

COVID-19: Queensland Health Operational Guidance for sponsors, trial sites, ethics committees, research governance officer/s and researchers (April 2020)

The Queensland Health Queensland Clinical Trials Coordination Unit (QCTCU) has issued this Queensland Health guidance for sponsors, researchers, HRECs and RGOs to enable continued conduct of clinical trials during the COVID-19 pandemic.

The Commonwealth Department of Health, with input from all state and territory jurisdictions, the NHMRC and Therapeutic Goods Administration (TGA) has also produced a set of national principles that will apply during the COVID-19 pandemic. These are available on the Australian Department of Health [website](#) (that will be updated weekly).

We gratefully acknowledge our utilisation of and references to: the UK NHS MHRA COVID-19: Guidance for Sponsors, Sites and Researchers; References from Bellberry <https://bellberry.com.au/?cat=-1> ; NSW Health COVID-19 Guidance on Clinical Trials; Queensland Hospital and Health Services local advice and Alfred Health.

Up to date information regarding Queensland border closures can be found at <https://www.qld.gov.au/about/newsroom/queensland-border-restrictions>

Please contact QCTCU if you need support to maintain your clinical trials essential to critical care at QCTCU@health.qld.gov.au

Management of Clinical Research and Non-Interventional Research within Queensland Health – Considerations of COVID-19 Impact

This operational guidance is designed to assist practical application of the national principles in Queensland and will be continually updated as the pandemic situation evolves. Updates will be highlighted in yellow at each issue.

While the intent of the guidance is specifically for clinical trials, institutions may apply it to other research domains.

For any queries, comments and feedback on the documents, please contact the Queensland Clinical Trials Coordination Unit at QCTCU@health.qld.gov.au

The overarching principle embodied in these guidelines is the safety of all patients and participants: safety is paramount and of the utmost importance.

If an HREC or Institution considers newly proposed research to be inadvisable in the current environment it is within their discretion to decline to approve or authorise the project.

Advice for Investigators for Active Clinical Trials

At this point in time, clinical trial activities are continuing across Health facilities. Individual trial principal investigators together with their clinical departments should be undertaking contingency planning to address the potential impacts associated with trial participants being unable to attend trial visits, clinical research staff being unavailable, clinical trial pharmacy support being diminished or unavailable and general clinical support staff also being unavailable.

Although the Study site team will call participants in advance to confirm an appointment, participants should be advised to call in advance of clinic appointments if they are experiencing any

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of the symptoms suggestive of COVID-19 infection and have recently returned from overseas (within the last 14 days) or have been in close contact with a known case of COVID-19.

The Principal Investigators (PI) will ensure appropriate follow up is arranged and may advise the participant to present to another site or service for testing. Trial sponsors will be notified of any admissions via the usual serious adverse event reporting process.

PIs should also have contingency plans in place to manage the continuation of clinically essential trial medication delivery to participants affected by self-isolation quarantine periods or testing positive to COVID-19.

Investigational product accountability must be maintained including where the product has originated and been handled to assist tracking in case of identified cases.

PIs have the responsibility to determine:

- (i) whether existing trial participants are required to attend their trial site, or other facilities for ongoing treatment or assessment, or
- (ii) whether alternative platforms such as telehealth can be utilised, eg using a telemedicine enabled facility, personal devices that have videoconferencing ability such as skype, facetime, messenger, WhatsApp etc, and
- (iii) whether the recruitment of new participants should continue for each of the trials they are leading and for liaising with trial sponsors regarding their decisions.

COVID-19 screening procedures that may be mandated by the health care system in which a clinical trial is being conducted do not need to be reported as a protocol deviation or an amendment to the protocol even if done during clinical study visits unless the sponsor is incorporating the data collected as part of a new research objective.

- Participant and patient safety is the primary consideration in all decision making.
- Impact on research budget should be reviewed with the funding party.
- Impact on project grants should be considered and it is recommended to consult with the Administering Institution's Research Administration Officers (RAOs) as the first point of contact.

In preparation for when an investigator becomes unavailable a back-up investigator should be trained and delegated to take on this role immediately. Safety of patients of course remains a priority. If the safety of a participant is at risk because they cannot complete key safety checks, then consideration to discontinuing that participant must be considered. Where necessary, urgent safety measures may be implemented first and notified subsequently.

If an Investigator will be absent greater than one month the authorising research office should be notified. If the Principal Investigator will be absent for greater than three months alternative arrangements should be put in place.

