facilities and trial sites.

9 ADMINISTRATIVE DETAILS

9.1 Sponsor and coordination

In each participating country, WHO and the local Ministry of Health will act as Co-sponsors of the trial. The trial will be coordinated by a Central Coordinating Office. The data will be collected, analysed, and published independently of the source of funding and any companies or organisations providing one or more of the study treatments.

9.2 Funding

WHO and the CCO will be responsible for organising funding for the trial.

9.3 Indemnity

WHO will provide indemnity for all individuals and organisations involved in the design, conduct and analysis of the trial, including members of the Trial Steering Committee, Data Monitoring Committee, Statistical Analysis Team, Central Coordinating Office, and participating site investigators and other study staff.

9.4 Supply of study treatments

For licensed treatments (e.g. corticosteroids) all aspects of treatment supply, storage, and management will be in accordance with standard local policy and practice for prescription medications. Treatment issue to randomised participants will be by prescription. Such study treatments will not be labelled beyond that required for routine clinical use. They will be stored alongside other routine medications with no additional monitoring. No accountability records will be kept beyond those used for routine prescriptions.

For unlicensed treatments, manufacture, packaging and delivery will be the responsibility of the pharmaceutical donor. For these treatments, inventory, dispensing and accountability of study treatment will be controlled and any requirements for specific storage conditions will be followed. Treatment dispensed but not used will not be returned due to infection control procedures and will be destroyed. Further details will be provided in trial Standard Operating Procedures.

9.5 End of trial

The end of the scheduled treatment phase is defined as the date of the last follow-up visit of the last participant.

9.6 Publications and reports

The Trial Steering Committee will be responsible for drafting the main reports from the study and for review of any other reports. In general, papers initiated by the Trial Steering Committee (including the primary manuscript) will be written in the name of the Trial Collaborative Group, with individual investigators (including those from each participating country and each participating site) named personally at the end of the report (or, to comply with journal requirements, in web-based material posted with the report). Pharmaceutical

companies donating treatments will be provided with a draft of the main reports for review and comment, but the decision to publish and authorship will remain under the control of the TSC. Data and analyses that were produced for the main reports will be provided to companies donating treatments.

The Trial Steering Committee will also establish a process by which proposals for additional publications (including from independent external researchers) are considered by the Trial Steering Committee. The Trial Steering Committee will facilitate the use of the study data and approval will not be unreasonably withheld. However, the Trial Steering Committee will need to be satisfied that any proposed publication is of high quality, honours the commitments made to the study participants in the consent documentation and ethical approvals, and is compliant with relevant legal and regulatory requirements (e.g. relating to data protection and privacy). The Trial Steering Committee will have the right to review and comment on any draft manuscripts prior to publication

Efforts will be made to disseminate the findings with relevant clinicians and at risk communities.

9.7 Substudies

Substudies (e.g. pharmacokinetics, biochemistry, clinical epidemiology, and disease natural history) may be conducted at some sites. Proposals for such substudies must be approved by the Trial Steering Committee and by the relevant ethics committee and competent authorities (where required) as a substantial amendment or separate study protocol before they begin. In considering such proposals, the Trial Steering Committee will need to be satisfied that the proposed substudy is worthwhile and will not compromise the main study in any way (e.g. by impairing recruitment or the ability of the participating sites to provide care to all patients under their care).

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11 VERSION HISTORY

Version number	Date	Brief Description of Changes
1.0	16-Nov-2022	Initial draft
2.0	8-Dec-2022	Response to WHO REC and Joint Review convened by National Council for Science and Technology (Uganda)
3.0	15-Feb-2022	Inclusion of Marburg Virus Disease.
4.0		Removal of treatment specifics to appendices

Appendix 1: Organisational Structure and Responsibilities

Principal Investigator(s)

The Principal Investigator has overall responsibility within his/her country for:

(i) Contributing to the study design for that country in collaboration with the Trial Steering Committee.
(ii) Ensuring necessary national regulatory and ethics committee approvals.
(iii) Conduct of the study in collaboration with the Central Coordinating Office.
(iv) Analysis of the study in collaboration with the Statistical Analysis Team.
(v) Monitoring and reporting safety information in line with the protocol and regulatory requirements and as agreed in terms of reference with the CCO.
(vi) Dealing with technical, medical, and administrative queries from LCCs.

Steering Committee

The Trial Steering Committee is responsible for:

(i) Agreement of the Protocol and the Statistical Analysis Plans.
(ii) Reviewing progress of the study and, if necessary, deciding on Protocol changes.
(iii) Review and approval of study publications and substudy proposals.
(iv) Reviewing new studies that may be of relevance.

Data Monitoring Committee

The independent Data Monitoring Committee is responsible for:

(i) Reviewing unblinded interim analyses according to the Protocol.
(ii) Advising the Trial Steering Committee if, in their view, the randomised data provide evidence that may warrant a change in the protocol (e.g. modification or cessation of one or more of the treatment comparisons).

Statistical Analysis Team

(i) Advising the Trial Steering Committee on statistical issues related to the development and implementation of the protocol.
(ii) Development of the Statistical Analysis Plan.
(iii) Conduct of statistical analyses for publications and presentations in accordance with the Statistical Analysis Plan and Protocol.

Central Coordinating Office (CCO)

The CCO is responsible for the overall coordination of the Study, including:

(i) Study planning and organisation of Trial Steering Committee meetings.

(ii) Ensuring necessary regulatory and ethics committee approvals.
(iii) Development of Standard Operating Procedures and computer systems.
(iv) Monitoring overall progress of the study.
(v) Provision of study materials to Principal Investigators.
(vi) Maintaining the Trial Master File.
(vii) Monitoring and reporting safety information to international bodies in line with the protocol and regulatory requirements and as agreed in terms of reference with the trial sponsor and Principal Investigators.

Local Clinical Centres (LCC)

The LCC Lead Investigator and LCC clinic staff are responsible for:

(i) All trial activities at the LCC, including appropriate training and supervision for clinical staff.
(ii) Conducting trial procedures at the LCC in line with all relevant local policies and procedures.
(iii) Dealing with enquiries from participants and others.

Appendix 2: Organisational Details

TRIAL STEERING COMMITTEE

(Major organisational and policy decisions, and scientific advice; blinded to treatment allocation)

Co-chairs

Principal Investigators*

Members

Co-chairs

Principal Investigators*

Members

*other PIs will be added for each outbreak and each country that is involved in the trial.

DATA MONITORING COMMITTEE

(Interim analyses and response to specific concerns)

<TBC>

Chair

Members

Statistician (non-voting)

STATISTICAL ANALYSIS TEAM

(Statistical analyses for publication and dissemination)

<TBC>

PROTOCOL AUTHORS

This protocol was written in accordance with the treatment and design recommendations given by the WHO Expert deliberations for candidate treatments prioritization and trial design for Filoviruses.

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National Investigators (Ghana):

National Investigators (DRC):