



World Health  
Organization

# SOLIDARITY PARTNERS

Platform Adaptive Randomised Trial for NEw and Repurposed  
Filovirus treatments

## CORE Trial Protocol

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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<sup>1</sup>**

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	

15

16

## 17 1 TRIAL SYNOPSIS

18

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

19

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

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

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

30 A platform trial is a clinical trial that can study multiple different interventions at the same  
 31 time and add, assess, and remove new interventions as time goes on, without having to  
 32 specify the new interventions at the start.\* Compared to a more traditional clinical trial design  
 33 (is this drug better than usual care?), a platform trial can be thought of as disease  
 34 focussed (what is the best treatment for this disease?).

35 As well as being able to add new interventions as time goes on, platform trials also have the  
 36 flexibility to update the control, or 'usual care' group as the study progresses. This is useful  
 37 for when, for example, the platform trial shows a drug it's testing to be much more effective  
 38 than 'usual care', then that drug can be used to benefit patients right away and become part  
 39 of the new 'usual care' against which all new drugs are tested in the trial, creating a potential  
 40 cycle of improvement in patient care.

41 Since some treatments might work across a variety of different filovirus diseases (e.g. host  
 42 directed therapies such as immunomodulatory drugs or drug that stabilise the vascular  
 43 endothelium) a trial that allows enrolment of patients with any type of filovirus disease would  
 44 be beneficial – a 'pan-filovirus' protocol. A pan-filovirus protocol is also favoured since it  
 45 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>

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

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

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

64

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

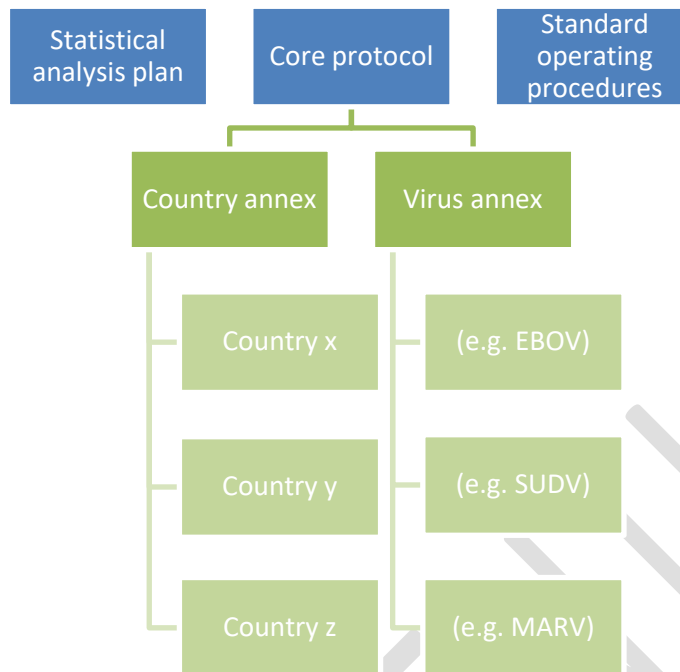
- 67 i. Promising new treatments are developed and are ready to be tested;
- 68 ii. Treatments no longer require evaluation in a trial because they have been shown to  
69 be effective or ineffective or unsafe;
- 70 iii. New countries wish to join the trial with their own regulatory requirements;
- 71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

73 This core protocol details the key requirements of the trial irrespective of the location or  
74 cause of an outbreak but is supplemented by appendices that describe more detailed  
75 information for an outbreak in a particular regulatory jurisdiction (Country appendices), or  
76 for a particular virus (Virus appendices). The country appendices name national  
77 investigators and partner institutions. They specifically detail adaptations to comply with  
78 local regulatory requirements. These are usually governance requirements, ethics  
79 considerations (such as proxy or minor consent processes) and changes to reporting  
80 timelines. The virus appendices provide details of the treatments to be evaluated for a  
81 particular filovirus, and any data collection additions.

82 The protocol sits alongside a detailed statistical analysis plan that will provide a pre-specified  
83 plan for assessing treatment safety and efficacy. Standard operating procedures provide  
84 site-level detail on how to interpret and implement the protocol.

85

86 **Figure 1: Protocol structure**



87

88

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

- 92
- 93 ● Monoclonal antibodies:
    - 94 ○ Targeted monoclonal antibody/cocktail\* vs no additional treatment
  - 95 ● Virus-directed therapy:
    - 96 ○ Antiviral therapy\* vs no additional treatment
  - 97 ● Host-directed therapy:
    - 98 ○ Host-directed therapy\* vs. no additional treatment

99 \*defined in Virus-specific annexes.

