

# COVID-19 Interventional Trials

## Pandemic Research Ethics

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The purpose of this document is to provide guidance regarding the ethical standards and safeguards in human subject research in the context of the COVID-19 pandemic. By identifying ways our ethical obligations may change or be limited in this context, we can also identify ways to maintain or implement new safeguards. In addition, the following conclusions should be incorporated into all COVID-19 related research.

1. Enrollment in COVID-19 Research studies will not be a factor for consideration in any application of a CCHS Pandemic Allocation/Re-allocation policy (once finalized) as it would subvert the just allocation processes that have been carefully considered and balanced within the allocation framework (with the exception of those treatments cited in #3 below).
2. Although a patient/participant or their LAR may choose to withdraw from a study (this is unchanged), their data may continue to be shared, as furthering the public health interests supersedes individual privacy interests during a public health crisis.<sup>1</sup>
3. Priority access to COVID-19 therapies developed through CCHS's research efforts found to be safe and effective should be given to all participants in (greater than minimal risk) COVID-19 intervention trials, so long as it is clinically indicated.<sup>2</sup>
4. Any results from these trial should be made available broadly and freely to contribute to national and international health (i.e. publishing on the web or open-access should be expected in the first year).
5. Consent needs to comport with best practices while accommodating for any limits to visitation. To the extent possible, consent should be obtained directly from the patient/participant; an LAR may be used when the patient is unable to consent. This includes virtual consent as well as clarity on true alternatives to participating and re-consent.
6. Increased oversight for agile integration of new information is needed to attend to ethical considerations such as judicious application of randomization, placebo, adaptive designs, and increased protection of human subjects. Efforts to include special populations (e.g. pregnant women, children) should be made.

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<sup>1</sup> World Health Organization. Guidance for managing ethical issues in infectious disease outbreaks. 2016. <https://apps.who.int/iris/bitstream/handle/10665/250580/9789241549837-eng.pdf>

<sup>2</sup> Emanuel EJ, Persad G, Upshur R, et al. Fair Allocation of Scarce Medical Resources in the Time of Covid-19. *N Engl J Med*. March 2020;NEJMsb2005114. doi:[10.1056/NEJMsb2005114](https://doi.org/10.1056/NEJMsb2005114)

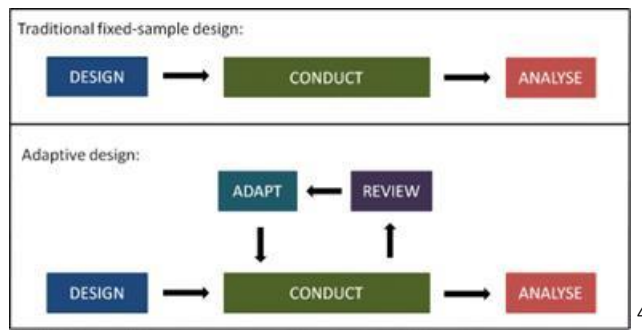
**Consenting Issues:** This COVID-19 Pandemic creates unique situations, as patients' families will be quarantined and unable to visit the patient, raising new ethical and practical issues around consent. The mortality risk and lack of known treatment options potentially increases fears and enhances the risk of both undue influence and therapeutic misconception. Steps should be taken to mitigate this risk.

- A. Consent should be obtained through usual and customary practices, with adjustment for virtual discussions, and with sufficient time for LARs to review the consent form.
  - i. When possible, begin conversations about future research participation directly with the patient, in anticipation of meeting inclusion criteria.
  - ii. Due to quarantine requirements, obtaining consent through a Legally Authorized Representative (LAR) must be done virtually, and should comply with the requirements established by the IRB.
  
- B. There should be a clear and consistent institutional approach as to whether patients can receive the study agent outside of the trial (such as off label or compassionate use).
  - i. Consenting process must include disclosure of whether the potential subject could receive the study drug at CCHS without enrolling in the study and whether enrollment limits participation in other studies.
  - ii. Expansion of COVID-19 research throughout CCHS enterprise should take place as soon as safely feasible (e.g. those hospitals with existing research infrastructure), to avoid justice issues around opportunities to participate in research as well as access to available off-label/compassionate use medications outside of research studies.
  - iii. Hospital transfer should be based on clinical needs, not for the purpose of participating in research. This avoids inappropriate diversion of resources from clinical care.
  
- C. Participants should be re-consented if/when the patient regains full decision-making capacity. In the event that the participant (or LAR) withdraws consent, previously collected data will not be removed from the study dataset, but there will be no additional data collection for research purposes only. Minimal necessary public health data will continue to be collected.
  
- D. In a public health emergency, there are additional limits to participants' privacy interests related to their data. Clearly communicate what identifiable information will go where; not all data can be de-identified given the public health interest.

**Study Design considerations: In a public health crisis, it is important to balance the need to get the best possible data as quickly as possible with the best possible study design and making sure that what is asked of participants is fair given the circumstances.**

- A. Randomization considerations: Consider trial design alternatives to randomizing participants into non-treatment arms (e.g. single cross-over trial design, age-matched controls, publicly available data)
  - i. There should be no cross-over for responders, understanding that this may undermine usefulness of this trial design; guarantee non-treatment arm gets crossed-over for non-responders or placebos.
  - ii. Use of placebo is not ideal, and would need to be very flexible to quickly integrate changes in standard of care. Strongly encourage adaptive design and frequent DSMB review (see below).

- B. Adaptive trial design: Adaptive trial design may offer flexibility needed during public health crisis. “Adaptive trial designs (ATDs) are trial designs which are adapted during a study according to interim results about the (in)effectiveness of an intervention (rather than a fixed, pre-determined protocol). ATDs may offer the flexibility required during GHEs: the Global Forum on Bioethics in Research reports that in ATDs, “a much higher percentage of patients receive some kind of treatment and study arms are dropped if interim analysis shows another arm is better. In all cases, therefore, fewer patients are assigned to an arm that is believed “currently” to be the inferior arm”.”<sup>3</sup>



- C. Special Study Population Inclusions: Given the circumstances of the public health emergency we advocate including children, pregnant women and incapacitated patients (including those with developmental disability who are not expected to regain decision-making capacity) in this research. Additional support of vulnerable participants should be considered to assure adequate protection for the duration of trials.
- D. Additional Research Oversight: Adaptations to research oversight provide a mechanism for agile integration of new information, redirection of research strategy, and further protections of participations.
- i. COVID-19 Interventional Research Committee should coordinate with pandemic response efforts to align research priorities and to avoid unnecessary duplication of research efforts.
  - ii. Institute robust Data Safety and Monitoring Boards with expertise and access to review the progress, safety profile, and justification frequently (perhaps weekly or every two weeks). Should consider a centralized Committee for oversight of DSMBs for this research or at least a coordinator to liaise between DSMBs.
  - iii. Recommend appointing an Information Manager across all COVID-related interventional research who would be responsible for integrating new information and making recommendations about appropriate changes to the protocols to reflect the new information.
  - iv. Rapid development of new information may lead to rapid changes in standard of care. There needs to be consensus as to what constitutes a significant enough shift in the standard of care to warrant changes to the existing research protocols.

<sup>3</sup> Section five: the ethics of research design (page 19) <https://www.nuffieldbioethics.org/assets/pdfs/Research-in-global-health-emergencies-background-paper.pdf>. Accessed March 23, 2020.

<sup>4</sup> Pallmann, P., Bedding, A.W., Choodari-Oskooei, B. *et al.* Adaptive designs in clinical trials: why use them, and how to run and report them. *BMC Med* 16, 29 (2018). <https://doi.org/10.1186/s12916-018-1017-7>