Optimizing evidence and access for COVID-19 therapeutics

18 December 12:00-15:00 CET

WHO In collaboration with Unitaid and the Wellcome Trust
Objectives

- To advocate for continued commitment to the development of and access to safe, effective and affordable therapeutics for COVID-19;
- To share information about WHO research and development activities, regulatory processes and clinical practice guideline development;
- To share information about ACT-A activities on accelerating evidence, country readiness and procurement; and strategic priorities.
- To foster continued and expanded collaboration.
ACT Accelerator Therapeutics Partnership

End of Year Therapeutics Landscape – WHO Webinar

December 18th, 2020
Recap: The pathophysiology of COVID-19 provides two main therapeutic strategies for improving clinical outcomes

1 Antiviral Therapeutics

An early-stage intervention, antiviral therapeutics aim to stop the spread of virus in the lung and respiratory tract by interfering with viral entry, trafficking, or replication,

2 Host-directed Therapeutics

Host-directed therapeutics are a late-stage intervention and aim to prevent the downstream consequences of severe COVID-19, including hypercoagulation, hyper-inflamm., fibrosis, and fluid buildup
610+ assets are being developed to treat Covid-19, with assets focused primarily on host-directed treatments for severe disease.

1. The number of plasma-based therapies is relatively low because all producers were collapsed into a single asset entry unless a source of sufficient differentiation was found.

Sources: BIO, WHO, Clinicaltrials.gov, press releases
Clinical trial efforts: Only ~20-25% of ongoing efforts are actionable

~1600+ total trials
~350 actionable trials

<table>
<thead>
<tr>
<th>Category</th>
<th>Plasma-derived products</th>
<th>Antibodies</th>
<th>Antivirals</th>
<th>Host-directed Immunomodulators</th>
<th>Host-directed–Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>PrEP/PEP</td>
<td>~3</td>
<td>~4</td>
<td><del>90</del>35</td>
<td>~2 1</td>
<td>MoAs not applicable</td>
</tr>
<tr>
<td>Mild Outpatients</td>
<td><del>40</del>10</td>
<td>16~6</td>
<td><del>330</del>60</td>
<td><del>40</del>4</td>
<td><del>30</del>15</td>
</tr>
<tr>
<td>Moderate</td>
<td><del>100</del>15</td>
<td>15~5</td>
<td><del>400</del>70</td>
<td><del>230</del>30</td>
<td><del>130</del>30</td>
</tr>
<tr>
<td>Severe/Critical</td>
<td><del>160</del>25</td>
<td><del>20</del>4</td>
<td><del>450</del>90</td>
<td><del>300</del>60</td>
<td><del>200</del>45</td>
</tr>
</tbody>
</table>

1. Based on ICMRA definition: Ph2/3 or beyond, randomized, >250 enrollees per arm Note: totals differ from sum of breakdown given most clinical trials cover multiple use cases
We expect many upcoming readouts to provide more evidence for priority assets

<table>
<thead>
<tr>
<th>Monoclonal Antibodies</th>
<th>Antiviral Small Mol.</th>
<th>Host-directed Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2020</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2</td>
<td>REGN-CoV2 (Mild)</td>
<td>DXM (RECOVERY)</td>
</tr>
<tr>
<td></td>
<td>LY-CoV555 (BLAZE-1)</td>
<td></td>
</tr>
<tr>
<td>Q3</td>
<td>Remdesivir (ACTT-1)</td>
<td>Tocilizumab (COVACTA)</td>
</tr>
<tr>
<td></td>
<td>Remdesivir (SIMPLE-M)</td>
<td>Sarilumab (REGN)</td>
</tr>
<tr>
<td>Q4</td>
<td>Remdesivir (SOLIDARITY)</td>
<td>PegIFNA (ILIAD)</td>
</tr>
<tr>
<td></td>
<td>Nitazoxanide (SARITA-2)</td>
<td>PegIFNA (Stanford)</td>
</tr>
<tr>
<td></td>
<td>Nitazoxanide (SARITA-1)</td>
<td>Losartan (Sharp, INTENSE)</td>
</tr>
<tr>
<td></td>
<td>Favipiravir (Turkey MoH)</td>
<td>Losartan (COVIDMED, ACOVACT, PRAETOR)</td>
</tr>
<tr>
<td></td>
<td>Famotidine (Northwell)</td>
<td>Baricitinib (ACTT-2)</td>
</tr>
<tr>
<td></td>
<td>AT-527 (Atea Ph2)</td>
<td>Colchicine (COLOCOVID)</td>
</tr>
<tr>
<td></td>
<td>MK-4482 (Ridgeback Ph2)</td>
<td>Rivaroxaban (GMRI, ACTION)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rivaroxaban (PREVENT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(C-19 ACS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Losartan (UMN)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Losartan (CRASH-19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Losartan (ARB CORONA II)</td>
</tr>
<tr>
<td><strong>2021</strong></td>
<td>REGN-CoV2 (Mild, SubQ)</td>
<td>DXM (WHO Meta-analysis)</td>
</tr>
<tr>
<td>Q1</td>
<td>REGN-CoV2 (Hospitalized)</td>
<td>PegIFNA (LIILIAD)</td>
</tr>
<tr>
<td></td>
<td>REGN-CoV2 (RECOVERY, est.)</td>
<td>Rivaroxaban (GMRI, ACTION)</td>
</tr>
<tr>
<td></td>
<td>LY-CoV555 (ACTIV-2)</td>
<td>Rivaroxaban (PREVENT)</td>
</tr>
<tr>
<td></td>
<td>LY-CoV555 (BLAZE-4)</td>
<td>(C-19 ACS)</td>
</tr>
<tr>
<td></td>
<td>CT-P59 (Mild)</td>
<td>Losartan (RECOVER)</td>
</tr>
<tr>
<td></td>
<td>VIR-7831 (COMET-ICE)</td>
<td>Losartan (UMN)</td>
</tr>
<tr>
<td></td>
<td>LY-CoV555 (BLAZE-2)</td>
<td>Losartan (CRASH-19)</td>
</tr>
<tr>
<td>Q2</td>
<td>REMG-CoV2 (PEP)</td>
<td>Losartan (ARB CORONA II)</td>
</tr>
<tr>
<td></td>
<td>TY027 (Mild)</td>
<td></td>
</tr>
<tr>
<td>Q3</td>
<td>AZD7442 (PPE &amp; PEP)</td>
<td></td>
</tr>
</tbody>
</table>

**Legend**
- **✓** Novel Tx
- **×** Repurposed Tx
- **♀** Novel Tx
- **♂** Final positive results
- **♀** Final negative results
- **♀** Prelim. negative results
- **♀** Prelim. positive results
- **♀** Trial Delayed

**Abbreviations:** ASAQ: Artesunate-Amodiaquine; FPV: Favipiravir; PA: pyronaridine-artesunate; PegIFNA: Peg-Interferon-Lambda; NTZ: Nitazoxanide; SOF/DAC: Sofosbuvir/Daclatasvir; Note: Dots represent preliminary readout dates only.