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

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

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

109

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

115

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

125

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

133

134 Pregnancy and foetal outcomes will also be recorded.

135

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

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

150

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

154 The protocol, informed consent form(s), recruitment materials, and all participant materials  
155 will be submitted to the WHO Ethical Review Committee and, in each country where the  
156 protocol will be implemented, the relevant human research ethics and regulatory agencies.  
157 Approval of both the protocol and the consent form must be obtained before any participant  
158 is enrolled.

159 Any amendment to the protocol will require review and approval by WHO and country Ethics  
160 Review Committees before the changes are implemented to the study (unless they  
161 constitute an urgent safety measure). In addition, all changes to the consent forms will be  
162 approved by these committees.

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## 164 2 BACKGROUND AND RATIONALE

### 165 2.1 Setting

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

170 Ebola Disease is a complex multi-system illness that begins following an incubation period  
171 of 2-21 days. Illness usually begins with non-specific symptoms including fever, fatigue, and  
172 gastrointestinal distress. As the disease progresses, it is complicated by worsening  
173 gastrointestinal losses, shock, multi-organ failure, and sometimes haemorrhage. The  
174 pathogenesis of Ebola Disease is reviewed comprehensively elsewhere<sup>4-6</sup>. The virus  
175 disseminates broadly in body tissues and increasing viral load is a predictor of severe  
176 disease and death<sup>7</sup>. Severe disease is associated with coagulopathy<sup>8</sup>, disruption of  
177 endothelial function<sup>5</sup> and a strong inflammatory response<sup>9-12</sup>. Estimates of the case-fatality  
178 rate are variable depending on the outbreak, but for *SUDV* infection range between 36-  
179 65%<sup>13</sup>, and is usually between 50-70% for *EBOV* outbreaks.

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

### 192 2.2 Treatment Options

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

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

199 The treatment domains to be assessed in the protocol are:

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

- 202       • Host-directed therapy: [all patients].

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

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

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

### 216 **2.2.1 Modifications to the number of treatment comparisons:**

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

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

### 228 **2.3 Design Considerations**

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

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

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

240 **2.3.1 Evolving standard of care**

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

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## 247 3 DESIGN

### 248 3.1 Study aims

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

### 251 3.2 Eligibility

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

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

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

#### 266 3.2.1 Pregnancy and breastfeeding

267 There is a high maternal mortality in pregnant women with Ebola Disease<sup>25</sup>, and foetal  
268 survival is rare. There are only three known cases of Marburg Disease in pregnant women.  
269 All women died, and the only neonate delivered died shortly after birth<sup>26</sup>. Therefore, pregnant  
270 women will be eligible for enrolment in the trial. Expert obstetric and teratology advice will  
271 be provided to the Trial Steering Committee prior to the inclusion of a new treatment in the  
272 protocol.

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

#### 279 3.2.2 Children

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

283 **3.2.3 Vaccination**

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

288 **3.3 Randomisation**

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

290 **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)		

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

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

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

308 **3.4 Interventions**

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

311 **3.5 Study outcomes**

312 **3.5.1 Primary outcome**

- 313
  - All-cause mortality at 28 days following randomisation

314 **3.5.2 Secondary outcome**

- 315
  - Time (days) to *Filovirus* RNA <LLOQ (lower limit of quantitation) within 28 days

316 [Viral clearance, using results from study or routine clinical samples, is defined as

317 the first negative *Filovirus* RT-PCR test without a subsequent positive test result

318 or subsequent death. In the unlikely scenario that a patient is discharged home

319 without two successive negative RT-PCR tests, the date of the first negative test

320 or, if there is no negative test result, the date of medical discharge will be used.]

321 **3.5.3 Other outcomes**

- 322
  - Viral load (measured by cycle threshold) on blood samples taken at Day 3, 5, 7

323 and 10.

324 
  - Progression of organ dysfunction, measured on blood samples taken at Day 3, 5,

325 7, 10.

326 **3.5.4 Safety outcomes**

327 In addition to study outcomes (e.g. mortality), Adverse Events will be recorded if they fall

328 into one of the following groups:

329

- 330 a. Adverse Events of Special Interest (AESIs; e.g. infusion-related reactions).
- 331 b. Serious Adverse Events that are not considered to be due to the underlying *Filovirus*
- 332 infection.
- 333 c. Serious (per standard regulatory definition) that are considered with reasonable
- 334 probability to be related to one of the study medications (i.e. Suspected Serious
- 335 Adverse Reactions, which includes Suspected Unexpected Serious Reactions
- 336 [SUSARs]).
- 337

338 Pregnancy and foetal outcomes will also be recorded.

339

340 Study outcomes will be assessed based on data recorded up to the time of death, hospital

341 discharge or 28 days after randomisation (whichever occurs first). Pregnant women will be

342 followed up to completion of pregnancy.

