Treatment trial context

- Outbreaks are sporadic, but there is reasonable geographic certainty
- Some outbreaks are quickly contained and short lived, and treatment trials occur in parallel with public health measures (inc vaccination campaigns)
- Treatment trials have been incorporated in outbreak response since 2014. Many have failed to reach sufficient size.
- Patients with Filovirus Disease deserve evidence-based care
Describes pre-positioning of an adaptive platform trial of Filoviridae treatments. The rationale is:

i. A research response dependent on de novo clinical trial initiation is usually too slow to enrol within the timeframe of a single epidemic;

ii. A failure to conserve protocols across outbreaks risks under-powered trials;

iii. New promising interventions may emerge and their efficient evaluation would benefit from an adaptive platform trial approach;

iv. Certain interventions may be applicable to >1 filovirus and therefore may be evaluated in a pan-filovirus protocol.
Key features

Assumptions

• Prepositioned, harmonised pan-Filo protocol will increase likelihood of successful recruitment
• Simplicity of procedures critical to success in range of potential settings
• Simultaneous evaluation of different intervention domains in a factorial design is an efficient approach to improving evidence
• May not reach a definitive conclusion in all comparisons in one outbreak

Flexibility

• Adaptive design: Steering committee may add new comparisons (or remove comparisons) as evidence emerges
• Allows for one or more randomisations depending on what is available and suitable for an individual patient

Simplicity of procedures

• Proportionate to risk of study procedures vs severity of infection
• Streamlined with minimal data collection, recognising operational complexity of collection
Open-label, randomised controlled adaptive platform trial for patients with laboratory-confirmed acute Filovirus Disease

**Evaluation domain**
- Small molecule antiviral:
- Biological antiviral:
- Host-directed therapy:

**Initial products**
- E.g. Remdesivir
- Monoclonal(s)
- Low-dose corticosteroids

Primary outcome: 28-day mortality.
Enrolment criteria

• All laboratory confirmed patients
• Includes neonates born in ETU to laboratory confirmed cases
• Includes pregnant and breastfeeding women*
• Includes participants in vaccine and other trials

*Following expert teratology advice
Evolving standard of care

All patients will receive usual standard of care (including licensed therapies) where these exist or become available over time.
Proposed trial design

Preference for full factorial design with SOC comparator throughout

1. Will generate most easily interpreted evidence
2. Efficient evaluation of multiple interventions
3. Evaluation of additive or synergistic effects
4. Reduces bias that may be introduced by non-randomised treatments

However, this is dependent on acceptability of randomisation to a ‘no additional treatment’ arm
## Factorial design

<table>
<thead>
<tr>
<th>Randomisation 1</th>
<th>MARV</th>
<th>SUDV</th>
<th>EBOV and emerging strains</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Monoclonal antibody vs no additional treatment (1:1)</td>
<td>Monoclonal antibody vs no additional treatment (1:1)</td>
<td>Emergent therapy vs no additional treatment (1:1)</td>
</tr>
<tr>
<td>Randomisation 2</td>
<td></td>
<td></td>
<td>Antiviral vs no additional treatment (1:1)</td>
</tr>
<tr>
<td>Randomisation 3</td>
<td></td>
<td></td>
<td>Low-dose corticosteroids vs no additional treatment (1:1)</td>
</tr>
</tbody>
</table>

Selection of candidates based on WHO expert working group recommendations
Management of factorial design in statistical analysis

Theoretical impact of e.g. corticosteroids effect on other comparisons

<table>
<thead>
<tr>
<th>Reduce by 40%</th>
<th>Reduce by 20%</th>
<th>No effect</th>
<th>Increase by 20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>• All antiviral arms would be affected similarly so comparisons would not be biased</td>
<td></td>
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<tr>
<td>• Antiviral arms might require about 1/5 more patients</td>
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<tr>
<td>• Corticosteroids would from this point on become standard of care, any future consideration of antivirals would estimate their effects on a background of corticosteroid use.</td>
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<tr>
<td>• All antiviral arms would be affected similarly so comparisons would not be biased</td>
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<td></td>
</tr>
<tr>
<td>• Antiviral arms might require about 1/10 more patients</td>
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</tr>
<tr>
<td>• again, corticosteroids would from this point on become standard of care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• No impact on the antiviral comparisons</td>
<td></td>
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</tr>
<tr>
<td>• The event rate in the antiviral arms would be a bit higher (about 1/10 higher)</td>
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<tr>
<td>• The heterogeneity of prognosis between those given corticosteroids and those not would be slight in comparison with the substantial heterogeneity of prognosis between sicker and less sick patients.</td>
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</tr>
</tbody>
</table>
Alternative – a vs b vs ab design

• If randomisation to a standard of care arm alone is not accepted, an a vs b vs a+b comparison is considered to be the next best available approach for making inferences about the efficacy and safety of these drugs.

• As small molecule antivirals and monoclonal antibodies work by different mechanisms, this analysis strategy is appropriate because it is likely that if one therapeutic is effective then it will be effective even in the presence of the other.

Limitations
• Assumes the drugs are not harmful
• Inferences & regulatory conclusions more challenging – licensure of monotherapy
• Evidence for one drug may accrue faster than another
• If there is unavailability of one drug (or it is not suitable for a particular patient) the opportunity to test the other is lost
• If there are supply limitations, allocation decisions are challenging
Primary outcome

All-cause mortality at 28 days following randomisation

Discharge alive before the relevant time period (28 days after randomisation) will be assumed as absence of the event (unless there are additional data confirming otherwise)
Secondary outcome

• Time (days following randomization) to viral clearance

Other outcomes

• Viral load (measured by cycle threshold) on samples taken at Day 3, 5, 7 and 10

Safety assessments

• Suspected Serious Adverse Reactions (SSARs)
• Suspected Unexpected Serious Adverse Reactions (SUSARs)
• Infusion related reactions
• Pregnancy outcome
Sample size

- The larger $n$ the more accurate and informative, and the more potential treatments that can be assessed.

- In general, each comparison should be sufficiently large to provide good power (90% power at $2\alpha=0.01$) 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.

- Even limited numbers, perhaps from a single outbreak, might deliver clear results and change clinical practice:

- The Trial Steering Committee will monitor blinded event rates and adjust the target sample size as data accrue.
Capacity sharing

Movement to devolved operations:

Achieved through . . .

• Partnership in governance and operations structures
• Training programme
• Fellowships (where feasible) for national PIs
• Global collaborative network opportunities