



COVID-19: Guidance on clinical trials for institutions, HRECs, researchers and sponsors

Preface

COVID-19 represents an unprecedented challenge to the health and research sectors. Our response to this challenge should be in line with several key principles and considerations. These are:

- The safety and well-being of patients, research participants and their families, and health care professionals, researchers and other staff involved in patient care and research are paramount.
- It is critical that public health systems remain able to respond to the needs of the community, both those impacted by COVID-19 and in terms of regular workloads.
- The conduct of research related to COVID-19 is a significant priority; however, the initiation and continuation of other ongoing and proposed research may also be critical for the well-being of patients, participants, communities and the research sector.
- Compliance with or adherence to regulations, guidelines, codes, policies and other standards remains necessary. However, interpretation of research responsibilities in the context of a crisis such as COVID-19 should be informed by flexibility, consultation and good sense so as to retain the focus on the safety and well-being of those most at risk in our institutions and communities.

Purpose and scope

This guidance provides general information and advice to institutions conducting or overseeing research, Human Research Ethics Committees (HRECs), researchers and sponsors in the context of the COVID-19 pandemic. It is directed towards those involved in clinical trial research and other relevant clinical research, but also may be of use to institutions, HRECs and researchers in other fields.

The purpose of this guidance is twofold:

1. to assist those overseeing, conducting and reviewing clinical trial research to maximise the safety of research participants and to minimise risks to participants and the community, to researchers and other institutional staff and to trial integrity, and
2. to address prioritisation of clinical trial research.

This advice represents current thinking and best practice at the government level. It reflects the shared views of the all state and territory Departments of Health, the Therapeutic Goods Administration (TGA), National Health and Medical Research Council (NHMRC) and the Clinical Trials Project Reference Group (CTPRG), of which all of these entities are members. Although it may refer to legislation or regulation, it is not legal advice and should not be cited for this purpose. It is a set of recommendations and is not legally enforceable.

COVID-19 and the challenges of responding to it are rapidly evolving and this guidance will be updated in response to changes globally and in Australia, and to reflect feedback received from you and our other stakeholders in the clinical trial research sector. Please check <https://www1.health.gov.au/internet/main/publishing.nsf/Content/Clinical-Trials> for updates.

Ongoing management of current clinical trials

Contingency planning

- Institutions, individual principal investigators (PIs) and sponsors should be undertaking contingency planning to address the potential impact of COVID-19 and responses to the crisis on current, ongoing clinical trials. This planning should include:
 - priority: assessment of the importance of and the risks associated with continuing the trial as designed or with necessary modifications. Responses could include continuing the trial in its present form, conducting the trial in a modified form, suspending the trial or closing the trial.
 - participation: assessment of the ability of participants to participate in the trial in accordance with protocol requirements and consideration of alternative models for participation that would not compromise the integrity of the trial.
 - capacity: assessment of the resources available for continuing the trial, including research staff, clinical support staff, pharmacy support, other support staff, space, equipment, supplies, etc. A component of a capacity assessment will be consideration of the need to re-allocate research staff to clinical care and other areas of patient support.
- Contingency planning will need to be an ongoing process.

Communications

- Decisions and actions in response to the crisis will be most effective if they are taken after appropriate consultation with the key stakeholders in a clinical trial: institutions, researchers, sponsors, regulators (if relevant) and, in some cases, participants. However, the need for rapid responses may require decisions and actions by one or more parties without prior consultation with the others. In such cases, all key stakeholders should be informed of the decisions and actions taken at the earliest opportunity.

Participants

- The safety and well-being of trial participants, other patients, family members, researchers and other clinical and support staff is paramount.
- In trials that proceed without modification, participants should explicitly be given the following options:
 - continuing to participate in the trial
 - suspending their participation, if this is viable, or
 - withdrawing from the trial.
- Participants who do not attend clinic visits or complete other trial activities may be reminded that these are required; however, if a patient declines or actively refuses to participate in trial activities, then their decision should be respected and they should be considered to have withdrawn from the trial. These participants should be informed that their decision will not affect their ongoing treatment or participation in future clinical trials.
- Participants who choose to move off the investigational product and onto standard care, and who do not wish to continue with site visits may be able to remain on trial for follow-up only.
- Participants should be informed of any modifications to the trial, including medical and other trial procedures, ongoing treatment or care and any tests or assessments that will have, or have the potential to have, an impact on them.