343

## 344 4 STATISTICAL ANALYSIS

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

### 351 4.1 Main analysis approach

352 For all each randomised comparison, the outcomes will be made between all participants  
353 randomised to the different treatment comparisons, irrespective of whether they received  
354 some, none, or all of their allocated treatment (i.e. these comparisons will be based on  
355 “intention-to-treat” analyses).

356 The primary analyses will involve pairwise comparisons between the active ‘experimental’  
357 and ‘reference’ arms as follows:

- 358 • Effect of monoclonal antibody: monoclonal vs. no additional treatment.
- 359 • Effect of antiviral: antiviral vs. no additional treatment.
- 360 • Effect of host-directed therapy: host-directed therapy vs no additional treatment.

361 Logistic regression adjusted for baseline levels of key prognostic factors will be used to  
362 estimate the conditional odds of 28-day mortality for each treatment group relative to its  
363 control (ie, the 28-day conditional odds ratio) and its 95% confidence interval. A two-tailed  
364 P-value <0.05 will be considered as statistically significant. Logistic regression (based on  
365 vital status at Day 28, regardless of the time to death within this 28-day range) will be used  
366 in preference to Cox regression because the latter might give undue weight to the exact  
367 times of death of the very poor-prognosis patients (thereby giving inadequate weight to the  
368 death or survival of the better-prognosis patients). However, for illustrative purposes,  
369 Kaplan-Meier plots showing the pattern of survival over the first 28 days will also be created,  
370 both overall and within prognostic categories. For the primary objective of assessing the  
371 effects of each study treatment on 28-day mortality, discharge alive before day 28 will be  
372 assumed as survival to day 28 (unless there are additional data confirming otherwise).

373 For the secondary objective of assessing the effects of each treatment on time to filovirus  
374 RNA <LLOQ within 28 days, differences in median days to filovirus RNA <LLOQ will be  
375 tested using the Wilcoxon rank-sum test, imputing deaths prior to day 28 as the worst ranks,  
376 with earlier deaths having a worse rank than later deaths. The study will collect viremia data  
377 at baseline and approximately days 3, 5, 7, 10. Patients who are discharged from inpatient  
378 care but without an available *Filovirus* RT-PCR test result will be assumed to have *Filovirus*  
379 RNA <LLOQ on their day of discharge (unless in a particular case there is good evidence to  
380 the contrary).

381 For each treatment, the main comparisons will ignore any other treatments that the patient  
382 may have been randomised to in a factorial manner. However, subgroup analyses of each  
383 treatment effect will include analyses by such factorial treatments.

#### 384 4.1.1 Management of control groups

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

#### 391 4.1.2 Adjustment for baseline characteristics

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

#### 401 4.1.3 Pre-specified subgroup analyses

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

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

419 Further exploratory subgroup analyses will include:

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

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

#### 426 4.1.4 Allowance for multiple comparisons

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

#### 431 4.2 Sample size estimation

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

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

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

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

#### 464 4.2.1 Review and potential to modify sample size

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

478

## 479 5 DATA MONITORING COMMITTEE (DMC) [ NOW SEPARATED ]

480

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

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

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

### 497 5.1 Early stopping for benefit

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

### 510 5.2 Blinding

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

## 515 6 STUDY PROCEDURES

### 516 6.1 Practical considerations

517 Detailed information on how to implement trial procedures will be provided in standard  
518 operating procedures. Trial operations will be embedded in routine clinical workflow where  
519 possible to maintain high levels of familiarity, reduce error, and minimise duplication of effort.

520 A focused approach to clinical data collection will be used in recognition of the resource-  
521 limitation and clinical demand that may occur at some participating sites, the infectious risks  
522 to healthcare workers with study procedures, and that the critical research question is  
523 whether these treatments improve survival in diseases with high mortality.

524 Country-specific modifications to this core protocol (e.g. due to differences in age of consent,  
525 or proxy consent regulations) are contained in the relevant annexes.

