WHO Ad Hoc Consultation: —Therapeutics to address the Monkeypox Outbreak—

Design options for the evaluation of efficacy: ...advantages and disadvantages...

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WHO R&D Working Group
Learnings from: Therapeutics for Ebola Virus Disease (EVD)

• The 2014-’15 major outbreak of EVD in West Africa ⇒ ‘urgent’ need for more effective approaches, both for prevention of spread and for treatment

• In treatment settings, 28-day mortality appeared to be substantially impacted by ‘optimized Standard of Care’ (e.g., aggressive IV fluid resuscitation, hemodynamic monitoring & support, point-of-care diagnostic modalities, other aspects of critical care medicine)

• Considerable interest in experimental interventions (e.g., monoclonal antibodies & antiviral drugs)

• Debate: *Is randomization ethical in a public health emergency?*
“Medical interventions must be evaluated in a manner that is ethically acceptable, efficient, and reliable.

Ethical considerations relate to safeguarding the interests of study participants, and to achieving timely and reliable insights about interventions to enhance the health of the public.

While we strive to achieve efficiency by reducing financial costs, number of participants, burdens on medical personnel and study duration, these efforts should not lead to diminished reliability;

The goal of clinical research is not simply to provide those pursuing safe and effective interventions a ‘choice’, but rather an ‘informed choice’.”

Therapeutics for Ebola Virus Disease (EVD)

“Randomized trials are the preferable approach, and unless there are compelling reasons not to do so, every effort should be made to implement randomized trial designs.”

NAM (2017); WHO R&D Working Group (2018)

“PREVAIL II”

\[
\begin{align*}
\text{oSOC + ZMapp (Monoclonal Antibody)} & < \text{Optimized Standard of Care (oSOC)} \\
\text{Primary Endpoint: 28-day Mortality} & \\
\text{Sample Size: Beginning in March 2015, 200 participants to be enrolled from the outbreak in Liberia, Guinea, & Sierra Leone}
\end{align*}
\]
## “PREVAIL II”
Therapeutics for Ebola Virus Disease

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Deaths</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ZMapp</td>
<td>36</td>
<td>8</td>
<td>(22%)</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>35</td>
<td>13</td>
<td>(37%)</td>
<td></td>
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</tbody>
</table>

\(2p = 0.18\)

(Intended **100/arm** not reached, when outbreak waned in late 2015 in Liberia, Guinea, and Sierra Leone)

NIH October 13, 2016 Press Release

“Study finds Ebola treatment ZMapp holds promise, although results not definitive”
At the end of an outbreak, the release of promising but inconclusive results from partially completed trials may support the belief that confirmatory trials comparing the investigational agents against the previously accepted placebo or standard-of-care comparator could no longer be conducted.

Reference: “Accumulating evidence from randomized clinical trials across outbreaks”

*N Engl J Med* 382; 14: 1366-1369, 2020

(WHO R & D Working Group)

Therapeutics for Ebola Virus Disease (EVD)

_Palm Trial Design for ‘18-’19 EVD Outbreak in DRC_

- o SOC
- o SOC + ZMapp
- o SOC + Exp’l Treatment

(‘o SOC’ denotes ‘Optimized Standard-of-Care’)

(Aggressive IV fluid resuscitation, hemodynamic monitoring and support, point-of-care diagnostic modalities, and other aspects of critical care medicine)
## WHO MEURI and PALM RCT
### EVD Case Fatality Rate

<table>
<thead>
<tr>
<th>Intervention Group</th>
<th>MEURI 20 Sept 2019</th>
<th>PALM RCT 9 Aug 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Died/N   CFR%</td>
<td>Died/N   CFR%</td>
</tr>
<tr>
<td>ZMapp</td>
<td>24/51   47%</td>
<td>63/129  49%</td>
</tr>
<tr>
<td>Remdesivir</td>
<td>113/221 51%</td>
<td>70/131  53%</td>
</tr>
<tr>
<td>mAb114</td>
<td>81/252  32%</td>
<td>43/127  34%</td>
</tr>
<tr>
<td>REGN-EB3</td>
<td>73/232  31%</td>
<td>32/112  29%</td>
</tr>
</tbody>
</table>
Therapeutics for Ebola Virus Disease (EVD)

Trial Design in ‘18-’19 EVD Outbreak in DRC

- o SOC
- o SOC + ZMapp
- o SOC + Exp’l Treatment

Some additional learnings:

✓ oSOC Control: proper & more informative
- Still lacking direct evidence about effects of ZMAPP & Remdesivir
- If ZMAPP mortality were 40% (not 50%) ⇒ REGN-EB3 & mAb114 results unreliable

‘o SOC’ denotes ‘Optimized Standard-of-Care’

(Aggressive IV fluid resuscitation, hemodynamic monitoring and support, point-of-care diagnostic modalities, and other aspects of critical care medicine)
“A new clinical trial paradigm is needed to enable reliable evaluations of interventions of vaccines and treatments for outbreak pathogens. We advocate the use of a “Master Protocol” in this setting.

To avoid premature release of data, ‘Master Protocols’ specify that efficacy data from a trial not yet been completed due to insufficient enrollment, should not be released.

After an outbreak has ended at a given site, the study would be paused... the investigators would remain blinded to any results of analyses; the study data would only be released if the trial were either stopped on the basis of a recommendation from the monitoring committee or had reached its targeted number of endpoints or amount of subject follow-up.”
Designs of Monkeypox Therapeutics Trials

Even in Public Health Emergencies, “Randomized trials are the preferable approach, and unless there are compelling reasons not to do so, every effort should be made to implement randomized trial designs.”

NAM (2017); WHO R&D Working Group (2018)

A Master Protocol...

Primary Endpoint:
Duration/Severity of Symptoms
Potential Design of Monkeypox Therapeutics Trials

**Primary Efficacy Endpoint**
Duration and Severity of Symptoms

**Secondary Endpoints**
Hospitalization-free survival
Overall Survival
Designs for Evaluating Monkeypox Therapeutics

Experimental Monkeypox Therapeutic (EXP) vs. Placebo

- 1º Endpoint: Duration/Severity of Symptoms

Tecovirimat or Brincidofovir + EXP vs. Tecovirimat or Brincidofovir + Placebo

- 1º Endpoint: Duration/Severity of Symptoms

Experimental Monkeypox Therapeutic (EXP) vs. Active Comparator (AC)

- 1º Endpoint: Duration/Severity of Symptoms

- Efficient design
- Yields results that are: Interpretable & Reliable
- Could use factorial design
- If EXP has complementary MOA
- Yields results that are: Interpretable & Reliable
- Lack of non-inferiority margin \[ \Rightarrow \text{need to establish superiority} \]
Some Principal Issues in Pursuit of Monkeypox Interventions

✓ Safe and effective interventions are needed in a timely manner to more effectively address the outbreaks on an international scale

✓ **Randomized clinical trials** provide reliable & interpretable results regarding whether Monkeypox interventions are safe & provide worthwhile efficacy
  
  • **Clinical endpoints** provide increased reliability
  
  • Assessments of safety are of key importance
  
  • RCTs using **Placebo Controls** have enhanced efficiency & interpretability
  
  • When randomization against Placebo Controls is not possible, use of **Active Controls** might enable a reliable evaluation of efficacy and safety

✓ Outbreaks of limited size & duration, in diverse clinical settings ⇒ creative approaches
  
  • **Master Protocols** enable accumulating evidence from RCTs across outbreaks