Strategies to support the COVID-19 response in LMICs

A virtual seminar series
Randomized Controlled Clinical Trial Implementation Challenges
Lessons from the Adaptive COVID-19 Therapeutics Trial (ACTT)

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Objectives

• Adaptive Clinical Trials

• Briefly outline the SOLIDARITY and ACTT clinical trials

• What resources are useful when conducting a clinical trial

• What are the essential elements of infrastructure required

• What are some of the challenges of recruitment encountered
## COVID-19: Global Snapshot

### Situation in numbers (by WHO Region)

<table>
<thead>
<tr>
<th>Region</th>
<th>New cases (new)</th>
<th>Deaths (new)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Globally</strong></td>
<td>7,690,708</td>
<td>4,276,300</td>
</tr>
<tr>
<td><strong>Africa</strong></td>
<td>1,675,666</td>
<td>3,998</td>
</tr>
<tr>
<td><strong>Americas</strong></td>
<td>3,711,768</td>
<td>199,252</td>
</tr>
<tr>
<td><strong>Eastern Mediterranean</strong></td>
<td>758,551</td>
<td>16,640</td>
</tr>
<tr>
<td><strong>Europe</strong></td>
<td>2,398,779</td>
<td>188,001</td>
</tr>
<tr>
<td><strong>South-East Asia</strong></td>
<td>455,439</td>
<td>12,526</td>
</tr>
<tr>
<td><strong>Western Pacific</strong></td>
<td>197,864</td>
<td>7,200</td>
</tr>
</tbody>
</table>

**Source:** WHO Situation Report – 146; Data are as of 14JUN2020; 10:00 CSET
Adaptive Clinical Trials

- Defining characteristic: results from INTERIM data analyses used to modify ongoing trial
  - Does NOT undermine study integrity (data & processes not compromised) or validity (assurance that trial answers original research questions)

- Mid-course adaptations allows for more efficient trials
  - Stop early with futility outcome
  - Earlier indication of efficacy
  - Earlier conclusions reached

SOLIDARITY Trial

• Multinational Phase III-IV trial of potential “repurposed” or “repositioned” treatments for COVID-19

• Organized by WHO and partners and announced on 18 Mar 2020

• Design: compare 4 untested treatments for hospitalized persons with severe COVID-19 illness

  • **Remdesivir**
    • Lopinavir/ritonavir
    • Lopinavir/ritonavir combined with interferon-beta
    • Hydroxychloroquine or chloroquine
    • The Americas

• Includes ~100 sites in Africa, Asia, Europe and The Americas
SOLIDARITY TRIAL

• Study Design
  • Adaptive
    • Rapid assessment of existing antiviral and anti-inflammatory agents not previously evaluated for COVID-19
    • Use agents approved for other purposes or have almost completed regulatory pathway for another purpose
  • NOT double blind

• Key Clinical Questions to answer regarding any of the trial drugs
  • Reduce mortality?
  • Reduce time in hospital?
  • Reduce time on mechanical ventilation or in intensive care?
  • Minimize illness in HCP and those at high risk of severe illness?
Standardized Approach with WHO Support

• Solidarity Trial WHO Website
  • Ethical and regulatory approvals of the WHO core protocol
  • Consent and enrollment forms
  • Training hospital physicians in the web-based randomization and data management system

• Shipping the trial drugs requested by countries

• Identification of hospitals participating in the trial (As of 3JUN2020)
  • 35 countries participating (>100 interested in joining)
  • >400 hospitals
  • >3,500 patients recruited

• Safety Monitoring Board
  • Examine interim results for Safety and Effectiveness
  • Alter the trial design or recommend an effective therapy
A Multicenter, Adaptive, Randomized Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults

Short Name: Adaptive COVID-19 Treatment Trial (ACTT)
ACTT

- Adaptive, double blind, placebo-controlled
- Hospitalized adults with COVID-19
- Multicenter: ~70 sites globally
  - Asia
  - Europe
  - North America
- Primary outcome: time to recovery

- Interim monitoring
  - Introduce new arms
  - Early stopping for:
    - Futility
    - Efficacy
    - Safety

- Examine repurposed drugs in an effort to find a treatment
- Many sites to allow rapid subject accrual
ACTT-1: Remdesivir (RDV) vs Placebo

- RDV: prodrug of broad spectrum nucleoside analog
  - MOA not verified but likely inhibits RNA-dependent RNA polymerase
- Rhesus macaques with SARS-CoV-2: RDV effective
**ORDINAL SCALE**

- Death;
- Hospitalized, on invasive mechanical ventilation or ECMO;
- Hospitalized, on non-invasive ventilation or high flow oxygen devices;
- Hospitalized, requiring supplemental oxygen;
- Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);
- Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;
  - This would include those kept in hospital for quarantine/infection control, awaiting bed in rehabilitation facility or homecare, etc.
- Not hospitalized, limitation on activities and/or requiring home oxygen;
- Not hospitalized, no limitations on activities

