Implementing MEURI to accelerate access and collection of evidence

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Objectives

- **Why** a MEURI protocol?
- **What** is a MEURI protocol
- **How** to use a MEURI protocol?
- **Examples** of successful implementation
Why?

We all aim to save lives during filovirus outbreaks using the most effective and safe tools available.

What tools do we have available for treatment?

Safe and community centered treatment areas

mAb114 and REGN-EB3 proven for Ebola virus disease (Zaire ebolavirus).
But…

We don’t have proven therapeutics yet for Sudan virus disease or Marburg virus disease, and **mortality is high**.

For EVD, we have proven treatments but if given late, mortality still remains too high.

More clinical research is needed. Standardized clinical data collection is priority to describe disease and conduct clinical trials.

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What?

• **MEURI** is an ethical framework that aims to give access to unproven clinical interventions (i.e. therapeutics) outside of clinical trials during international public health emergencies.

• **MEURI** replaces older terms such as compassionate use calls for strict oversight and accountability for the use of unproven interventions.

• **MEURI** is commonly referred to as expanded access or emergency use protocols.

• **Unproven interventions** can also refer to pre-authorized interventions, investigation products, off-label use of intervention, or interventions with only animal or laboratory data.
What?

MEURI framework aims to mitigate risks/harms:

• **uncontrolled use** of unsafe or ineffective interventions,

• **undue interference** with research,

• **unnecessary stockpiling** and creation of shortages of proven interventions for other diseases or conditions.
**When?**

**We consider MEURI when...**

- **International public health emergency**: member state can also apply to national health emergency (WHO IHR)

- **Absence of proven interventions** determined by a qualified scientific committee that informs national regulatory agency (WHO)

- **Impossibility of initiating research immediately**: determined by national regulatory or relevant authority with support of qualified scientific committee.

- **Scientific support for selection of interventions** based on **favourable risk–benefit analysis** (at minimum animal or laboratory data) by qualified scientific committee (WHO)

- **Effective use of resources**. Relevant authority responsible for response to emergency ensures that emergency use of unproven interventions does **NOT delay trials** nor **divert resources** from effective clinical care or public health measures.
How?

1. **A protocol.** Manufacturers may have expanded access protocol that are ready for use; if not, can use WHO MEURI framework to develop protocol.

2. **Local ethical committee** review and approval of protocol; including **informed consent**, plans to **minimize risk** and ensure **fair access** to scarce resource.

3. **National regulatory authorities** review and approval for importation of novel investigational products. Plans to minimize risk, including early termination criteria.

4. **Community engagement.** Refrain from overstating the evidence and potential benefits, understating the risks and uncertainties, and exploiting hope of populations including political or economic gain.

5. **Responsible transition.** National authorities have plan on how to transition care for research or normal care at end of the emergency.
How?

6 Data monitoring. Set up data management system to collect relevant clinical data, outcomes and safety which is then analysed and reported.

Data monitoring committee: Assemble independent experts to monitor safety, pharmacovigilance, communicate with other DSMB when needed.

Dissemination: results communicated to scientific community in timely manner.

7 Logistics: supply of required medicines and biomedical equipment available (biochemistry tests, infusion sets, oxygen) and reach last mile.

Health and care workers: trained on emergency protocols, including treatment of adverse events, data collection and optimized supportive care.

WHO Global clinical platform has standardized clinical case records and provides data management support for MEURI and clinical characterization, including convening DMC. Global Clinical Platform (who.int)
MEURI framework in action
**Success**

EVD outbreak, N Kivu DRC 2018-2019

- **809 patients** enrolled in MEURI at **7 treatment centres**.

- **3 months** between onset of MEURI protocol and Pamoja Tulinde Maisha (PALM [“Together Save Lives” in the Kiswahili language]) randomized clinical trial (INRB and NIH sponsor) that enrolled **681 patients**

Success due to **collaboration** between sponsors INRB and NIH, NGO partners (ALIMA, MSF, SP, IMC), WHO & EDCARN/GOARN with common vision, shared logistics and skilled workforce.

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**Results:** Increased probability of survival; when Ct-NP > 22, shorter time between illness onset and treatment, and being vaccinated and treated, and treated with mAb114 or REGN-EB3 **(manuscript under review)**.
Successes

More recent outbreaks, that have used MEURI framework

- **SUDV, Uganda (2022)** 2 investigational products used in 21 high risk and severe patients (manuscript under preparation). Collaboration between MOH, IDI, WHO, NGO.

- **MVD Equatorial Guinea (2023)** used 1 off-label (manuscripts under review) in five patients. Collaboration between MOH, WHO, GOARN partners
Conclusions

• MEURI is an **ethical framework** to be used when clinical trials are impossible and scientifically sound unproven treatment would like to used during international public health emergencies for high mortality disease, without diverting resources.

• MEURI framework requires **strict regulatory and ethical monitoring** with commitment to report results to scientific community in timely manner.

• **Be ready** with pre-designated treatment centres, access to optimized supportive care, logistics/supply chain and trained health and care workforce.
Thank you

Contact Dr Janet Diaz for any questions
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Monitored Emergency Use of Unregistered and Investigational Interventions – MEURI and RCT: overview of preparedness activities

* 10-14 May 2018: WHO approaches Sponsors of investigational therapeutics to access data for scientific assessment under WHO ethical framework
13 May 2018: WHO forms expert working group to prioritize candidate investigational Ebola therapeutics for MEURI.

** The experts discussed the available data for Favipiravir and noted considerable uncertainty as to whether it provides benefits for patients with EVD. The experts also noted that it is important to conduct appropriate clinical trials to establish the dosing selection and whether Favipiravir provides benefits to patients or not.
MEURI for therapeutics in the treatment of EVD: implementation of response activities
### WHO MEURI EVD Case Fatality Rate

<table>
<thead>
<tr>
<th>Group</th>
<th>Outcome/ Discharged</th>
<th>Outcome/ Ongoing</th>
<th>Outcome / Died</th>
<th>Total</th>
<th>CFR (%)</th>
<th>CFR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mAb114</td>
<td>167</td>
<td>4</td>
<td>81</td>
<td>252</td>
<td>32.1</td>
<td>(26.7, 38.1)</td>
</tr>
<tr>
<td>REGN-EB3</td>
<td>158</td>
<td>1</td>
<td>73</td>
<td>232</td>
<td>31.5</td>
<td>(25.8, 37.7)</td>
</tr>
<tr>
<td>Remdesivir</td>
<td>108</td>
<td>0</td>
<td>113</td>
<td>221</td>
<td>51.1</td>
<td>(44.6, 57.6)</td>
</tr>
<tr>
<td>ZMapp</td>
<td>27</td>
<td>0</td>
<td>24</td>
<td>51</td>
<td>47.1</td>
<td>(34.1, 60.5)</td>
</tr>
<tr>
<td>OVERALL</td>
<td>460</td>
<td>5</td>
<td>291</td>
<td>756</td>
<td>38.5</td>
<td>(35.1, 42.0)</td>
</tr>
</tbody>
</table>

- The following factors were associated with increased probability of survival
  - **lower viral loads** ~CFR 15% when Ct-NP > 22, treated with mAb114 or REGN-EB3
  - **shorter time between illness onset/initiation of treatment** ~CFR 24% when ≤ 5 days, treated with mAb114 or REGN-EB3
  - **and being vaccinated** ~CFR 7% when vaccinated, treated with mAb114 and REGN-EB3

*Overall CFR 66% (1963/2980 confirmed cases) - 10 August 2018 to 10 September 2019*