This view is not meant to show prioritized drug candidates but rather provide a non-comprehensive overview on actionable and non-actionable clinical trial read-outs in the coming months; Source: Clinicaltrials.gov, press releases, WHO

Analysis current as of 12/14
Existing Wave 1 mAb efficacy data to be complemented with confirmatory trials and dosage/formulation modifications

What we know today

There are ~19 clinical-stage mAbs, of which 8 are in Ph2/3 registry trials (wave 1 mAbs)

- REGN-CoV2 (2.4 g) and Bamlanivimab (0.7 g) received FDA EUA in high-risk mild outpatients based on the results of Ph2 trials

- Some trial arms of REGN-CoV2 and Bamlanivimab in severe patients were halted for futility – other trials of REGN-CoV2 (e.g., RECOVERY) are ongoing

Expected developments

We expected significant learnings on “Wave 1” mAbs; in addition, earlier stage mAbs will progress through the clinic

- Pivotal Ph3 data on mono (700 mg), comb. therapy (700/1400 – 2800/2800 mg) and SubQ equiv.; Ph2 data on low dose by end of Q2 2021

- Ph3 data in mild outpatients (2.4/8 g IV), hosp. patients (8 g IV), PEP, and SubQ eq./low dose (volunteers & mild OP) by end of Q3 2021

- Ph3 efficacy in PreP/PEP (300 mg IM) by late Q4 2021 or early Q1 2022

- Ph2/3 data in mild outpatients (IV, 500 mg) by Q3 2021 (prelim. in Jan)

- Ph2/3 data in mild outpatients (IV, unknown dose) by Q3 2021 (prelim. in Dec)
Despite promise in earlier stages of disease, no AV small molecule has proven efficacy in these use cases – Molnupiravir read-out in Q1 2021 will be pivotal

**What we know today**

**Little efficacy in hospitalized patients**
- Results of HCQ, RDV, LPV/RTV, IFN1 are inconsistent with a significant mortality benefit
- Remdesivir moderately effective in improving time to recovery in the least-severe hosp. patients
- Scientific community believes that antivirals are less likely to be efficacious in severe/critical patients

**No data yet and pipeline is severely limited, with only four direct-acting novel AVs in the clinic**
- Molnupiravir is the only asset in Ph2/3 trials
- Other assets (Atea’s AT-527, Pfizer’s PF-07304814, BioCryst’s Galidesivir) in Ph1/2 trials
- Only Molnupiravir & AT-527 are orally bioavailable and have shown modest preclinical efficacy

**Expected developments**

**Confirmation of efficacy in mild patients**
- Definitive readouts of key assets in mild patients in Q1 and Q2 of 2021 (FVP, NTX, SOF/DAC, IVM)
- Read-out of RDV in outpatients in Q1 2021, incl. more favorable formulations (IV bolus, 3-day IV)

**Read-out of Molnupiravir is pivotal point**
- Molnupiravir read-out in mild and low-severity hospitalized patients in Q1 2021
- Atea/Roche to initiate Ph3 trial of AT-527 in Q1 2021; Molnupiravir read-out will inform probability of success

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1. SubQ/IV Type I Interferon (e.g., interferon beta 1a); does not apply to pegylated formulations, Type III interferons, or alternative formulations (eg, SNG001)
Broad-spectrum immuno-modulators have reduced mortality for severe patients; awaiting key readouts for organ protection (anti-coagulants & RAAS modulators)

What we know today

- Dexamethasone reduces mortality by 17% overall – confirmed by WHO meta-analysis¹

- Baricitinib received FDA EUA for treatment hospitalized, severe patients based on results of the NIH ACTT-2 trial

- Other targeted mechanisms of immune-suppression (IL-6, IL-1β, BTK)² have largely failed to reduce mortality or progression to ventilation

- Due to significant evidence from autopsies and case series, anticoagulants (e.g., LMWHs) have been recommended for inpatients by several organizations (e.g., NIH COVID-19 guidelines)

Expected developments

- Immunomodulators: Large number of actionable trials with cytokine, targeted and complement inhibitors to provide definitive results in 1H 2021

- Organ protection: For both anti-coagulants and RAAS-modulators (e.g., losartan), we expect clear evidence from actionable randomly controlled trials in Q1 2021

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² IL-6 (Tocilizumab, sarilimumab); IL-1β (Canakinumab, anakinra) ; BTK (Acalabrutinib)
WHO Target Product Profiles for COVID-19 Therapeutics

Vasee Moorthy MD PhD
R&D Blueprint co-lead
Senior Advisor, Science Division
Research for Health Department, WHO
A COORDINATED GLOBAL RESEARCH ROADMAP: 2019 NOVEL CORONAVIRUS

MARCH 2020

There is broad consensus on the need for research to: focus on actions that can save lives now; facilitate actions so that those affected are promptly diagnosed and receive optimal care; and catalyse the full integration of all innovations within each research area.

Moreover, there is an imperative to support research priorities in a way that leads to the development of sustainable global research platforms pre-prepared for the next disease X epidemic. This will allow for accelerated research, innovative solutions, and R&D of diagnostics, therapeutics and vaccines, as well as the timely and equitable access to these life-saving tools for those at highest risk.
Identified knowledge gaps

**Human-animal interface**
1. Animal species of origin of the virus
2. Animal species involved in spill over to humans: reservoir/ intermediate host
3. Modalities of transmission between animals and humans
4. Risk factors due to animal trade and consumption

**Clinical considerations**
1. Spectrum of clinical disease
2. Groups at high risk of severe disease
3. Pathophysiology of severe disease
4. Clinical prognosis associated with viral loads and immunomarkers
5. Potential for antibody dependent enhancements to disease/infection
6. Adequate animal models that can mimic human disease characteristics

**Transmission**
1. Modes/duration of person-to-person transmission, role of different age groups
2. Importance of pre-/asymptomatic transmission
3. Surrogate markers for infectivity
4. Environmental stability of the virus and conditions associated with increased transmission
5. Virus compartments of replication, duration shedding
6. Risk factors due to animals

**Therapeutics**
1. Optimal strategies for supportive care interventions
2. Role of host-targeted therapies
3. Safety and efficacy of candidate therapeutics and their combinations
4. Context for post-exposure prophylaxis trials conduct

**Vaccine**
1. Strength, duration of immunity, cellular immunity
2. Possibility of enhanced disease after vaccination
3. Animal models for prioritizing vaccines
4. Animal models for evaluating potential for vaccine-enhanced disease
5. Assays to evaluate immune response to vaccines
6. Design of late phase vaccine clinical trials

**Healthcare workers**
1. Risks factors for healthcare workers’ exposure
2. Approaches to support healthcare workers’ health/ psychosocial needs
3. Perception/compliance to infection prevention and control measures
4. Isolation, quarantine, optimal pathways to deliver care safely

**Behaviors and educations**
1. How to address drivers of fear, anxieties, rumours, stigma
2. How to promote acceptance, uptake, adherence to public health measures and implement ethics, R&D innovations into education

**Ethical considerations**
1. Ethics questions around the inclusion of vulnerable populations in research
2. Best methods to involve and sensitize communities regarding their participation in research
What are WHO TPPs?

• Needs-based and focused on public health priorities
• Pathogen-specific (not product-specific)
• Strategic reference document for transparency on alignment between WHO’s preferences and development programmes underway
• Facilitates end-to-end R&D by allowing for product development with the public health goals in mind
How many TPPs has WHO developed?
In addition to COVID19 there are over 30 profiles covering HIV, TB, malaria, many vaccine-preventable diseases, emerging ID, AMR and others.

Which product classes are covered?
Vary by disease area: spans diagnostics, devices, therapeutics, vaccines and vector control products so far
Many more are in development
All visible through WHO R&D Observatory
Role of WHO TPPs in Product Development

Horizon scanning

Target Product Profile development and refinement

Evidence Generated to support submissions

PQ & Policy recommendation activities
Status of WHO COVID19 therapeutics TPPs

WHO TPPs available for all severities of hospitalized patients

Under public consultation now for non-hospitalized patients

Vaccine and diagnostics TPPs available
Key features of TPPs

Key target population is adults >60, and with co-morbidities increasing the risk of poor outcomes

Data in pregnant women and children also preferred
Mortality is critical endpoint for hospitalized patients
Other key endpoints include reduced progression of disease and reduced duration of symptoms

Understood that mortality benefit unlikely to be feasible in out-patients

Viral load endpoints alone are not considered sufficient
Key features of TPPs

Route of administration

Parenteral or inhaled for critical

Oral, inhaled or parenteral for less severe hospitalized

Shorter courses preferred

For out-patients either oral or single dose parenteral
For out-patients sc or im highly preferred over iv
Key features of TPPs

Frequency of administration

No more than twice a day
Once a day preferable
Key features of TPPs

Drug-drug interactions

No DDI with glucocorticoids and other drugs routinely used in ICU patients if for severe to critical patients
Key features of TPPs

Storage and shipping at -20, 2-8 or room temperature acceptable.

