“Mock IRB”: Ebola treatment trial

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The views expressed are my own and do not represent the views of the NIH, PHS or DHHS
1) Appreciate the challenge of evaluating research protocols
2) Appreciate the challenge of coming to agreement in a diverse group with limited time and information
Ebola virus disease (EVD) (Feldmann et al 2011)

... before 2013:

- Total of ~2,400 infections
- Mortality of up to 90%
- Targeted treatments/vaccines in early development
2013-2016 EVD epidemic

(WHO 2016)

- >28,000 infected
- ~11,300 deaths
- West Africa
Conditions for clinical trials

- Ebola virus disease (EVD)
  - Very limited prior knowledge
  - Unprecedented epidemic
- Highly unproven interventions
- Context
  - Fear & distrust
  - Humanitarian emergency
  - Multitude of national & international actors
Key challenges

• Ebola virus disease (EVD)
  – Very limited prior knowledge
  – Unprecedented outbreak

• Highly unproven interventions

• Context
  – Fear & distrust
  – Humanitarian emergency
  – Multitude of national/international actors

Urgency

Uncertainty

Feasibility

Ethical ambiguity & disagreement
## EVD treatment trials
(Rojek, Horby & Dunning 2017)

<table>
<thead>
<tr>
<th>Investigational agent</th>
<th>Design</th>
<th>Results (as of 11/2016)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZMapp</td>
<td>iRCT with adaptive design</td>
<td>No statistically conclusive survival benefit</td>
</tr>
<tr>
<td>TKM-130803</td>
<td>Single arm (multi-stage)</td>
<td>No overall survival benefit</td>
</tr>
<tr>
<td>Favipiravir</td>
<td>Single arm</td>
<td>No overall survival benefit</td>
</tr>
<tr>
<td>Brincidofovir</td>
<td>Single arm (multi-stage)</td>
<td>Suspended</td>
</tr>
<tr>
<td>Azithromycin, sunitinib, erlonitib, atorvastatin, irbesartan</td>
<td>iRCT with adaptive design</td>
<td>Not yet open</td>
</tr>
<tr>
<td>Interferon β</td>
<td>Single arm</td>
<td>Completed</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>iRCT</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Convalescent plasma</td>
<td>Single arm</td>
<td>No overall survival benefit</td>
</tr>
</tbody>
</table>
# EVD vaccine trials

(Rojek, Horby & Dunning 2017)

<table>
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<tr>
<th>Investigational agent</th>
<th>Design</th>
<th>Results (as of 11/2016)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rVSV ZEBOV</td>
<td>cRCT w/ ring vaccination</td>
<td>Substantial protection</td>
</tr>
<tr>
<td></td>
<td>Single arm</td>
<td>Completed</td>
</tr>
<tr>
<td>VSV-ZEBOV or Ad26.ZEBOV, MVA-BN-Filo boost</td>
<td>RCT</td>
<td>Not yet open for recruitment</td>
</tr>
<tr>
<td>SVG-ZEBOV or ChAd3-EBO Z</td>
<td>RCT</td>
<td>Ongoing/not recruiting</td>
</tr>
<tr>
<td>Ad5-EBOV</td>
<td>RCT</td>
<td>Completed</td>
</tr>
<tr>
<td>Ad26-ZEBOV, MVA-BN-Filo boost</td>
<td>Single arm &gt; RCT</td>
<td>Recruiting</td>
</tr>
</tbody>
</table>
2018 EVD epidemic

(WHO 2019)

- >3,000 infected
- >2,100 deaths
- Democratic Republic of Congo (DRC)
Ebola MCM RCT or PALM study

A Multicenter, Multi-Outbreak, Randomized, Controlled Safety and Efficacy Study of Investigational Therapeutics for the Treatment of Patients with EVD
Primary objective

• To compare the mortality at 28 days in patients with EVD who receive different investigational therapeutics relative to the control arm
Inclusion criteria

- Males and females of any age with acute Ebola Virus infection within 3 days prior to enrollment and symptoms of any duration
- Agree to use contraception as needed
- Agree not to enroll in other study
- Provide informed consent or able to obtain surrogate consent
Study design

Randomization 1:1:1:1

ELIGIBLE SUBJECTS

CONTROL ARM

INTERIM ANALYSIS

Standard of Care
+ zMAPP™

Standard of Care
+ Remdesivir

Standard of Care
+ MAb114

Standard of Care
+ REGN-EB3
“It is assumed that this study will continue across more than one outbreak and in several countries. To allow for country specific preferences about what constitutes an ethical and scientifically acceptable control arm, there are two design options … the Democratic Republic of Congo … has chosen Option 1”
Alternative study design

Randomization 1:1:1:1:1

ELIGIBLE SUBJECTS

Standard of Care

Standard of Care + Remdesivir

Standard of Care + MAb114

Standard of Care + REGN-EB3

Standard of Care + zMAPP™

CONTROL ARM

INTERIM ANALYSIS
1) Would you approve the study as described?
2) If not… What further information do you need? What changes would you require?
What makes research ethical?

(Emanuel, Wendler & Grady 2000)

• At least (in chronological order):

1) Socially valuable research question
2) Scientific validity
3) Fair subject selection
4) Acceptable risk-benefit ratio
5) Informed consent
And more…

(Emmanuel, Wendler & Grady 2000)

• Engage community
• Protect confidentiality
• Share results
• Respect the right to withdraw
• Provide additional clinical care
• …