### NATIONAL EARLY WARNING SCORE (NEWS)

<table>
<thead>
<tr>
<th>PHYSIOLOGICAL PARAMETERS</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiration Rate</td>
<td>≤8</td>
<td>9 - 11</td>
<td>12 - 20</td>
<td>21 - 24</td>
<td>≥25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen Saturations</td>
<td>≤91</td>
<td>92 - 93</td>
<td>94 - 95</td>
<td>≥96</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Supplemental Oxygen</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td>≤35.0</td>
<td>35.1 - 36.0</td>
<td>36.1 - 38.0</td>
<td>38.1 - 39.0</td>
<td>≥39.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>≤90</td>
<td>91 - 100</td>
<td>101 - 110</td>
<td>111 - 219</td>
<td>≥220</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Rate</td>
<td>≤40</td>
<td>41 - 50</td>
<td>51 - 90</td>
<td>91 - 110</td>
<td>111 - 130</td>
<td>≥131</td>
<td></td>
</tr>
<tr>
<td>Level of Consciousness</td>
<td></td>
<td></td>
<td></td>
<td>A</td>
<td></td>
<td>V, P, or U</td>
<td></td>
</tr>
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</table>
INCLUSION CRITERIA

1. Admitted to a hospital with symptoms suggestive of COVID-19 infection.
2. Subject (or legally authorized representative) provides written informed consent prior to initiation of any study procedures.
3. Understands and agrees to comply with planned study procedures.
4. Agrees to the collection of oropharyngeal (OP) swabs.
5. Male or non-pregnant female adult ≥18 years of age at time of enrollment.
6. Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other commercial or public health assay in any specimen collected < 72 hours prior to randomization.
   
   Note – 72 hours is not necessarily time from initial diagnosis. If ≥72 hours since positive PCR, the PCR may be repeated to assess eligibility.

7. Illness of any duration, and at least one of the following:
   • Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR
   • Clinical assessment (evidence of rales/crackles on exam) AND SpO2 ≤ 94% on room air, OR
   • Requiring supplemental oxygen, OR
   • Requiring mechanical ventilation.

8. Women of childbearing potential must agree to either abstinence or use at least one primary form of contraception not including hormonal contraception from the time of screening through Day 29.

9. Agrees to not participate in another clinical trial for the treatment of COVID-19 or SARS-CoV-2 through Day 29.

EXCLUSION CRITERIA

1. ALT/AST > 5 times the upper limit of normal.
2. Estimated glomerular filtration rate (eGFR) < 50 or requiring dialysis.
3. Pregnancy or breast feeding.
4. Anticipated transfer to another hospital which is not a study site within 72 hours.
5. Allergy to any study medication.
Conduct of ACTT-1

**Adaptive Trial:** Defining characteristic: results from INTERIM data analyses used to modify ongoing trial

- >70 sites randomized 1063 patients in 2 months!
- DSMB recommended unblinding due to shortened time to recovery in RDV group
ACTT-1 Preliminary Findings

REF: Beigel JH et al. NEJM, 22 May 2020
ACTT-1 Challenges

- Rapidly standing up the research team
  - Investigators
  - Coordinators
  - Research Nurses
  - Data entry personnel
  - Regulatory expert
  - Laboratorians to process samples
  - Budget personnel
  - Operating space & equipment

- Repeated study pauses for protocol updates (3 in 2 months)

- Conducting an RCT in “bio-mode”
  - Training staff
  - Consenting/enrollment
    - In-room
    - Legally authorized representative

- PPE shortages at some sites
ACTT-2: RDV + Baricitinib/Placebo

**Stage I** (Early Infection)
- Viral response phase
- Mild constitutional symptoms
  - Fever >99.6°F
  - Dry cough, diarrhea, headache
- Clinical Symptoms
  - Lymphopenia, increased prothrombin time, increased D-Dimer and LDH (mild)
  - Clinical Signs
  - Potential Therapies
  - Remdesivir, chloroquine, hydroxychloroquine, convalescent plasma transfusions
  - Reduce Immunosuppression

**Stage II** (Pulmonary Phase)
- Shortness of Breath
- Hypoxia (PaO2/FiO2<300mmHg)
- ARDS, SIRS/Shock, Cardiac Failure
- Host inflammatory response phase
  - Elevated inflammatory markers
    - CRP, LDH, IL-6, D-dimer, ferritin
    - Troponin, NT-proBNP elevation
  - Abnormal chest imaging
    - Transaminases
    - Low-normal procalcitonin

**Stage III** (Hyperinflammation Phase)
- Siddikat and Mehra. J Heart Lung Transplant. DOI: 10.1016/j.healun.2020.03.012
Baracitinib

- Hypothesis: may damp down cytokine release syndrome accompanied by high levels of INF alpha and beta and IL-6 \( \rightarrow \) all signal through JAK-STAT (Janus kinase-signal transducer and activator of transcription) pathway
- Baracitinib: oral JAK1/2 inhibitor approved for RA \( \rightarrow \) broad spectrum cytokine inhibitor AND numb associated kinase inhibitor \( \rightarrow \) use as Phase III drug
ACTT-2 Challenges

• Inclusion criteria the same BUT exclusion criteria now at 20 (only 5 in ACTT-1) related to baracitinib

• Enrolling more slowly than ACTT-1 due to “flattening” of epidemic curve anticipate completed enrollment by mid to late July 2020

• Increasing number of IRB-approved clinical trials among in-patient adults

• Trained personnel returning to other research with “re-opening” the academic research setting
COVID-19 Clinical Research Coalition

• FOCUS: accelerating COVID-19 clinical research in areas where the virus could wreak havoc on already fragile health systems and cause the greatest health impact on vulnerable populations

• AIM: fast track research that will provide evidence on COVID-19 prevention, diagnosis, and case management in resource-limited settings → the evidence needed to guide policy and practice
  • Working groups to assist researchers: WorkingGroups@covid19crc.org or go to website: covid19crc.org/working-groups/

• General Website: www.covid19crc.org
Thanks!

Questions?