Room temperature shipping and storage preferable, ideally with heat stability demonstrated.
Key features of TPPs

Accessibility

Capability to rapidly scale-up production at cost/dose that allows broad use, including in low income, and low middle income countries
Key features of TPPs

Registration and Prequalification

Manufacturers are recommended to interact with the WHO medicines PQ team
Points arising from WHO’s R&D perspective

Major progress in platform trials during this pandemic

Aim should be for actionable data rather than numbers of trials

Trial design, and in particular sample size and endpoints chosen are critical for public health value

Sometimes lack of clarity of implications of EUA for further clinical trials
WHO Clinical Practice Guidelines: Therapeutics and COVID-19

Janet Victoria Diaz, MD
Lead, Clinical management COVID-19 response
WHO Emergency Programme
Why make a guidelines matter especially during a pandemic?

• Current practices to treat COVID-19 are variable, reflecting a large scale of uncertainty.

• There is one intervention that has been proven to reduce mortality in patients: systemic corticosteroids for patient with severe and critical COVID-19 (moderate certainty evidence, strong recommendation).

• Numerous randomized clinical trials ongoing, including large platform trials, with read-outs on a daily basis.
Why make a guidelines matter especially during a pandemic?

- **Transforming evidence into trustworthy guideline** to inform clinical practice and policy

  - RCTs preferable
  - Important outcomes
  - Sufficient enrollment
  - Geographies

  - Living network meta-analysis
  - Prospective meta-analysis

  - GRADE
  - Values & preferences
  - Patient-important outcomes
  - Key factors

  - Publication platforms
  - Educational platforms
  - Tools for use

**Trigger:** likelihood to change practice, sufficient RCT data to inform high quality evidence synthesis, relevant to global audience
Step 2: Innovation in evidence monitoring and synthesis

- **Living systematic reviews**: COVID-NMA (WHO and Cochrane), LNMA (BMJ-MAGIC Evidence Ecosystem Foundation, WHO REACT PMA (WHO-trialists)
Step 2: Innovation in evidence monitoring and synthesis

- Presenting evidence synthesis is easy to read format to GDG: the summary of findings table

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality 28 days</td>
<td>Relative risk: 0.79 (CI 95% 0.7–0.9) Based on data from 1703 patients in 7 studies Follow up 28 days</td>
<td>415 per 1000</td>
<td>Moderate</td>
<td>Systemic corticosteroids probably reduce the risk of 28-day mortality in patients with critical illness due to COVID-19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>328 per 1000</td>
<td>Due to serious risk of bias\textsuperscript{a}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Difference: 87 fewer per 1000 (CI 95% 124 fewer – 41 fewer)</td>
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<td></td>
</tr>
<tr>
<td>Need for invasive mechanical ventilation 28 days</td>
<td>Relative risk: 0.74 (CI 95% 0.59–0.93) Based on data from 5481 patients in 2 studies Follow up 28 days</td>
<td>116 per 1000</td>
<td>Moderate</td>
<td>Systemic corticosteroids probably reduce the need of mechanical ventilation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>86 per 1000</td>
<td>Due to serious risk of bias\textsuperscript{b}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Difference: 30 fewer per 1000 (CI 95% 48 fewer – 8 fewer)</td>
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</tr>
</tbody>
</table>
Working faster while maintaining quality: cannot compromise standards

Table: GRADE’s approach to rating quality of evidence (aka confidence in effect estimates)
For each outcome based on a systematic review and across outcomes (lowest quality across the outcomes critical for decision making)

<table>
<thead>
<tr>
<th>Study design</th>
<th>Initial confidence in an estimate of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized trials ➔</td>
<td>High confidence</td>
</tr>
<tr>
<td>Observational studies ➔</td>
<td>Low confidence</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reasons for considering lowering or raising confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower if</td>
</tr>
<tr>
<td>Risk of Bias</td>
</tr>
<tr>
<td>Inconsistency</td>
</tr>
<tr>
<td>Indirectness</td>
</tr>
<tr>
<td>Imprecision</td>
</tr>
<tr>
<td>Publication bias</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Confidence in an estimate of effect across those considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
</tr>
<tr>
<td>★★★★★</td>
</tr>
</tbody>
</table>

*upgrading criteria are usually applicable to observational studies only.
Step 3: Innovation in Drafting Recommendations:

A nimble, flexible responsible team: meets on average 2 x for each recommendation (3 hour meetings)

- **Clinical Chair:** content expert
- **Methods support:** experts in methodology, experience in interpretation of evidence, development of recommendations
- **Panel members:** > 32 non-conflicted experts, regional representation, different specialist, ethics/equity expert, patient panel members

**WHO steering committee:** members from various departments, and regional offices.
Step 3: Innovation to facilitate process
Pre-specified Values and Preferences (GDG)

- Mortality would be the outcome most important to patients, followed by need and duration of mechanical ventilation, time to clinical improvement, and serious intervention-related adverse events.

- Most patients would be reluctant to use a medication for which the evidence left high uncertainty regarding effects on the outcomes listed above. This was particularly so when evidence suggested treatment effects, if they do exist, are small, and the possibility of important harm remains.

- In an alternative situation with larger benefits and less uncertainty regarding both benefits and harms, more patients would be inclined to choose the intervention.

The GDG acknowledged, however, that values and preferences are likely to vary. There will be patients inclined to use a treatment in which evidence has not excluded important benefit, particularly when the underlying condition is potentially fatal.

On the other hand, there will be those who have a high threshold of likely benefit before they will choose the intervention.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death at 28 days</td>
<td>9.0</td>
<td>0.0</td>
<td>9-9</td>
</tr>
<tr>
<td>Need for invasive mechanical ventilation</td>
<td>8.4</td>
<td>0.8</td>
<td>7-9</td>
</tr>
<tr>
<td>Duration of invasive mechanical ventilation</td>
<td>7.7</td>
<td>1.0</td>
<td>5-9</td>
</tr>
<tr>
<td>Time to clinical improvement</td>
<td>7.2</td>
<td>1.5</td>
<td>4-9</td>
</tr>
<tr>
<td>Serious adverse effect leading to drug discontinuation</td>
<td>7.1</td>
<td>1.4</td>
<td>4-9</td>
</tr>
<tr>
<td>Time to symptom resolution</td>
<td>6.6</td>
<td>1.5</td>
<td>3-9</td>
</tr>
<tr>
<td>Duration of oxygen support</td>
<td>6.6</td>
<td>1.3</td>
<td>5-9</td>
</tr>
<tr>
<td>Duration of hospitalization</td>
<td>6.4</td>
<td>1.3</td>
<td>3-8</td>
</tr>
<tr>
<td>Hepatitis (increased liver enzymes)</td>
<td>5.3</td>
<td>1.8</td>
<td>2-9</td>
</tr>
<tr>
<td>Duration of viral shedding</td>
<td>4.9</td>
<td>2.4</td>
<td>2-9</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>4.5</td>
<td>1.7</td>
<td>2-9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.3</td>
<td>1.5</td>
<td>2-8</td>
</tr>
</tbody>
</table>

Step 3: Innovation to facilitate process
Key factors in decision making: evidence to decision streamlined

What makes a strong recommendation?
- Benefits clearly outweigh risks/hassle/cost, OR
- Risk/hassle/cost clearly outweighs benefit

What can downgrade strength to a conditional recommendation?
- Close balance between up and downsides (benefits/harms)
- Values and preferences
- Costs, practical limitations
- Low certainty evidence
Step 3: Innovation in Drafting Recommendation: using accepted approach

Facilitates more rapid review by WHO PRC and external reviewers

<table>
<thead>
<tr>
<th></th>
<th>Strong recommendation</th>
<th>Conditional recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For patients</strong></td>
<td>Most individuals in this situation would want the recommended course of action and only a small proportion would not.</td>
<td>The majority of individuals in this situation would want the suggested course of action, but many would not.</td>
</tr>
<tr>
<td><strong>For clinicians</strong></td>
<td>Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.</td>
<td>Different choices are likely to be appropriate for different patients and therapy should be tailored to the individual patient’s circumstances. Those circumstances may include the patient or family’s values and preferences.</td>
</tr>
<tr>
<td><strong>For policy makers</strong></td>
<td>The recommendation can be adapted as policy in most situations including for the use as performance indicators.</td>
<td>Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.</td>
</tr>
</tbody>
</table>
Step 4: Innovations in dissemination

