Monitored Emergency Use of Unregistered Investigational Interventions (MEURI)

Operationalizing MEURI in Filovirus Outbreaks

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- 22 year old pregnant woman admitted with fever, diarrhea, vomiting, joint pain and abdominal pain
  → Optimized Supportive Care (oSOC)
  → Pathogen specific treatment?

No proven or approved therapeutics
In the absence of approved interventions, a randomized controlled trial must be prioritized.
Aug 1 MOH Declares Outbreak

Mangina ETU

3 Month Gap → MEURI

Oct 31 PALM RCT

Adapted from Kalenga, O. NEJM 2019
2023 SVD Epidemic - MEURI Timeline

- SUDV Outbreak Declared
- WHO Therapeutics Prioritization
- MoH Approval
- RCT Protocol Developed
- Entebbe Surge
- Mubende Surge

1.5 Month Gap → MEURI

https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON428
## MEURI Ethical Framework

<table>
<thead>
<tr>
<th>I. Justification</th>
<th>II. Ethical and regulatory oversight</th>
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</thead>
<tbody>
<tr>
<td>1. Public health emergency</td>
<td>6. Review and approval by authority and ethics committee</td>
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<tr>
<td>2. Absence of proven intervention</td>
<td>7. Minimization of risks</td>
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<td>3. Impossibility of initiating research immediately</td>
<td>8. Responsible transition</td>
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<td>4. Scientific support based on a favourable risk-benefit ratio</td>
<td>9. Fair access to scarce unproven interventions</td>
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<td>5. Effective use of resources</td>
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<table>
<thead>
<tr>
<th>III. Consent process</th>
<th>IV. Contribution to evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>10. Individual informed consent</td>
<td>12. Monitoring, collecting and sharing relevant data</td>
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<td>11. Community engagement</td>
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### Ethical considerations

**Emergency use of unproven clinical interventions outside clinical trials:**

- **Justification and Prioritization**
- **Regulatory and Ethical Oversight**
- **Minimizing Risk (Monitored Delivery + pSOC)**
- **Contribution to Evidence**
Pre-Outbreak – Accelerating MEURI Timeline

- Justification and prioritization of investigational interventions
  - This can happen in advance of the next outbreak and updated yearly by a qualified scientific committee

- Regulatory and ethical oversight
  - MEURI protocol can be pre-positioned, socialized, and approved prior to the outbreak

- Contribution to evidence
  - Data collection platforms + analysis plans can be established prior to the next outbreak
Operational Considerations - Minimizing Risk
(Monitored Delivery + oSOC)

- Strategy
- Space
- Staff
- Stuff
Community Engagement is Critical for Acceptance of Vaccines, Therapeutics and Research

- Early community engagement increases transparency and understanding about:
  - Regulatory and ethical review
  - Supportive care
  - Investigational interventions
  - Importance of timing

https://www.afro.who.int/fr/node/16724
### Timing and MEURI

<table>
<thead>
<tr>
<th>Duration prior to randomization</th>
<th>28-day mortality (deaths/total)</th>
<th>Mean CtNP</th>
<th>Mean creatinine (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1 day</td>
<td>0.19 (5/27)</td>
<td>26.93</td>
<td>0.91</td>
</tr>
<tr>
<td>2 days</td>
<td>0.33 (30/90)</td>
<td>25.61</td>
<td>1.62</td>
</tr>
<tr>
<td>3 days</td>
<td>0.28 (30/108)</td>
<td>24.73</td>
<td>1.54</td>
</tr>
<tr>
<td>4 days</td>
<td>0.44 (45/102)</td>
<td>23.51</td>
<td>2.16</td>
</tr>
<tr>
<td>5 days</td>
<td>0.47 (36/77)</td>
<td>22.21</td>
<td>2.43</td>
</tr>
<tr>
<td>6 days</td>
<td>0.54 (31/57)</td>
<td>22.34</td>
<td>2.92</td>
</tr>
<tr>
<td>7 days</td>
<td>0.47 (28/59)</td>
<td>23.25</td>
<td>3.16</td>
</tr>
<tr>
<td>8 days</td>
<td>0.62 (21/34)</td>
<td>23.79</td>
<td>3.89</td>
</tr>
<tr>
<td>9 days</td>
<td>0.58 (22/38)</td>
<td>23.47</td>
<td>3.91</td>
</tr>
<tr>
<td>10 days</td>
<td>0.64 (14/22)</td>
<td>23.68</td>
<td>4.89</td>
</tr>
<tr>
<td>&gt; 10 days</td>
<td>0.47 (24/51)</td>
<td>25.33</td>
<td>4.54</td>
</tr>
</tbody>
</table>

- Patients enrolled a mean 5.5 days from symptom onset
  - → highest viral load
  - → organ failure
- Filovirus-specific therapy cannot be uncoupled from optimized supportive care (oSOC)
- We need to put providers and patients in a position to be successful

Adapted from Mulangu, S. et al. NEJM 2019
Treatment Unit Must Facilitate Monitoring and Delivery of Care

- MEURI requires close contact between patients and providers
  - Informed consent process
  - Close monitoring of patients before, during, and after intervention
  - oSOC
Experienced STAFF

- Outcome is closely linked with early diagnosis + oSOC + Effective pathogen-specific treatment
- Experienced providers
  - Laboratory
  - oSOC
  - Informed consent
  - MEURI
- Coordination to ensure community engagement, diagnostics, logistics support for monitored investigational intervention delivery
Similar Logistics Support Required for oSOC, MEURI, and RCT

- Infrastructure
  - Electricity
  - Oxygen
  - Equipment (oxygen saturation monitors, blood pressure cuffs, monitors, infusion pumps etc.)

- Laboratory support
  - Rapid diagnostics - delays can push patients outside of therapeutic windows
  - Clinical chemistries and hematology

- Medications for oSOC
  - IV fluids, electrolytes, etc.

- Streamlined therapeutic delivery (kits)
“Stephanie”

- Sudan virus disease complicated by
  - Miscarriage
  - Acute renal failure
  - Hypoglycemia
  - Severe hepatitis
  - Shock
  - Hemorrhage
- Received oSOC including management of miscarriage
- Received MEURI intervention (?Efficacy)
- Survived
Data Sharing

- A key requirement of MEURI is that “the results are documented and shared in a timely manner with the wider medical and scientific community”
  - To inform clinical trials
  - To advance how we care for patients – a key knowledge gap

- Failure to analyze and share data represents a missed opportunity to advance our ability to care for patients
Key Messages

- MEURI provides a framework for use of investigational interventions during the gap between outbreak onset and RCT initiation

- Implementation requires
  - Pre-approved MEURI framework
  - Treatment centers that facilitate rapid diagnostics, optimized supportive care, monitored investigational intervention delivery
  - Experienced personnel (coordination, informed consent, oSOC, MEURI)

- MEURI can provide critical information about operationalizing therapeutics and serve as an “on-ramp” for the RCT
- Epidemics are global problems – data, like diagnostics, vaccines, and therapeutics must be shared rapidly and widely
Thank You

• To the patients who have trusted us and taught how to prepare, respond and recover

**Uganda**
- Dr. Henry Bosa
- Dr. Moha Lamord
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- Uganda HCWs
- Dr. Muzafalu
- Dr. Boris
- Dr. Amanda
- Dr. Romeo
- Many others

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- Dr. Shevin Jacob
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