Scientific and Ethical Issues in Covid-19 Clinical Trials

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GCP Challenges : Covid-19

• Benefits of investigational / repurposed therapy unknown/unsupported vs. Risks unknown / uncertain
• Interest of science / society overriding interest of individual participant
• Available non-clinical & clinical information on therapy inadequate
• Clinical trials – challenge of science and ethics
• Sponsor and investigator - training and experience in pandemic /trials
Bias in COVID-19 RCTs (BMJ 31 Jul20)

- Randomisation process
- Departures from the intended intervention
- Missing outcome data
- Measurement of the outcome
- Selection of the reported results
- 21 of 23 RCTs high or high risk of bias in the domains of randomisation or deviation from the intended interventions.
Disease Severity: WHO

Non-severe:
- Absence of signs of severe or critical disease

Severe:
- SpO₂ < 90% on room air
- Respiratory rate > 30 in adults
- Raised respiratory rate in children
- Signs of severe respiratory distress

Critical:
- Requires life sustaining treatment
- Acute respiratory distress syndrome
- Sepsis
- Septic shock
Corticosteroids: WHO Recommendation (BMJ 4 Sep 20)

<table>
<thead>
<tr>
<th>Event</th>
<th>Events per 1000 people</th>
<th>Evidence quality</th>
<th>Evidence quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality with critical illness</td>
<td>415</td>
<td>★★★★</td>
<td>Moderate</td>
</tr>
<tr>
<td>Mortality with severe illness</td>
<td>334</td>
<td>★★★★</td>
<td>Moderate</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>48</td>
<td>★★★★</td>
<td>Low</td>
</tr>
<tr>
<td>Superinfections</td>
<td>186</td>
<td>★★★★</td>
<td>Low</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>286</td>
<td>★★★★</td>
<td>Moderate</td>
</tr>
<tr>
<td>Neuromuscular weakness</td>
<td>69</td>
<td>★★★★</td>
<td>Low</td>
</tr>
<tr>
<td>Neuropsychiatric effects</td>
<td>35</td>
<td>★★★★</td>
<td>Low</td>
</tr>
</tbody>
</table>

- **Critically ill**
- **Severely ill**
# Clinical Trials on COVID-19 - Examples

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Remdesivir</th>
<th>Favipiravir</th>
<th>Tocilizumab</th>
<th>Itolizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>• 1063</td>
<td>• 150</td>
<td>• 243</td>
<td>• 30</td>
</tr>
<tr>
<td></td>
<td>• Severe 89%</td>
<td>• Mild to moderate</td>
<td>• Severe</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td></td>
<td>• Non-severe 11%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Design</td>
<td>Double blind</td>
<td>Open</td>
<td>Double blind</td>
<td>Open</td>
</tr>
<tr>
<td>RCT</td>
<td>Placebo</td>
<td>Standard care</td>
<td>Placebo</td>
<td>Standard care</td>
</tr>
<tr>
<td>Efficacy</td>
<td>• Shorter time to recovery</td>
<td>• Viral clearance faster</td>
<td>• Not effective for preventing intubation or death</td>
<td>• Significant Mortality benefit</td>
</tr>
<tr>
<td>end points</td>
<td>• No effect on mortality</td>
<td>• Clinical cure higher %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Published</td>
<td>• Yes</td>
<td>• No</td>
<td>• Yes</td>
<td>• No</td>
</tr>
</tbody>
</table>
Covid-19 Trials: Participants

- **Trial Patients**
  - Vulnerability vs Voluntariness
  - Recruitment
  - Informed Consent process
    - Timing of consent
    - Time for explanation
    - Time for participant
    - Communication
    - Non-availability of LAR
    - Documentation – AV recording

- **Vaccine Volunteers**
  - Vulnerability vs Voluntariness
  - Recruitment
    - Hospital staff
    - Media / social media advertisement
  - Concerns about visiting hospitals
  - Informed Consent process
RECOVERY Trial Informed Consent Process (Oxford)

• For patients who lacked capacity to consent due to severe disease requiring ventilation, and for whom an LAR was not available, randomization could be done with consent provided by a treating physician, who was independent of the investigator conducting the clinical trial, and who would act as the legally designated representative.

• Consent would be obtained from the patient’s LAR or directly from the patient if they recover promptly at the earliest opportunity.
## Ethical Responsibilities for Vulnerable Participants (ICMR 2017 & 2020)

<table>
<thead>
<tr>
<th>Category</th>
<th>Responsibilities</th>
</tr>
</thead>
</table>
| **Sponsor**           | • Justification for inclusion  
                        | • Provisions for protecting safety  
                        | • Enable monitoring and quality assurance                                      |
| **Investigator**      | • Recognition of vulnerability  
                        | • Ensure additional safeguards for protection  
                        | • Empower the participant to make decisions  
                        | • Respect dissent from the participant  
                        | • Avoid exploitation/retaliation/reward/credits  
                        | • Well-documented informed consent process                                      |
| **Ethics Committee**  | • Review of justification for inclusion  
                        | • Careful assessment risk- benefit, and risk minimization  
                        | • More frequent review and monitoring                                           |