Population
This recommendation applies only to people with these characteristics:

Patients with confirmed covid-19

Disease severity
Non-severe

Severe

Critical

Absence of signs of severe or critical disease

SpO₂<90% on room air

Requires life sustaining treatment

Respiratory rate >30 in adults

Acute respiratory distress syndrome

Raised respiratory rate in children

Sepsis

Signs of severe respiratory distress

Septic shock

Interventions

Hydroxychloroquine
Recommendation against (strong)

Lopinavir-ritonavir
Recommendation against (strong)

Remdesivir
Recommendation against (weak)

Corticosteroids
Recommendation in favour (strong)
Step 4: Innovations in dissemination: new pilot in app


https://app.magicapp.org/#/guideline/4649
Conclusions

• Evidence to recommendations requires massive collaboration at all phases of the process
  • generation->synthesis->draft recommendation->publications/dissemination

• A streamlined, transparent methodology is the only way to create trustworthy guidelines
  • this now takes as little as 4-6 weeks from availability of data to guideline

• Ideally, simultaneous release of guidelines, evidence generation and synthesis is way to expedite the process.
  • WHO can lead the convening of this process

•
WHO Therapeutics Steering Committee

The committee includes representatives from various WHO departments at headquarters and the regions and has been approved by the WHO Director of the Country Readiness Department and the WHO Chief Scientist. The WHO Secretariat meets on a regular basis to discuss when to trigger guideline updates based on evidence updates from the WHO rapid review team, and other sources of evidence and selects the members of the Guideline Development Group (GDG) for living guidance.

Janet V Diaz (Lead, Clinical Team for COVID-19 Response, Health Emergencies Programme, Geneva); John Appiah (Lead, case management, WHO Regional Office for Africa); Lisa Askie (Quality Assurance of Norms and Standards Department); Silvia Bertagnolio (Communicable and Noncommunicable Diseases Division/Clinical Team for COVID-19 Response); Nedret Emiroglu (Country Readiness Strengthening, Health Emergencies Department); John Grove (Quality Assurance of Norms and Standards Department); Rok Ho Kim (Quality Assurance of Norms and Standards Department); Chiori Kodama (Regional Office for the Eastern Mediterranean/Health Emergencies Programme); Gary Kuniyoshi (WHO Regional Office for the Western Pacific/Health Emergencies Programme); Lorenzo Moja (Health Products Policy and Standards Department); Olufemi Oladapo (Sexual and Reproductive Health and Research Department); Dina Pfeiffer (WHO Regional Office for Europe/Health Emergencies Programme); Jacobus Preller (Clinical Team for COVID-19 Response); Pryanka Relan (Integrated Health Services Department/Clinical Team for COVID-19 Response); Ludovic Reveiz (Evidence and Intelligence for Action in Health Department, Incident Management Systems for COVID-19, Pan American Health Organization); Soumya Swaminathan (Office of Chief Scientist); Wilson Were (Maternal, Newborn, Child and Adolescent Health and Ageing Department); Pushpa Wijesinghe (Lead, case management, Regional Office for South-East Asia). Supporting project officer: Jacqueline Lee Endt (Health Care Readiness Unit, Health Emergencies Department).

The WHO Therapeutics Steering Committee is fully responsible for decisions about guidance production and convening the GDG.
Acknowledgements: massive team to get this done

Methods Chair: Bram Rochwer (McMaster University).

Clinical Chair: Michael Jacobs (Royal Free London NHS Foundation Trust).

Methods resource persons: Arnav Agarwal (University of Toronto, Canada); Thomas Agoritsas (University Hospitals, Geneva, Switzerland); Romina Brignardello-Petersen (McMaster University, Canada); Gordon Guyatt (McMaster University, Canada); George Tomlinson (University Health Network Toronto, Canada); Per Olav Vandvik (MAGIC, University of Oslo Norway), Linan Zeng (West China Second University Hospital, Sichuan University, Chengdu, China; McMaster University, Canada).

Acknowledgements: massive team to get this done

Guideline Development Group (GDG)
Wagdy Amin (Ministry of Health and Population, Egypt); Frederique Bausch (Geneva University Hospital, Switzerland); Erliana Bursan (Infection Division Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia); Maurizio Ceconi (Humanitas Research Hospital Milan, Italy) Duncan Chanda (Adult Infectious Disease Centre, University Teaching Hospital, Lusaka, Zambia); Vu Quoc Dat (Department of Infectious Diseases, Hanoi Medical University, Viet Nam); Bin Du (Peking Union Medical College Hospital); Heike Geduld (Emergency Medicine, Stellenbosch University, South Africa); Patrick Gee (patient panel member, United States of America); Madiha Hashmi (Izuddin University Karachi, Pakistan); Manai Hela (Emergency Medical Service Tunis, Tunisia); Sushil Kumar Kabra (All India Institute of Medical Sciences, New Delhi, India); Seema Kanda (patient panel member, Ontario, Canada); Leticia Kawano-Dourado (Research Institute, Hospital do Coração, São Paulo, Brazil); Yae-Jean Kim (Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Republic of Korea); Niranjan Kiosoos (Department of Paediatrics and Emergency Medicine, University of British Columbia, Vancouver, Canada); Arthur Kwizera (Makerere College of Health Sciences, Kampala, Uganda); Imelda Mahaka (patient panel member, Pngaera Harare, Zimbabwe); Greta Mino (Alcivar Hospital, Guayaquil, Ecuador); Emmanuel Nsutebu (Sheikh Shakhbout Medical City, Abu Dhabi); Natalia Pshenichnaya (Central Research Institute of Epidemiology of Rospotrebnadzor, Moscow, Russia); Nida Qadir (Pulmonary and Critical Care Medicine, David Geffen School of Medicine, University of California, Los Angeles, USA); Saniya Sabzwari (Aga Khan University Karachi, Pakistan); Rohit Sarin (National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India); Michael Sharland (St George’s University Hospitals NHS Foundation Trust, London); Yinzhong Shen (Shanghai Public Health Clinical Center, Fudan University, Shanghai, China); Joao Paulo Souza (University of São Paulo Brazil); Shalini Sri Ranganathan (University of Colombo, Sri Lanka); Sebastian Ugarte (Faculty of Medicine Andres Bello University, Indisa Clinic, Santiago, Chile); Sridhar Venkatapuram (King’s College, London); Dubula Vuyiseka (patient panel member, University of Stellenbosch, South Africa); Ananda Wijewickrama (Ministry of Health Sri Lanka).
Special thanks to the study investigators for joining the Q&A session and providing additional data as requested to strengthen the analysis:
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WHO COVID-19 evaluation strategy for Therapeutics

Information sharing webinar on optimizing evidence and access for COVID-19 therapeutics

18 December 2020

Deus Mubangizi, Unit Head, WHO Prequalification (PQT)
Department of Regulation and Prequalification (RPQ)
## Current status of NRAs based on WHO GBT Performance Maturity Levels

<table>
<thead>
<tr>
<th>ISO 9004</th>
<th>WHO GBT</th>
<th>Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No formal approach</td>
<td>100 Countries (73%)</td>
</tr>
<tr>
<td>2</td>
<td>Reactive approach</td>
<td>41 Countries (27%)</td>
</tr>
<tr>
<td>3</td>
<td>Stable formal system approach</td>
<td>53 Countries (Advanced and well resourced regulatory systems)</td>
</tr>
<tr>
<td>4</td>
<td>Continual improvement emphasized</td>
<td>46 Countries (Target of WHA Resolution 67.20)</td>
</tr>
</tbody>
</table>

- **1. No formal approach**
  - Some elements of regulatory system exist
  - Can ensure the quality of products if rely on ML 3/ML 4 regulatory systems
  - 100 Countries

- **2. Reactive approach**
  - Evolving national regulatory system that partially performs essential regulatory functions
  - 41 Countries

- **3. Stable formal system approach**
  - Stable, well-functioning and integrated regulatory system
  - 53 Countries

- **4. Continual improvement emphasized**
  - Regulatory system operating at advanced level of performance and continuous improvement
  - 46 Countries

Target of WHA Resolution 67.20
Prequalification/EUL: **International norms, standards and guidelines used to ensure wide applicability**