- In trials that have been modified, participants should explicitly be given the following options:
 - participating in the trial, as modified, inclusive of alternative mechanisms for engagement such as remote visits, data collection, monitoring, etc., as appropriate
 - suspending their participation, if this is viable, or
 - withdrawing from the trial.
- In a situation where a trial participant is unable to attend a visit or otherwise fulfil a condition of participation due to public health directives or government policy (such as restricted travel between states and territories), sponsors and researchers are encouraged to facilitate the participant being able to continue to participate in the trial at a site that is within the limits of any such restrictions. If available, such adjustments could be 'pre-approved' per the guidance provided below for amendments. Data collected could then be transmitted to the site that the participant would normally have attended.

Participants who are symptomatic for COVID-19

- Participants should be informed of the importance of notifying the research team in advance of attending any trial visits if
 - they are experiencing one or more symptoms suggestive of COVID-19 infection
 - they have recently (within 14 days) returned from overseas or have been in close contact with someone who is known to have contracted COVID-19 or has symptoms suggestive of COVID-19 infection, or
 - they are experiencing one or more symptoms not suggestive of COVID-19 infection, but suggestive of influenza or other infectious disease or condition that includes respiratory symptoms.
- The PI should ensure that appropriate follow-up with symptomatic participants is arranged and may advise the participant to present to another site or service for assessment, testing and/or further investigation.

Recruitment of new participants

- Decisions to recruit new participants to ongoing trials should take into account the potential benefits and burdens on Australia's health system and should depend on individual trial factors. The focus should remain on the safety and well-being of those most at risk in our institutions and communities. Any new recruitment should reflect the most current public health advice on social distancing.

Alternative models for conducting clinical trials

- Researchers and sponsors should educate themselves about novel approaches to the conduct of clinical trials, such as decentralised trials (i.e. teletrials) in which participants can be recruited and participate remotely and data can be captured remotely via available technology.
- Changes to clinical trials that enable remote data verification are in the public interest and should be understood as arising from the obligation to protect the safety of participants, researchers and others involved in research. In keeping with other published guidance, such changes should be notified to HRECs as time permits; however, they should not be subject to HREC requirements for amended individual participant information and consent forms (PICFs). For this category of changes, individual participant consent should be presumed, rather than needing to be obtained.
- HRECs should consider whether to actively encourage alternative models for conducting clinical trials, where possible and appropriate.

Notification of serious adverse events, significant safety issues, urgent safety measures, serious breaches, amendments and protocol deviations

- Researchers, sponsors, institutions, and HRECs should consult and adhere to existing guidance for safety monitoring and reporting published by NHMRC and the TGA (see <https://www.nhmrc.gov.au/about-us/publications/safety-monitoring-and-reporting-clinical-trials-involving-therapeutic-goods>). Any proposed modifications to standard practice should be discussed between the relevant parties and authorised, if appropriate, by the responsible party.
- Any incidents associated with the attendance at a clinic (or other relevant context) of a participant known, or later discovered, to be symptomatic should be promptly reported as an adverse event or safety issue, as relevant, in accordance with existing guidance.
- If a planned modification of a protocol is likely to have a negative impact on participants' safety or increase risk to participants, then review by an HREC, or an approved delegated process, is required. Institutions should consider identifying an individual, such as the HREC Chair or the most senior ethics officer, to make the decision as to whether a review is required prior to implementation of the proposed change. Substantial amendments should be submitted and approved by the HREC or via delegation as per processes authorised by the institution.
- The use of strategies to pre-approve certain categories of amendments is encouraged and should be adopted subject to the directions of jurisdictional health departments. Amendments eligible for pre-approval would be at the discretion of the institution and/or HREC and might include modification of a trial to:
 - employ virtual visits, telehealth, electronic consent or otherwise implement teletrials
 - change the 'site' to a location outside of a hospital or clinic or permit referral to another hospital or clinic
 - extend protocol timeframes for visits, procedures, trial medication delivery or follow-up to accommodate isolation periods or other disruptions
 - ensure that all returned investigational medical product is destroyed in accordance with standard protocols for the destruction of biohazards, and
 - any other changes that do not implicate participants' safety or well-being and are intended for the purpose of safeguarding the health of participants, researchers and staff or the community via infection control or reducing the burden of participation in a trial for the participants or researchers.
- Amendments to existing protocols that are designed to limit exposure of participants, researchers or staff to infectious agents or to change methodology, procedures or project activity to ease the burden on participants, researchers or staff do not need to be approved by HRECs before being implemented, if timing does not enable this. In addition, necessary amendments that suspend recruitment or testing of participants, or that modify research locations or staffing and other administrative matters can be implemented as necessary. If there is time for an amendment of this type to be reviewed in accordance with existing administrative amendment approval processes, that is optimal; but, participant and staff safety are the paramount concerns in all cases.
- If such changes are made, they should be reported to the sponsor in accordance with usual processes and to the HREC, when that becomes possible, in accordance with usual processes and in conformance with the National Statement.
- Protocol deviations can be reported to HRECs in the usual manner or collected and submitted in bulk form at the end of the crisis.
- Researchers are reminded that, although all deviations must to be reported to the trial sponsor, only the sub-set of deviations that have a significant impact on the continued safety or rights of participants or the reliability and robustness of the data generated in the clinical trial must be reported to the HREC. These deviations (also known as 'serious breaches') should also be reported by the PI to their institution, as they may impact on

