

# Evidence Standards and Quality Assessment for COVID-19 Therapeutic Interventions

Multiple stakeholders have responded to the COVID-19 global pandemic in force. According to the [NIHR Innovation Observatory](#), there are currently over 1,400 clinical trials targeting COVID-19 registered with the WHO, clinicaltrials.gov, EU Clinical Trials Register, and other sources. While the assessment of new and/or repurposed treatments to address this outbreak is of critical importance, it is equally important for HTA bodies and advisory organizations to reaffirm their standards for evidence and rigorously interrogate the quality of available studies, making adjustments as necessary for relevance to the current topic as well as evolving efficacy and safety concerns.

Any weakening of evidence standards is unavoidably linked to an increase in uncertainty, with potential consequences for patients and society. HTA assessments of therapeutic interventions are based on established international standards of evidence-based medicine [and are relevant for ascertaining effectiveness and value at multiple points in the technology lifecycle](#). While we recognize the urgent need for interventions against the current pandemic, we believe that efficient design, conduct, and interpretation of meaningful and informative clinical studies is the goal that all stakeholders should strive for rather than trading off standards of design and conduct in the name of speed alone. Below we state a concise set of standards to achieve this goal.

We note that our current focus is on studies of therapeutic interventions; we anticipate developing standards for diagnostics, vaccines, and public health interventions at a later date, as well as for ethical and biosafety considerations. This document should also in no way be interpreted to supersede or replace detailed guidance developed by any individual HTA body, regulatory authority, or multi-stakeholder collaboration such as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

## Study Design

- Studies should be registered on relevant platforms (e.g., clinicaltrials.gov, EU Clinical Trials Register) with publicly posted protocols that are amended as necessary
- Multicenter, randomized, controlled and blinded clinical trials are the preferred design
  - Single-center trials are acceptable given likely challenges in study enrollment
  - Adaptive and pragmatic designs are acceptable given the evolving nature of COVID-19 and multiple plausible treatments, but potentially higher levels of uncertainty from such designs should be clearly reported

- Controls must be contemporaneous and represent the current treatment standard (i.e., best supportive care)
- Study power and sample-size calculations should take planned interim analysis into account
- Observational comparative studies (e.g., “real-world” community-based evaluations) and use of historical controls should be considered primarily hypothesis-generating in nature
- In anticipation of a high degree of uncertainty in many COVID-19 clinical studies, use of extensive scenario and other exploratory analysis is recommended, particularly if data will be used in “susceptible-infectious-recovered” (SIR)- or agent-based models to predict the clinical and/or economic impact of interventions

## Outcomes of Interest

- All-cause mortality is the preferred primary endpoint
- Secondary clinical endpoints should be kept to a minimum, developed in consultation with patients and caregivers, and focus on patient-relevant endpoints that are appropriate for the treatment setting
  - For inpatient treatment, endpoints could include an ordinal scale measure (see example on page 3), length of stay in ICU and in total, duration of oxygen/ventilation, etc.
  - For outpatient treatment, endpoints could include activities of daily living, attendance at work or school, pulmonary function, viral negativity, etc.
- Other secondary endpoints could consider health-related quality-of-life using validated instruments (for example, as measured with EQ-5D or SF-36) as well as healthcare resource utilization and costs by setting (e.g., inpatient, outpatient, labs, etc.) and in total
- Where possible, all endpoints should be reported using internationally-recognized and standard measurement systems (e.g., ICU vs. step-down status, oxygen/ventilation support) and efforts to set international standards for core outcome sets (<https://www.covid-19-cos.org/>)
  - This is of particular importance for comparisons across single-center studies

## Study Quality and Documentation

- The quality of individual studies should be assessed using a validated approach such as the [Cochrane Risk of Bias tool](#)
- Reviewers should consider measurement and reporting of intervention effects from both “intent-to-treat” and “per-protocol” perspectives, given a reasonably high likelihood of protocol violation in a pandemic emergency
- Abstracts or preprints are sufficient for HTA assessment but should be updated once a peer-reviewed publication is available
- As soon as is practical, a concise, lay-friendly summary of study design, methods, and key findings should be prepared and made publicly available (e.g., at the time of submission for peer-review publication)

- Study sponsors should be discouraged from submitting data-in-confidence given the need for public and transparent reporting in a pandemic emergency
- Special attention should be paid to concealment concerns (i.e., patients and clinicians able to identify treatment given in a blinded study) given the high level of interest accorded to treatments in a pandemic emergency, particularly among family and/or caregivers
- The potential for systematic differences in outcome measurement and reporting is always cause for concern but may be of special interest in multicenter trials of COVID-19 treatments that lack stringent criteria for outcome definition

### Example of Ordinal Outcome Scale for COVID-19 Treatment Trials\*

Patient State	Descriptor	Score
<b>Uninfected</b>	Uninfected; no viral RNA detected	0
<b>Ambulatory: Mild disease</b>	Asymptomatic; viral RNA detected	1
	Symptomatic; Independent	2
	Symptomatic; Assistance needed	3
<b>Hospitalized: Moderate disease</b>	Hospitalized; no oxygen therapy	4
	Hospitalized; oxygen by mask or nasal prongs	5
<b>Hospitalized: Severe disease</b>	Hospitalized; Oxygen by NIV or High flow	6
	Intubation & mechanical ventilation, pO <sub>2</sub> /FIO <sub>2</sub> ≥150 or SpO <sub>2</sub> /FIO <sub>2</sub> ≥200	7
	Mechanical ventilation pO <sub>2</sub> /FIO <sub>2</sub> <150 (SpO <sub>2</sub> /FIO <sub>2</sub> <200) <b>or</b> vasopressors	8
	Mechanical ventilation pO <sub>2</sub> /FIO <sub>2</sub> <150 <b>and</b> vasopressors, dialysis, or ECMO	9
<b>Death</b>	Dead	10

\*Source: [https://www.who.int/blueprint/priority-diseases/key-action/COVID-19\\_Treatment\\_Trial\\_Design\\_Master\\_Protocol\\_synopsis\\_Final\\_18022020.pdf](https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf)

Dr. Dan Ollendorf, Chair of the HTAi Global Policy Forum, led the development of this position statement in consultation with the HTAi COVID-19 response team, an interdisciplinary collective of members of the HTAi Board, Secretariat staff, and others with leadership roles within the society.

This is intended to be a living document, to be updated based on input from members and other stakeholders as well as evolution in the treatment paradigm for COVID-19. Please share your thoughts with Lucy Henry (lhenry@htai.org).