Other guidelines e.g. ICH, ISO
Role of regulation:
Promoting and protecting public health

Access  |  Market Control

Scale with blocks balancing on each side.
WHO EUAL/EUL background

- WHO Emergency Use Assessment and Listing (EUAL) mechanism developed in response to the 2014 - 2016 Ebola outbreak
- Risk-based approach to expedite the availability of health products needed in public health emergency situations
- It is intended to assist interested procurement agencies and Member States on the suitability for use of a specific health products, based on a minimum set of available quality, safety, and performance data
- EUL status is time-limited
Features of PQ and EUL:
Both are WHO recommendations to UN agencies, international procurers and member states

**Prequalification (PQ) 2001**

- Review of extensive quality, safety and efficacy and Programmatic characteristics for suitability for use in LMIC
- Assessment performed by WHO independent experts
- Reliance on WHO Listed Authority (WLA) - abbreviated process under oversight of mature regulators (evaluation and oversight of programmatic aspects by WHO)
- Pre-submission meetings encouraged
- Post-PQ monitoring
- Reassessment/requalification

**Emergency Use Listing (EUL) 2015**

- Risk benefit assessment of essential set of quality, safety and efficacy data for use during PHEs
- Rolling review of data
- Assessment performed by WHO independent experts in collaboration with National Regulatory Authorities (WLA)
- Reliance on WLA - abbreviated process under oversight of mature regulators (evaluation and oversight of programmatic aspects by WHO)
- Pre-submission meetings encouraged
- Post-deployment monitoring
- Time limited recommendation
- Development should continue for MA/PQ
WHO drives policy guideline development & defines EUL/PQ procedures and timelines for evaluation of therapeutics candidates

<table>
<thead>
<tr>
<th>Objective</th>
<th>Regulatory</th>
<th>Normative and standard setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promote access to quality, safe and effective therapeutics in a timely manner through mapping of regulatory requirements and pathways incl. use of reliance &amp; collaboration in evaluation processes.</td>
<td>Provide evidence-based recommendations for clinical practice or public health policy to achieve the best health outcomes possible.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Examples of key processes &amp; tools</th>
<th>Evaluation pathways &amp; reg. recommendations:</th>
<th>Technical/policy recommendations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Prequalification (PQ) – listing of approved manufacturers for specific products</td>
<td>• Ethics guidelines – ensuring ethical conduct of research, decision making in clinical care, and public health policymaking</td>
<td></td>
</tr>
<tr>
<td>• EUL (Emergency Use Listing) – time-limited listing of manufacturer for specific products in an emergency context</td>
<td>• Clinical guidance for COVID-19- includes Living Guidance for therapeutics and COVID-19</td>
<td></td>
</tr>
<tr>
<td>• Support for regulatory pathways – alignment of regulatory requirements and promotion of use of reliance and collaboration in processes</td>
<td>• EML (Essential Medicines List) – identifying the most efficacious, safe and cost effective Tx</td>
<td></td>
</tr>
</tbody>
</table>

WHO processes rely on external inputs – leading to variable lead times for both Regulatory and Normative & std setting.

**EUL/PQ processes**
- Determination of need for PQ or EUL – **WHO**
- Expression of interest for PQ/EUL issued – **WHO**
- Support to manufacturers – **WHO**
- Dossier submission – **Manufacturers**
- Typically 2-3 rounds
  - Dossier review and assessment – **WHO**
  - Dossier revision and resubmission – **Manufacturers**
- If accepted then listed – **WHO**

**WHO normative and std setting processes**
- Generation and publication of evidence – **External**
- Determination of need for guideline – **WHO**
- Evidence synthesis – **WHO/Independent experts**
- Formulation of recommendations – **Independent experts**
- Drafting – **WHO**
- External peer review – **External reviewers**
- Publication and dissemination – **WHO**

**Indicative lead time from go decision**
- ~2-4 months

**High-level key steps**

**Accelerating factors**
- Early determination of need for EUL/PQ – **WHO**
- Publication of trial outcomes – **Manufacturers**
- Reliance on previous SRA/NRA approval – **External / WHO**
- Parallel review – **External / WHO**
- Presubmission meetings – **Manufacturers / WHO**
- (-)⁴ additional manufacturing sites – **Manufacturers**

**Indicative lead time from go decision**
- ~ 1 month

Relevant for both sequential and parallel pathways; ². From evidence of data – publication or NRA/SRA approval – to EUL/PQ decision. Assuming 2-3 rounds of review and assessment of dossiers 3-5 weeks in first round, 1-3 weeks in second and third rounds and 1-3 weeks for manufacturers to resubmit between rounds. Variable also depending on amount of evidence available.; ³. Guideline Development Group.; ⁴. Decelerating factor Source: WHO website, WHO Emergency Use Listing procedure, WHO Representative schematic and indicative timelines for key processes for WHO actions to enable access to therapeutic candidates for COVID-19.
Total lead time of ~2-4 months from evidence of data – publication – to EUL/PQ decision for originators

Key WHO Normative and standard setting milestones
- Evidence monitoring
- Start of WHO Tx guideline
- EUL/PQ EOs issued
- EUL/PQ decision

Key WHO EUL/PQ milestones
- Determination of need for EUL/PQ
- EUL assessment / PQ abridged pathway (2-3 rounds)

Factors accelerating timeline:
- Additional manufacturer sites
- Dossier revision & resubmissions (incl. site inspections)
- Key milestones required:
- Evidence monitoring
- Publication (IIb or III)
- Sufficient evidence
- Tx product-specific guidelines issued
- Start of WHO Tx guideline
- EUL/PQ decision

Factors decelerating timeline:
- Decelerating factor; need for comparability data (e.g., contract manufacturing)

Factors accelerating timeline:
- Additional manufacturer sites
- Dossier revision & resubmissions (incl. site inspections)

Factors decelerating timeline:
- Decelerating factor; need for comparability data (e.g., contract manufacturing)

Key national regulatory pathways (reliance on WHO EUL/PQ or SRAs or other reference NRAs or independent reviews)
- SRA/NRA emergency / conditional approval
- Approval for national regulatory authority
- Registration process
- Post-authorization safety monitoring

Key WHO EUL/PQ milestones
- Determination of need for EUL/PQ
- EUL assessment / PQ abridged pathway (2-3 rounds)

Factors accelerating timeline:
- Additional manufacturer sites
- Dossier revision & resubmissions (incl. site inspections)

Factors decelerating timeline:
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Factors accelerating timeline:
- Additional manufacturer sites
- Dossier revision & resubmissions (incl. site inspections)

Factors decelerating timeline:
- Decelerating factor; need for comparability data (e.g., contract manufacturing)
Early signals flagging potential need for further discussions with manufacturers of priority Tx candidates

To be revised based on dossier review

<table>
<thead>
<tr>
<th>Importance of early discussions with manuf.</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Quality</th>
<th>Target pop’n</th>
<th>Programmatic</th>
<th>Product complexity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower importance</td>
<td>All endpoints assessed</td>
<td>Safety profile similar or superior to available therapeutic agents</td>
<td>100%+ threshold</td>
<td>Adults including those &gt;60 years of age, and higher risk (e.g., co-morbidities, HCW)</td>
<td>Oral, once per day dosing, room temperature shipping and storage in climatic Zone IV (30°C)</td>
<td>Low (repurposed)</td>
</tr>
<tr>
<td></td>
<td>1 endpoint not assessed</td>
<td>Overall acceptable risk / benefit profile in the target population OR no info available</td>
<td>80%-100% threshold</td>
<td>Adults including those &gt;60 years of age OR higher risk (e.g., co-morbidities, HCW)</td>
<td>Oral, twice per day dosing or 8-25°C shipping/storage</td>
<td>Mid (novel AV)</td>
</tr>
<tr>
<td>Greater importance</td>
<td>≥ 2 endpoints not assessed</td>
<td>Adverse events reported</td>
<td>&lt;80% threshold</td>
<td>Not including adults &gt;60 years of age nor higher risk (e.g., co-morbidities, HCW)</td>
<td>IV® or oral more than twice per day dosing or 2-8°C shipping/storage</td>
<td>High (novel mAb)</td>
</tr>
</tbody>
</table>