medico-legal risk, the responsible conduct of research, or adherence to contractual obligations.

Amendments related to COVID-19 testing or analysis

- Amendments to clinical trial protocols that include the addition to an existing trial of new COVID-19 related elements, e.g. to enable epidemiological analysis of COVID-19, to add patients with COVID to an existing trial of a treatment or to add in testing for SARS-CoV-2 for safety purposes, (for example where studies include taking samples), is acceptable, so long as appropriate protection is put in place for handling of samples. Such arrangements would be treated as an urgent safety measure with subsequent notification in accordance with usual processes. Use of a separate specific information sheet and consent form to provide information about additional tests rather than modifying an existing form should be considered.
- Submission of template forms or separate individual PICFs for COVID-19 related testing for pre-approval by HRECs is recommended.

TGA response to COVID-19

- The Therapeutic Goods Administration (TGA) is providing active support for monitoring a number of issues relating to therapeutic goods including medicines and medical devices in response to COVID-19. Additionally, any trial that works toward a treatment or a vaccine for COVID-19 will be considered a priority by the TGA.
- With respect to clinical trials notified to the TGA under the CTN scheme, the TGA acknowledges that there may be deviations from trial protocols related to the supply of the Investigational Medicinal Product (IMP) and resulting from potential quarantine and travel restrictions or other factors that precipitate the need to manage patients remotely. Under the CTN scheme requirements, these deviations do not need to be notified to the TGA.
- With respect to variations to the trial responsive to COVID-19, such as trial start/finish date change, change in PI, number of participants, change in site address or the name of the trial approving authority, these do not need to be notified to the TGA. Variations to the trial such as changes to existing therapeutic goods, addition of therapeutic goods or addition of sites and those variations that are not responsive to COVID-19 will continue to require notification to the TGA. Whether a change in site is a change in site address or the addition of a new site is a determination that is made by the trial sponsor and the approving HREC.
- With respect to variations to clinical trials being conducted under the CTX scheme, where the TGA assesses only the safety aspects of a trial protocol, these can be assessed on a case by case basis.

Continuation of delivery of trial medication

- PIs, pharmacies and sponsors, where relevant, should develop plans to manage the continuation of clinically essential trial medication delivery to participants affected by self-isolation quarantine periods or as a result of testing positive for COVID-19. While there are no specific requirements under TGA legislation or the CTN scheme regarding the movement of clinical trial medications across state and territory borders, sponsors should ensure compliance with all relevant state and territory legislation.
- Any such arrangements should include a process for obtaining the agreement of the participant to the delivery changes.

Sample Collection and Storage

- Researchers and institutions that are considering the impact of the COVID-19 pandemic on the collection and storage of biospecimens for future use will understand that all human biospecimens should always be treated as potentially infectious; this potential is simply reinforced and heightened by the current circumstances. In many ongoing clinical trials, biospecimens are being collected from participants where assessment of SARS-CoV-2 status is not required and won't be possible. In addition, there is data that suggests that viral shedding from both symptomatic and asymptomatic carriers may be significant. For biospecimens that are later processed without adequate biosafety containment protocols, there is a small risk of any virus being transmissible. Therefore, the COVID19 pandemic reinforces the need to process all human biospecimens in accordance with appropriate biosafety containment protocols.
- The following measures are recommended:
 - Current concerns about COVID19 serve to remind us of the need to apply Universal/Standard precautions to the management of all human biospecimens (see <https://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/clinical+resources/clinical+topics/healthcare+associated+infections/prevention+and+management+of+infections+in+healthcare+settings> or other suitable reference).
 - If biospecimens are collected from donors that are known to be actively infected with COVID19 or any other transmissible microorganism or vector (e.g. HIV, HepB, HepC)

this information should be noted in the clinical annotation dataset attached to the biospecimens.

- All human-derived biospecimens should be processed, managed and utilised within facilities that are approved to manage human biospecimens at the appropriate level of physical containment.