### 526 6.2 Identification

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

### 530 6.3 Consent

531 Informed consent must be obtained for each patient before enrolment into the study. To  
532 maximise the opportunity for potential participants to make their own decisions about  
533 participation prior to potential clinical deterioration, patients with suspected Filovirus Disease  
534 can be approached for consent, although they will not be enrolled in the study until laboratory  
535 confirmation of disease.

536 For children, consent will be sought from their parents or legal guardian. The age where a  
537 child is able to consent for themselves will adhere to legislation in the country of trial  
538 operation (provided in country-specific annexes). Where possible, children who are 10 years  
539 old or more will also be asked for assent.

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

542 Proxy consent must be witnessed but may be obtained over the telephone if a  
543 parent/guardian or legally acceptable representative cannot be physically present (e.g. due  
544 to treatment unit visiting rules or parental quarantine, isolation, or illness).

545 Due to the severity of Filovirus Disease, patients who lack capacity to consent due to severe  
546 disease, and for whom a relative to act as the legally designated representative is not  
547 available, randomisation and consequent treatment will proceed with consent provided by a  
548 clinician (independent of the clinician seeking to enrol the patient and not connected with  
549 the conduct of the trial) who will act as the legally designated representative (if allowed by  
550 local regulations). If a participant subsequently regains capacity prior to discharge, they  
551 should be provided with information about the trial, their rights, and how to exercise them.  
552 Provision of such information should be documented in the medical record.

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

#### 556 **6.4 Baseline information**

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

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

575

#### 576 **6.5 Randomised allocation of treatment**

577 All participants will receive usual standard of care guided WHO recommendations<sup>12</sup> and can  
578 receive licensed therapies (where they exist). Randomisation will be undertaken using a  
579 web-based service.

##### 580 **6.5.1 Treatments**

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

- 583 ● Antiviral.
- 584 ● Monoclonal antibodies.
- 585 ● Host-directed therapy.

#### 586 **6.6 Administration of allocated treatment**

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

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

597 **6.7 Schedule of assessments**

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

601

602 **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 <sup>s</sup>														
Pregnancy result <sup>a</sup>	X <sup>s</sup>												X <sup>b</sup>		X
Study assessments															
Survival													X	X	
RT-PCR Ct result	X <sup>s*</sup>	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			
Study treatment		R	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.																	

603 **6.8 Monitoring of patients**

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

609 **6.9 Collecting follow-up information**

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

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

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

627 **6.9.1 Duration of follow-up**

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

632 **6.9.1.1 Follow up of pregnant participants**

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

642 **6.10 Withdrawal of consent**

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

## 652 7 DATA AND SAFETY MONITORING

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

- 655
- 656 1. Adverse Events of Special Interest (AESIs; e.g. infusion-related reactions).
  - 657 2. Serious Adverse Events that are not considered to be due to the underlying *Filovirus*  
658 infection.
  - 659 3. Serious (per standard regulatory definition) that are considered with reasonable  
660 probability to be related to one of the study medications (i.e. Suspected Serious  
661 Adverse Reactions, which includes Suspected Unexpected Serious Reactions  
662 [SUSARs]).
- 663

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

666

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

672

### 673 7.1 Adverse Events of Special Interest

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

- 678
- 679 • Mild: no specific treatment required.
  - 680 • Moderate: treatment with antihistamines or steroids required.
  - 681 • Severe: treatment with adrenaline required, including anaphylaxis.

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

### 682 7.2 Serious Adverse Events that are not considered to be due to the underlying 683 *Filovirus* infection

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

693 **7.3 Suspected Serious Adverse Reactions**

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

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

703  
704 All SSARs will be reported on the case report form as soon as possible and in addition  
705 notified to the Central Coordinating Office by the site investigator (or delegated staff) on the  
706 same day by telephone so that the details required for potential expedited reporting can be  
707 collected and confirmed.

708 **7.3.1 Central assessment and onward reporting of SUSARs**

709 The CCO with the national Principal Investigator are responsible for expedited review of  
710 reports of SSARs received. An assessment will be made of whether the event is “expected”  
711 or not (assessed against the relevant Summary of Product Characteristics or Investigator  
712 Brochure). Any SSARs that are not expected would be considered a Suspected Unexpected  
713 Serious Adverse Reaction (SUSAR).

714 All confirmed SUSARs will be reported to the Chair of the DMC and to relevant regulatory  
715 authorities, ethics committees, and investigators in an expedited manner in accordance with  
716 local regulatory requirements. In addition the DMC will receive all SSARs (whether expected  
717 or not) at the time of their regular meetings.

718 **7.4 Pregnancy and foetal outcome.**

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

721

722

---

<sup>†</sup> 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).