1 PEP/PrEP: incidence of disease, hospitalization, mortality. Mild/ Moderate/Severe: progression of disease, hospital stay duration, mortality. Critical: mortality, severity, hospital stay duration (WHO TPPs). 2 Defined by ICMA as randomized controlled trials in Phase 2 or beyond with expected enrollment of 250+ per arm for ventilated ICU, 500+ for hospitalized LRI, 1,000+ for early mild or asymptomatic, and 5,000+ for post-exposure prophylaxis (PEP) or pre-exposure prophylaxis (PreP). Enrollment per arm estimated from total enrollment by assuming even distribution of patients across all arms. It is not reflective of actual enrollment. 3 Pregnant women should be considered as preferable requirements in future data generation, children >6 years old as minimal / critical requirement 4 Detailed in appendix 5 Therapeutics requiring intravenous administration may be expected for use in hospital settings but may signal the need for additional considerations.
Definitions

• **Biotherapeutic**: a biological medicinal product with the indication of treating human diseases (WHO Technical Report Series No. 987, 2014)

• **Similar Biotherapeutic Product (SBP)**: a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product (Technical Report Series No. 977, 2009)

• **Reference Biotherapeutic Product (RBP)**: a biotherapeutic product that (a) has been licensed and approved by an SRA on the basis of a full dossier with comprehensive data on non-clinical and clinical studies; and (b) is used as the comparator for head-to-head comparability studies with the SBP in order to show similarity in terms of quality, safety and efficacy (WHO Pilot Procedure for Prequalification of BTPs: rituximab and trastuzumab)

• **Transfer of technology**: a logical procedure that controls the transfer of any process together with its documentation and professional expertise
EUL pathways for COVID-19 medicines

1. The emergency use authorization should have been granted based on review of available quality, safety and efficacy data.
2. The EUL assessment for Tech transfer products may be facilitated by access to the SRA assessment reports of the original emergency use authorization.
3. Depending on whether the EOI issued by WHO is for EUL or PQ, which in turn depends on the extent of the available clinical data.

Note: For mABs and other biologics, the same procedure and requirements for EUL will be followed but specific guidelines and requirements may be developed depending on the particular type of product.

Note: WHO will promote the use of the collaborative procedure to facilitate national emergency use authorization.
PQ pathways for COVID-19 medicines

1. For tech transfer versions, the assessment may be facilitated by access to the SRA assessment report for the product manufactured at the sending unit.

2. Depending on whether the EOI issued by WHO is for EUL or PQ, which in turn depends on the extent of the available clinical data.

3. Part reliance if the product is SRA approved/prequalified for indications other than COVID-19.

Note: For mABs and other biologics, the same procedure and requirements for PQ biotherapeutics product will be followed.

Note: WHO will promote the use of the collaborative procedure to facilitate national conditional or regular marketing authorization.
Requirements\(^1\): EUL abridged assessment procedure

- Pre-submission meeting (PSM)
- Evidence of emergency use authorization issued by an SRA based on scientific review of non-clinical, clinical and quality data
- A declaration that the product submitted for EUL is, and will after a possible EUL be, identical in all aspects including manufacturing sites
- Clinical data supporting the use of the product in the management of COVID-19 infection\(^2\)
- If required, safety concerns, PV activities, risk minimization measures, traceability of the product, risk management plan (RMP), reflecting the LMICs context
- For biotherapeutics, compliance with the WHO guidelines on the international packaging and shipping of vaccines to demonstrate suitability of the packaging to regions outside of climatic zone II

---

1. For PQ, the regular PQ guideline for SRA approved products apply
2. The required clinical data supporting the use of the invited medicine in the treatment of COVID-19 must have been obtained from appropriately designed clinical trials. An applicant can submit such data or refer to publicly available information
Requirements: EUL full assessment procedure

- Pre-submission meeting (PSM)
- All essential quality data, and if required safety data, requested in Annex 5 of the EUL procedure and identified in the PSM *
- Clinical data supporting the use of the product in the management of COVID-19 infection**
- If required, safety specification, pharmacovigilance plan, risk management plan (RMP) and post-marketing safety*

* Product specific requirements to be determined on a case by case basis
**The required clinical data supporting the use of the invited medicine in the treatment of COVID-19 must have been obtained from appropriately designed clinical trials. An applicant can submit such data or refer to publicly available information.
## Overview of priority Tx candidates

**As of Nov 3, 2020**

<table>
<thead>
<tr>
<th>Repurposed</th>
<th>Originator</th>
<th>STANDALONE BIOThERAPEUTIC</th>
<th>BIOSimILAR / GENERIC</th>
<th>ADD’N OF MANUF SITE FOR SAME PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Small molecules:</strong></td>
<td><strong>Original manufacturers &amp; formulation:</strong> need to generate the full clinical data</td>
<td>Similar product to originator but from a different manufacture/sponsor who has not chosen the biosimilar route. Need to generate the full toxicological and clinical, published data supportive</td>
<td>Generic – Bio-equivalence study; Biosimilar – similarity study. Need to generate a) proof of similarity to an appropriate RBP through comparability exercise (extensive quality characterization); b) Pilot Pk/Pd studies &amp; c) Pilot Phase 3 safety/efficacy studies appropriately powered and with appropriate end points)</td>
<td>Same formulation and manuf. process at new manuf. site. GMP compliant tech transfer and comparability studies (purely analytical if any difference are justified to have no impact)</td>
</tr>
<tr>
<td>Small molecules:</td>
<td>• SOF/DAC</td>
<td></td>
<td>Small molecules:</td>
<td>• SOF/DAC generics</td>
</tr>
<tr>
<td>Biologics:</td>
<td></td>
<td></td>
<td></td>
<td>Biologics:</td>
</tr>
<tr>
<td>• REGN-CoV2</td>
<td></td>
<td></td>
<td>• LY-CoV555 (FUJIFILM)</td>
<td></td>
</tr>
<tr>
<td>• LY-CoV555</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Nov el | | | | |
| Small molecules: | | | | |
| • MK-4482 | | | | |
| • AT-527 | | | | |

1 Examples for consideration in this document only (all candidates being tracked are not reflected here)
Steps and timelines\(^1\): EUL abridged procedure

1. For PQ, the regular steps for prequalification apply (assessments will be prioritized)
2. Interactions prior to issuance of the EOI are encouraged
Steps and timelines\(^1\): EUL full assessment procedure, for generic/biosimilar versions of an SRA authorized originator product\(^2\)

1. For PQ, the regular steps for prequalification apply (assessments will be prioritized)
2. New biological or chemical entity unlikely to be submitted to an SRA to be considered on a case by case basis
3. Interactions prior to issuance of the EOI are encouraged
4. In case of inadequate/deficient information or incomplete submission, the application may be rejected
The collaborative procedure enables NRAs to accelerate the registration of prequalified products so that they can enter local markets more quickly.

Process:
- WHO PQ shares the reports that served as the basis for the prequalification/EUL decision, so that NRAs do not conduct assessment and inspections.
- National registration based on PQT evaluation.

Principles of CRP:
- Voluntary for both applicant and NRA.
- Product and registration dossier in countries are 'the same' as prequalified by WHO.
- Shared confidential information to support NRA decision making in exchange for accelerated registration process.
- 'Harmonized product status' is monitored and maintained.