This advice may be updated periodically, and all researchers are advised to continually monitor the Australian Government, and the Queensland Health Research Ethics and Governance website www.health.qld.gov.au/hiiro/html/regu/regu_home

Management of Clinical Trials and Amendments and related activities

A. New studies relating to COVID-19 General principles

Human Research Ethics Committee (HREC):

It is important that all approvals are sent via digital copy rather than hard copy in order to assist with timely and efficient document management across all stakeholders as printing may not be an option.

- In line with our interstate counterparts (Aboriginal Health & Medical Research Council NSW) and advice from Haylene Grogan, Deputy Director-General Aboriginal and Torres Strait Islander Health, HIIRO recommends that all approvals for research involving Aboriginal and Torres Strait Islander participants, requiring face to face contact should be suspended for the foreseeable future. Researchers should carefully consider how to maintain the safety of Aboriginal and Torres Strait Islander as participants on interventional clinical trials and amendments to avoid face to face contact should be considered such as telehealth/teletrials and investigational product delivery directly to the participant's home to allow the continuation of that research.
 - Recruitment of new participants to the clinical trials should be suspended.
 - Further information can be sought from the Aboriginal Health & Medical Research Council (AH&MRC) Human Research Ethics Committee by selecting the following link: <https://www.ahmrc.org.au/ethics/>
 - We will inform Queensland Health HREC's as and when new information becomes available.
 - Please note, AH&MRC HREC encourages researchers to consider alternate data collection methods such as remote options including teleconference, videoconference and zoom.
- HRECs should proactively liaise with their research communities to horizon-scan COVID-19 projects that are being developed and proposed to be submitted in Queensland. The Queensland Health Research Forum (includes all Research Directors from Queensland Health's Hospital and Health Services) will discuss all known COVID-19 related research proposals on a timely basis during the pandemic and offer support to the reviewing HRECs as required and also give recommendations regarding statewide lead governance arrangements. If possible, HRECs should advertise extraordinary full HREC meeting dates, and prepare members to be able to attend via virtual platforms.
- HRECs should use their current SOPs to determine whether a proposed study meets the relevant requirements to warrant an extraordinary meeting of the full HREC to conduct an expedited review.
- If possible, multiple projects should be dealt with at the same extraordinary meeting in order to reduce the burden on the HREC and its members and administrative staff.
- HRECs may develop mechanisms to identify and provide rapid preliminary assessment and feedback on new COVID-19 protocols, prior to HREC submission.
- An expedited review process is available for studies relating to COVID-19 where there are public health grounds for rapid review. The HREC will ensure COVID-19 positive patients are not overburdened, and their health is not jeopardised in any way.

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- HREC should, in the first instance, use their current SOPs to conduct meetings.
- HRECs should review and modify their Terms of Reference and SOPs to support the mechanisms required to deal with the COVID-19 situation.
- HRECs should note that there is no requirement in either the National Statement for the HREC to meet face-to-face to conduct a quorate meeting.
- HRECs are encouraged to adopt technologies to meet remotely.
- HRECs should develop methods to allow non-symptomatic, self-isolating members to continue to actively participate in meetings and meeting processes.
- HREC members should discuss with their HREC Executive Officer if they are required to self-isolate and what their availability is for attendance at meetings.
- HRECs should review and determine what matters may be dealt with by an executive committee of the HREC and whether changes to the HREC's Terms of Reference are required.
- HRECs should accept and encourage study teams to use electronic transfers of documents over paper documents where possible and the use of digital/electronic signatures (where available) over "wet-ink" signing processes.
- HRECs should issue approval letters that do NOT require wet ink signatures. Approvals issued from a recognised HREC office email address will suffice. Letters with inserted images of signatures can accompany that email and any recognised established electronic/digital signatures will be accepted (e.g. Docusign).
- ***If expedited permission to access and use Queensland Health information for approved research is required, please contact PHA@health.qld.gov.au***

Research Governance Officers (RGOs):

- Wherever possible, RGOs should work with Reviewing HRECs (whether they be based at the same institution or another Certified HREC) to expedite review of proposed new studies.
- RGOs should ensure COVID-19 positive patients are not overburdened, and their health is not jeopardised in any way.
- ERM digital signatures will be accepted and electronic signatures will be accepted if the following conditions are satisfied:
 - Identity: The "signature" must identify the originator and indicate their intention in relation to the information communicated (e.g. intention to provide approval via an electronic form). The electronic signature should be applied by the signatory.
 - Authenticity: The authenticity of the person(s) involved in the transaction can be verified.
 - Reliability: the method used for electronic approvals must be as reliable as and appropriate considering the purpose of the communication, having regard to all circumstances including any relevant agreement. This includes, for example, the secure storage of personal information and appropriate security measures in place for the electronic transmission of the information.
 - Consent: The person to whom the signature is given must consent to the use of electronic signature the method of transaction.