## 723 8 QUALITY MANAGEMENT

### 724 8.1 Quality By Design Principles

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

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

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

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

### 746 8.2 Training and monitoring

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

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

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

762 and to provide extra training focussed on specific needs. There will be routine frequent  
763 communication between sites and the CCO.

764 No routine source data verification will take place – source data collected in the red-zone  
765 will be destroyed in line with infection prevention guidelines. [Verified copies will be collected](#)  
766 [and stored.](#)

### 767 8.3 Data management

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

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

### 784 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.

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

791 **Malaria testing:** Malaria diagnostic tests are performed on the triage blood sample as part  
792 of standard care. The result will be recorded at baseline.

793 **Pregnancy testing:** For women of childbearing age (15-49 years) a  $\beta$ HCG test is performed  
794 on the triage blood sample as standard of care. Urine testing is also acceptable. The result  
795 will be recorded at baseline. *A further test will occur at discharge or day 28 (which ever*  
796 *comes earliest)* as a study specific sample.

797 **Biochemistry:** Creatinine, AST, and ALT will be collected at baseline and days 3,5,7,10 per  
798 local clinical laboratory protocols.

## 799 **8.5 Source documents and archiving**

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

## 814 9 ADMINISTRATIVE DETAILS

### 815 9.1 Sponsor and coordination

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

### 820 9.2 Funding

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

### 822 9.3 Indemnity

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

### 827 9.4 Supply of study treatments

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

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

### 840 9.5 End of trial

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

### 843 9.6 Publications and reports

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

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

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

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

## 865 **9.7 Substudies**

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

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967 **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

968

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969 **Appendix 1: Organisational Structure and Responsibilities**

970 **Principal Investigator(s)**

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

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

980 **Steering Committee**

981 The Trial Steering Committee is responsible for:

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

986 **Data Monitoring Committee**

987 The independent Data Monitoring Committee is responsible for:

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

992 **Statistical Analysis Team**

- 993 (i) Advising the Trial Steering Committee on statistical issues related to the
- 994 development and implementation of the protocol.
- 995 (ii) Development of the Statistical Analysis Plan.
- 996 (iii) Conduct of statistical analyses for publications and presentations in accordance
- 997 with the Statistical Analysis Plan and Protocol.
- 998

999 **Central Coordinating Office (CCO)**

1000 The CCO is responsible for the overall coordination of the Study, including:

- 1001 (i) Study planning and organisation of Trial Steering Committee meetings.
- 1002 (ii) Ensuring necessary regulatory and ethics committee approvals.
- 1003 (iii) Development of Standard Operating Procedures and computer systems.
- 1004 (iv) Monitoring overall progress of the study.
- 1005 (v) Provision of study materials to Principal Investigators.
- 1006 (vi) Maintaining the Trial Master File.
- 1007 (vii) Monitoring and reporting safety information to international bodies in line with
- 1008 the protocol and regulatory requirements and as agreed in terms of reference with
- 1009 the trial sponsor and Principal Investigators.

1010 **Local Clinical Centres (LCC)**

1011 The LCC Lead Investigator and LCC clinic staff are responsible for:

- 1012 (i) All trial activities at the LCC, including appropriate training and supervision for
- 1013 clinical staff.
- 1014 (ii) Conducting trial procedures at the LCC in line with all relevant local policies and
- 1015 procedures.
- 1016 (iii) Dealing with enquiries from participants and others.

1017 **Appendix 2: Organisational Details**

1018 **TRIAL STEERING COMMITTEE**

1019 (Major organisational and policy decisions, and scientific advice; blinded to treatment allocation)

1020

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.

1021 **DATA MONITORING COMMITTEE**

1022 (Interim analyses and response to specific concerns)

1023 <TBC>

Chair

Members

Statistician (non-voting)

1024 **STATISTICAL ANALYSIS TEAM**

1025 (Statistical analyses for publication and dissemination)

1026 <TBC>

1027 **PROTOCOL AUTHORS**

1028 This protocol was written in accordance with the treatment and design recommendations given by the WHO  
1029 Expert deliberations for candidate treatments prioritization and trial design for Filoviruses.

1030

1031 University of Oxford: Amanda Rojek, Peter Horby, Martin Landray, Richard Haynes, Jonathan Emberson

1032 World Health Organization: Ana Maria Henao-Restrepo

1033 National Investigators (Uganda): Paska Apiyo, Pauline Byakika

1034 National Investigators (Ghana):

1035 National Investigators (DRC):