Target:
90 Days
Working Together

Department of Regulation and Prequalification, WHO
ACT-A Therapeutics Partnership
Market preparedness
Information Sharing Event

December 18, 2020

#UnitedAgainstCoronavirus
#StrongerTogether | #GlobalResponse
Three steps to ensure global access to most impactful therapeutics

- R&D
  - Discover fast
- Market Preparedness
  - Produce at scale & enable access
- Procurement & deployment
  - Deliver to all
Market preparedness workstream assesses ability for assets to be delivered at scale

Regulatory status
Intellectual property
Supply capacity
Price
Ease of distribution

Post-intervention assessment
Capacity to improve ability to deliver at scale after interventions
Market assessment revealed several common access and delivery challenges by asset type

**Repurposed Tx**
- Known safety; access
- Widely available for other indications
- Competitive prices, closer to manufacturing cost

**Novel Tx**
- High promise of efficacy
- Unknown safety
- IP constraints
- Potential for high prices without intervention

**Small molecules**
- Low to medium manufacturing complexity
- Medium to high supply capacity
- Generally adapted for delivery (oral, no cold chain- exceptions)

**Biologics**
- Limited market (very limited in LMICs)
- Very high prices
- Complex manufacturing & regulatory pathways
- Delivery and use challenges

LMICs = Low- and middle-income countries
Potential market interventions to address access & delivery challenges

<table>
<thead>
<tr>
<th>Root causes for constraints</th>
<th>Novel small. mol</th>
<th>Repurposed small. mol</th>
<th>Potential market interventions (non exhaustive; examples)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory status</td>
<td><img src="image" alt="Round Fill" /></td>
<td><img src="image" alt="Round Fill" /></td>
<td><img src="image" alt="Round Fill" /></td>
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<tr>
<td>Intellectual property</td>
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<tr>
<td>Supply capacity</td>
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<tr>
<td>Price</td>
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<tr>
<td>Ease of delivery</td>
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</tr>
</tbody>
</table>

mAbs = monoclonal antibodies

Need for intervention

69
Further challenge: anticipating therapeutics uptake constraints within LMICs

Sample demand / supply constraints leading to gap in potential uptake

- **Limited supply** of Tx in country, long-lead times, or limited financing
- Limited availability of **required health system infrastructure** or challenged ability for patients to **access health facilities**
- Lack of companion **Covid diagnostics**
- Product **delivery & administration** challenges (e.g., cold-chain or IV requirements)

LMICs = Low- and middle-income countries
Pursuing several avenues to shrink the anticipated uptake gap

Sample avenues to tackle uptake challenges

• Support responsible introduction of most efficacious products to LMICs
• Support country preparedness and demand generation
• Continue to support R&D efforts that drive towards fit-for purpose products (e.g., oral, non cold-chain)
• Investigate potential roll out of test & treat approach with ACT-A Dx Pillar

LMICs = Low- and middle-income countries; Dx = diagnostics
Steps to increase Tx uptake differs based on patient use case

Demand, delivery complexity & safety concerns vary significantly depending on the stage for which a therapeutic is considered

- Protect against infection
- Decrease transmission
- Prevent disease progression, reduce burden on health care system
- Directly prevent mortality

Early intervention use cases
- Pre-exposure prophylaxis (PrEP)
- Post-exposure prophylaxis (PEP)

Late intervention use cases
- Mild treatment
- Moderate treatment (e.g., pneumonia)
- Severe & critical treatment
- Long-COVID19

Demand, delivery complexity & safety concerns vary significantly depending on the stage for which a therapeutic is considered.
Untapping potential of emerging tools will help us end the current global health crisis

Vaccine candidates are emerging with very high efficacy

- Vx coverage reduces the need to focus therapeutics on PrEP and PEP populations
- Anticipate Vx coverage will enable Tx Partnership to focus market access efforts on mild/moderate use cases

Emerging diagnostics are increasingly accessible & affordable

- Supports Tx Partnership focus on mild/moderate patients by enabling more accessible & earlier testing
- Allows for the implementation of a "test & treat" approach, further motivating individuals to get tested

Cross-pillar coordination to maximize impact on pandemic trajectory

LMICs = Low- and middle-income countries; Vx = vaccine. Tx= Therapeutics
Objective of WS3 is to plan for the procurement & deployment of Tx prioritized via WS1/2

**WS1**
*Rapid evidence assessment*

- Monitor emerging Tx landscape, filter assets based on health impact
- Identify R&D gaps that require interventions & support as necessary

**WS2**
*Market preparedness*

- Prioritize assets based on ability to deliver at scale
- Identify potential market preparedness interventions & support as necessary

**WS3**
*Procurement & deployment*

**Supply Ops**
- Develop plans to procure & deploy priority candidates

**Allocation**
- Establish allocation mechanism for priority candidates facing supply constraints

Country Prep – TBC
Clinical status suggest that mAbs are the most advanced asset class to-date while clinical readouts for promising novel antivirals are expected EOY

<table>
<thead>
<tr>
<th>mAbs</th>
<th>Novel antivirals (SMs1)</th>
<th>Repurposed Tx (incl. repurposed antivirals &amp; host-directed therapies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>e.g., bamlanivimab (LY-CoV555), REGN-CoV2</td>
<td>e.g., molnupiravir (MK-4482), AT-527</td>
<td></td>
</tr>
<tr>
<td>• Bamlanivimab &amp; REGN-CoV2 reduced hospitalization in mild cases by 50-70%</td>
<td>• AT-527 and molnupiravir remain the only two oral direct-acting antivirals – maintain focus on molnupiravir &amp; AT-527 candidates</td>
<td>• Multiple Phase 2 / 3 trials delayed due to enrollment challenges (e.g. Colchicine)</td>
</tr>
<tr>
<td></td>
<td>• Ph2 read-outs for molnupiravir and AT-527 expected in ec</td>
<td>• Ongoing / planned trials with antivirals / combinations focusing on outpatient / mild patients</td>
</tr>
<tr>
<td></td>
<td>Potential focus with promising upcoming clinical readouts</td>
<td>Clinical status to be monitored going forward</td>
</tr>
<tr>
<td>Currently, most promising and advanced asset class</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Currently, most promising and advanced asset class

Potential focus with promising upcoming clinical readouts

Clinical status to be monitored going forward
Supply Operations
Supply Ops team driving towards three near-term deliverables, with immediate focus on a procurement mechanism for mAbs

Focus of next pages

Mechanism for procurement & deployment
- Determine approach to sourcing & supplier negotiations
- Defining roles of ACT-A partners across procurement & deployment value chain

Plan to operationalize mechanism
- Define plan to interface with countries
- Determine processes & tools to coordinate supply & demand among partners
- Define handovers with allocation mechanism

Launch supplier contracting process
- Define procuring organization(s) and supplier(s)
- Execute on contract negotiations
Range of options for procurement mechanisms available – proposed approach for mAbs is single contracting process with multiple procurement channels

- **More centralized**
  - One contract negotiation process with suppliers
  - One channel for country procurement

- **Less centralized**
  - Multiple contract negotiation processes
  - Multiple channels for country procurement, limited coordination

One contract negotiation process covering overall architecture

Multiple channels for country procurement, coordination on demand & supply

*mAbs approach (potentially applicable to nAVs too)*
Proposed approach incorporates learnings from Diagnostics

**Phase 1 – one channel per product**
- Global Fund
- Unicef
- WHO

Challenge for countries to access unfamiliar/new channels, and constrained in funding avenues

**Phase 2 – multiple channels, coordinated negotiation**
- Global Fund
- WHO
- Unicef
- PAHO

Partners jointly negotiated with suppliers
Each established own contract to execute POS
Coordinating closely on supply/demand and allocation

---

**Key takeaways**

- **Multiple procurement channels improves accessibility across countries**
- **Partner collaboration on terms and conditions and regulatory pathway is critical**
- **Strong coordination processes and online tools necessary to make this possible**
Allocation
Allocation mechanisms based on overarching principles for access and global allocation framework

A
Overarching principles for access
Global principles to ensure fair and equitable access to products

B
Global Allocation Framework
A global Allocation Framework for all COVID-19 products

C
Fair and equitable Allocation Mechanisms
Mechanisms tailored for each product

Tailored by product class
In the case of mAb, an allocation mechanism is needed

<table>
<thead>
<tr>
<th>Intended use</th>
<th>Setting</th>
<th>Type of molecule</th>
<th>Supply constraints</th>
<th>Time in the market</th>
<th>IP barriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary prophylaxis</td>
<td>Community/ First level of care</td>
<td>Biological</td>
<td>Difficult to scale up/ limited number of manufacturers</td>
<td>New</td>
<td>IP barriers</td>
</tr>
<tr>
<td>Reduce morbidity</td>
<td>Secondary/ low complexity</td>
<td>Small molecule</td>
<td>Easily scalable/ ToT/ multiple manufacturing sites</td>
<td>Repurposed</td>
<td>No IP barriers</td>
</tr>
<tr>
<td>Reduce mortality</td>
<td>ICU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

mAb supply will be constrained due to limited worldwide capacity, and complex manufacturing making scale up difficult.