Note that:

- I. electronic signature should not be used to execute a deed. A deed should be printed and signed in wet ink.
- II. Legal advice should be sought prior to accepting an electronic signature on an agreement, particularly from a company executing under s. 127 of the *Corporations Act 2001 (Cwth)*.

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- III. If the execution requires a witness, the witness must be physically present.
- IV. Specific legal advice should be sought if unsure about the execution requirements of a particular document. ***

B. Safety reporting

- As this situation is unprecedented, it is acknowledged that protocol, SOP and GCP breaches are inevitable. There is no suitable guidance covering reporting currently available. Queensland Health is making this document available to assist clinical trial teams and sponsors navigate this situation.
- As safety in clinical trials is the priority, all significant safety issues, urgent safety measures and serious breaches impacting on patient safety and rights should be reported to HREC, Sponsor and TGA as relevant according to current guidelines.
- With respect to non-serious breaches, in lieu of reporting individual events, a post COVID-19 bulk deviation report should be submitted to relevant bodies after the situation has resolved.
- The bulk deviation report will require summary information on:
 - number of patients impacted,
 - changes to medication dispensing,
 - dose interruptions,
 - changes to visit schedule and visit activities
 - use of external services (e.g. pathology, imaging, visit sites, pharmacy)
 - missing data

C. Amendments to existing studies

Human Research Ethics Committee (HREC)

- HRECs should communicate with their research communities to encourage the sponsors they are working with to prioritise those amendments that are critical to patient safety, recognising that the COVID-19 situation is likely to increase the number of amendments required to be reviewed by an HREC.
- HRECs should develop a triage and processing system to be able to rapidly deal with amendments to existing studies that are affected by COVID-19.
- HRECs should publicly communicate that they are using a triage and processing system in order to set expectations on turnaround time for those amendments not affected by COVID-19.
- HRECs may choose to use a 'virtual' full HREC meeting to process these or may develop criteria to delegate the responsibility for reviewing such amendments to the HREC executive committee.
- HRECs should recognise that their responsibilities remain unchanged in ensuring that investigators provide appropriately detailed information to participants to enable their informed consent to protocol amendments. Depending on the circumstances, HRECs should work with study investigators as to how this is obtained operationally.

Studies where sponsor is adding testing for SARS-CoV-2 for safety purposes

- This may be implemented for example where studies include taking samples, and safety checks need to be implemented so that the appropriate protection is put in place for sample handling.
- Sponsors should treat such arrangements and HRECs should accept these as urgent safety measures with subsequent notification in the usual way.

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- Sponsors and HRECs should consider agreeing to use a separate specific information sheet to provide information about additional tests rather than modifying an existing Participant Information Sheet and Consent Form.

Studies where sponsor is adding new COVID-19 related elements

- COVID-19 screening procedures that may be mandated by the health care system in which a clinical trial is being conducted do not need to be reported as a protocol deviation or an amendment to the protocol even if done during clinical study visits unless the sponsor is incorporating the data collected as part of a new research objective.
- If a sponsor wishes to add a sub-study or other component, such as enabling an epidemiological analysis of COVID-19, this should be submitted as an amendment in the usual way. Sponsors and study teams should alert HRECs to make it clear that the amendment relates to COVID-19 so that it may be considered for an expedited review. This may be implemented for example where studies include taking samples, and safety checks need to be implemented, so that the appropriate protection is put in place for sample handling. Consider using a separate specific participant information sheet and consent form to provide information about additional tests rather than modifying an existing participant information sheet and consent form. The expedited review process should be considered for this change in recruitment and activity.

Amendments to existing studies impacted by the wider COVID-19 response: (Largely adopted from NHS MHRA Guidance)

- There are a number of possible scenarios where there may be a need to rapidly amend an existing study under this category.
- All amendments requiring submission should be submitted using Ethics Review Manager (ERM), clearly marking them with the subject header: ref# COVID-19 Amendment, so that they can be expedited.
- All amendments should be sent to participating sites in accordance with existing guidance. To support site implementation, it is important that:
 - The changes and local implications are made clear
 - Any changes to documentation are provided in tracked changes
 - For multi-centre studies, amendments should be provided to all relevant sites through ERM as usual.
- Where a study needs to be amended, with no COVID-19 involvement but because it is impacted by government restrictions on meeting, travel and movement, these amendments should be sent to the reviewing HREC in accordance with the scenarios described below.
- Where a trial participant is affected by COVID-19 and cannot complete key safety checks or relevant parts of the protocol, then they should be considered for discontinuation from the study, in accordance with ordinary safety processes. As always, urgent safety measures may be implemented first and notified subsequently (refer above).