Site monitoring visits

- Remote monitoring visits are encouraged as the first option in all cases and sponsors and institutions should ensure that these are facilitated, taking into account the need to avoid undue burden on hospital or institutional resources. These arrangements must adhere to patient confidentiality protocols already in place. Remote source data verification may be done electronically as long as appropriate security arrangements either are or can be put in place.
- If remote monitoring visits are not feasible, then clinical research associates may continue to undertake on-site monitoring visits as long as they are not symptomatic, have not returned from overseas in the last 14 days or had contact with a known case of COVID-19, in accordance with the most current public health guidance and advice from jurisdictional health departments.

Investigator meetings

- Investigator meetings and other meetings to plan, conduct or monitor a clinical trial should employ the use of remote technology wherever possible. Where researchers are temporarily co-located for the purposes of the delivery of clinical care or the conduct of the trial, engaging in any necessary interaction may be efficient, but should be subject to current public health advice.

Suspension or cessation of research

- Decisions by researchers to halt a study or suspend recruitment can be dealt with administratively between institutions and sponsors; however, a decision to close a study where an investigational product (IP) or an unregistered device, diagnostic or biological is being provided is a substantial amendment requiring HREC review.
- In assessing the proposed closure of a study where an IP or an unregistered device, diagnostic or biological is being provided, careful consideration should be given to any post-trial care or access to the IP, device or biological that is planned, or not planned, for relevant participants.

Advice for HRECs and research governance offices

- HREC members, ethics administrative officers, research governance officers and executive officers should conduct contingency planning related to their operations and employ sensible approaches to fulfilling their responsibilities in accordance with the National Statement and institutional policy and procedures. These approaches should not be overly rigid or generate onerous requirements on researchers or sponsors.
- HREC members, ethics administrative officers, research governance officers and executive officers should be aware of the guidance provided in this document and any updated guidance or advice, as well as current public health advice related to COVID-19.
- NHMRC, TGA, all Australian Departments of Health and the CTPRG support efforts by institutions, HRECs, researchers and sponsors to ease the burden of adhering to relevant regulation and guidelines by employing creative and streamlined strategies for doing so.

HREC meetings and procedures

- HRECs are encouraged to consider conducting meetings remotely by the use of video technology. This approach is permitted by the National Statement. (NHMRC has released a statement to HRECs supporting and encouraging the use of remote technology for meeting, where indicated).
- HRECs should review and determine what matters may be dealt with by delegation from the HREC (as authorised by the host institution, if applicable). This may require the development and publication of interim terms of reference.
- HRECs should strongly encourage or require the use of electronic document transfer and the use of digital/electronic signatures, wherever possible.

New Clinical Trials

Prioritising and expediting approval and variations for COVID-19 research and other clinical trials

- An expedited review process should be made available for research relating to COVID-19 or where there are public health grounds for rapid review. Researchers are advised to consult their institutions and their jurisdictional health departments for more information.
- Extraordinary meetings of HRECs should be organised where review of this research is indicated. These meetings should be promoted at the institutional and jurisdictional level.
- When assessing other proposed research, where proposals have already been submitted for review, HREC requests for modifications to protocols that are designed to limit physical contact between researchers or staff and participants (or between participants and each other) are appropriate.
- If researchers feel that changes intended to limit physical contact between researchers or staff and participants (or between participants and each other) should be put in place subsequent to approval, but prior to commencement of the research, then the change does not need to be approved by HRECs before being implemented, but should be notified to the HREC at the earliest opportunity.
- Researchers and sponsors should educate themselves about novel approaches to the conduct of clinical trials, such as decentralised trials (i.e. teletrials) and hybrid models in which participants can be recruited and participate remotely and data can be captured remotely via available technology.
- In proposing and reviewing new research, and in considering authorisation of new research, researchers, reviewers and institutions should consider the impact of the proposed research on patient and participant well-being and institutional resources (including ward and clinic capacity and availability of supporting services) and the impact on the health system and the community, more generally.
- If an HREC considers new proposed research to be inadvisable in the current environment, either as designed or with necessary modifications to accord with public health guidelines, then it is within the HREC's discretion to decline to approve the project. In such cases, the HREC may choose to indicate an in-principle acceptance of the merits and design of the research, but defer its approval until circumstances permit approval and commencement of the research.

Authored by:

All State and Territory Departments of Health through the Clinical Trials Project Reference Group <https://www1.health.gov.au/internet/main/publishing.nsf/Content/Clinical-Trials>

The National Health and Medical Research Council
<https://www.nhmrc.gov.au/research-policy/COVID-19-impacts>

The Therapeutic Goods Administration
<https://www.tga.gov.au/>