New molecules imply IP barriers and thus potentially higher price.

Usage to reduce morbidity (ie. mild / moderate cases) means demand can be significant.
## Characteristics of mAbs inform application of global allocation framework

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>mAb definition</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Use case</strong></td>
<td>Mild &amp; moderate – Ph 2/3 data indicates reduction in hospitalization by 50-70%(^1)</td>
<td>High overall potential demand</td>
</tr>
<tr>
<td><strong>Novel vs. repurposed</strong></td>
<td>Novel</td>
<td>No existing supply chain, production capacity highly constrained, costly</td>
</tr>
<tr>
<td><strong>Molecule</strong></td>
<td>Biologic</td>
<td>More complex regulatory pathway and barriers to scale-up manufacturing</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>IV, single dose, outpatient (^2)</td>
<td>Infrastructure req's – IV &amp; hospitals, beds not required</td>
</tr>
<tr>
<td><strong>Pre- or co-requisites</strong></td>
<td>Diagnostics</td>
<td>Requires adequate Dx deployment, preferably RDT</td>
</tr>
<tr>
<td><strong>Supply chain requirements</strong></td>
<td>Cold chain, 2-8°C</td>
<td>Requires sufficient cold chain capabilities</td>
</tr>
</tbody>
</table>

1. mAbs not likely to be applicable for severe & critical cases – Lilly trial among hospitalized patients stopped due to futility
2. Ongoing work to lower doses & reformulate into SubQ & IM formulations
Currently refining parameters to incorporate in algorithm to allocate between countries

<table>
<thead>
<tr>
<th>Allocation algorithm</th>
<th>Health system readiness</th>
<th>Volume thresholds</th>
<th>Country readiness &amp; demand</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potential need</strong></td>
<td>How large is the potential need by country?</td>
<td>What is the HC system readiness to absorb mAbs?</td>
<td>Does allocation meet minimum and/or maximum threshold?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Allocate based on the actual country demand. Non-requested material to be re-allocated.</td>
</tr>
</tbody>
</table>

- **COVID cases or incidence**
- ? Population at risk of progression to severe (>65, underlying conditions)
- **Population of HCWs**

Potential parameter to include:
- Target population to be addressed in Tx guidelines

Key parameter to include:
- Diagnostics deployment
- Health infrastructure
- Supply chain strength

Which parameters to include?
- Minimum volume threshold
- Maximum volume threshold

Readiness factors to be assessed with countries, informing actual allocated quantity:
- Key parameter to include
- Potential parameter to include
- Do not include in algorithm
Objective of WS3 is to plan for the procurement & deployment of Tx prioritized via WS1/2

WS1
Rapid evidence assessment

- Monitor emerging Tx landscape, filter assets based on health impact
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WS2
Market preparedness

- A: Prioritize assets based on ability to deliver at scale
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WS3
Procurement & deployment

Supply Ops
- Develop plans to procure & deploy priority candidates

Allocation
- Establish allocation mechanism for priority candidates facing supply constraints

Country Prep – TBC
Thank you
ACT-A Therapeutics Partnership
Strategic priorities and financing

Information Sharing Event

December 18, 2020

#UnitedAgainstCoronavirus
#StrongerTogether | #GlobalResponse
Defeating Covid requires a comprehensive approach

People receive **vaccine** and reduce risk of contracting Covid

People have faster access to **Covid testing**, speeding treatment and isolation decisions

Patients have access to **therapeutics** to improve morbidity and mortality outcomes

Reduction in COVID-19 infection rates and patient morbidity/mortality due to increased access to vaccines, diagnostics and treatments

**Tx Partnership adds unique value to Covid response by bringing expertise of member orgs**

<table>
<thead>
<tr>
<th>Description</th>
<th>Lead organizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid evidence assessment of candidates</td>
<td>Wellcome</td>
</tr>
<tr>
<td>Market preparedness</td>
<td>Unitaid</td>
</tr>
<tr>
<td>Adequate deployment in all countries</td>
<td></td>
</tr>
<tr>
<td>Costing / financing (cross-cutting)</td>
<td></td>
</tr>
</tbody>
</table>

**Tx Partnership co-convenors:** Wellcome and Unitaid

1. Rapid evidence assessment of candidates: Coordinate clinical trials portfolio & candidate selection
2. Market preparedness: Facilitate market entry and supply at scale
3. Adequate deployment in all countries: Ensure procurement, equitable distribution & delivery
4. Costing / financing (cross-cutting): Identify resource needs for successful delivery
ACT-A Tx Partnership achievements in 2020

1. Low- and middle-income countries

- Analyzed over 1,700 ongoing clinical trials to prioritize the most promising treatments and supported accelerated evidence gathering
- Estimated potential need for COVID-19 therapeutics in LMICs\(^1\) over the next 12 months in light of emerging Vx evidence
- Assessed market situation of over 30 treatment candidates to anticipate potential constraints
- Secured dexamethasone supplies for up to 2.9M patients in LMICs\(^1\)
- Coordinated with Gates on capacity reservation for monoclonal antibodies for LMICs\(^1\)

1. Low- and middle-income countries
Accelerating access for low- and middle-income countries to effective Tx

1. Monitor therapeutics R&D landscape, assessing and informing on potential gaps in trials

2. Identify and implement market access interventions as necessary for priority assets

3. Procure and equitably deploy priority products

4. Ensure countries are prepared to properly receive and deploy products
Partnership interventions are adapted to the specific needs and challenges of each asset class.

- Monoclonal antibodies
- Novel antivirals
- Repurposed therapeutics
**Tx Partnership 2021 priorities support equitable access to therapeutics – but require funding**

### Earlier readouts

<table>
<thead>
<tr>
<th>Monoclonal antibodies (mAbs)</th>
<th>Novel small molecule antivirals</th>
<th>Repurposed therapeutics incl. repurposed antivirals &amp; host-directed therapies (e.g., anti-coagulants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>e.g., bamlanivimab, REGN-CoV2</td>
<td>e.g., molnupiravir, AT-527</td>
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<tr>
<td>➢ Bamlanivimab &amp; REGN-CoV2 reduced hospitalization in mild cases by 50-70% and received FDA EUA for mild/mod high-risk pts</td>
<td>➢ AT-527 and molnupiravir only two novel oral direct-acting antivirals</td>
<td>➢ Multiple Phase 2/3 trials delayed due to enrollment challenges</td>
</tr>
<tr>
<td>➢ Bamlanivimab Ph2/3 results expected in Q1</td>
<td>➢ Molnupiravir Ph2 mild readout by Jan; Ph2/3 preliminary readout in April 2021</td>
<td>➢ Ongoing &amp; planned trials focusing on outpatient / mild patients and PrEP/PEP</td>
</tr>
</tbody>
</table>

### Later readouts

**Clinical status**
- Manufacturing: high cost, limited global capacity, complex tech transfer
- Potential IV administration
- Regulatory & policy processes

**Access challenges**
- Support responsible introduction of mAbs to LMICs through FUJI capacity reservation, pending clinical readouts
- Assess need for additional manufacturing capacity beyond 2021 or for additional R&D support (e.g., for more potent mAbs)

**ACT-A 2021 priorities**
- Monitor clinical trials for key assets and assess/inform on potential gaps to be fit-for purpose
- Support and accelerate responsible introduction of SM NAVs to LMICs, pending clinical readouts
- Monitor clinical trials for key assets and assess/inform on potential gaps to be fit-for purpose
- Prepare for rapid scale up and deployment support in case of positive clinical read-outs

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**Acronyms:**
- EUA = emergency use authorization
- LMIC: low- and middle-income countries (generally excluding China)
- mAbs = monoclonal antibodies
- mmf = manufacturer
- Ph2/Ph3 = Phase 2/3 clinical trial
- PrEP/PEP = Pre-Exposure Prophylaxis and Post-Exposure Prophylaxis
- pts = patients
- SM NAVs = small molecule novel antivirals