Sponsor-instigated changes

- Under NO circumstances is it acceptable for a sponsor to create an amendment that creates an additional burden on a public health site. If there is a possibility that this may occur, sponsors must liaise immediately with the principal investigator to discuss.

D. Monitoring arrangements

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- Site monitoring or administrative arrangements to reduce the burden or physical contact with sites may be made as process deviations or amendments to the monitoring plan that do not require HREC approval. They may be implemented at the site through communication with the study team. It is the responsibility of the CRA to disclose this information.
- Remote monitoring must not result in confidential patient information being sent to the sponsor if this has not already been addressed in the participant information sheet. Source data verification may be done remotely by electronic means if the necessary security arrangements can be put in place.

Monitoring Visits

- Clinical Research Associates can undertake monitoring visits as long as they are not symptomatic, have not travelled from overseas in the last 14 days or had contact with a known case of COVID-19 in accordance with Queensland Department of Health advice <https://www.qld.gov.au/health/conditions/health-alerts/coronavirus-covid-19>. The department has a right to rescind this privilege in accordance with changing hospital and government policies.
- Where remote monitoring visits may be feasible, they should be preferred to on-site visits. Non-essential visits should be limited at all public hospitals.
- Videoconferencing / webinars is another option that should be considered.
- Sponsors may consider delaying audits and individual PIs should liaise with trial sponsors directly to determine the most appropriate action required for individual trial monitoring requirements.

Investigator Meetings

- The research team will be unable to attend investigator meetings if interstate or international travel is required. Videoconferencing and other options such as webinars may be available as an alternative means of employees being involved in essential meetings.

E. Participant visit arrangements

- Sponsor-proposed changes to avoid exposing patients or to reduce the burden on clinical services may be made as an amendment that does not require HREC approval. They may be implemented at the site through communication with the study team. Sponsors and PIs have the responsibility to determine (i) whether existing trial participants are required to attend their trial site, or other facilities for ongoing treatment or assessment, or whether alternative platforms such as telehealth can be utilised, e.g. using a telemedicine enabled facility, personal devices that have videoconferencing ability such as skype, facetime, messenger, WhatsApp and so on, and (ii) whether the recruitment of new participants should continue for each of the trials they are leading and for liaising with trial sponsors regarding their decisions.
- Where the facility is available, PIs should implement the use of telemedicine/ teletrials as Medicare now has item codes for all telehealth related consultations (note commercially sponsored clinical trials cannot be funded by Medicare). Refer to Teletrial Consultation User Guide and the Australian ICH GCP including Teletrials) Standard Operating Procedures links below

<https://www.servicesaustralia.gov.au/organisations/health-professionals/subjects/coronavirus-information-health-professionals>

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<https://www.servicesaustralia.gov.au/organisations/health-professionals/news/new-mbs-telehealth-items-coronavirus>

https://www.health.qld.gov.au/__data/assets/pdf_file/0027/836217/Teletrial-Clinical-Consultation-User-Guide-V4.0_post-HSD.pdf for use)

https://www.health.qld.gov.au/hiiro/html/regu/for_researcher/gcp,research-ethics-and-governance-standard-operating-procedures-sop

- Where an amendment may potentially increase the risk to participants (e.g., resulting in fewer participant checks), the HREC must be notified and the amendment processed through the expedited pathway. Refer to the above.
- HRECs should recognise that their responsibilities remain unchanged in ensuring that investigators provide appropriately detailed information to participants to enable their informed consent to protocol amendments. Depending on the circumstances, HRECs should work with study investigators as to how this is obtained operationally.

F. Study product sent directly to participants

- Sponsors must assess the risks relating to the shipment of product directly to the participant and consider any shipping and storage arrangements. Participants must consent verbally to providing contact details for shipping purposes. Where participants are self-isolating or in quarantine, arrangements for a nominated person to collect the product may be implemented with the participant's verbal consent. The participant will not have to sign for this delivery package. The courier will not collect unused study drug or empty bottles.¹ This is to ensure that the study drug and the empty bottles have not been contaminated by the SARS-CoV-2 virus from asymptomatic or symptomatic participants, and ensures the virus will be non-viable when study drug and the empty bottles are returned to site after the pandemic has passed.**
- Any such temporary arrangements should be handled as deviations (to be reported in bulk at the end of the pandemic as per above) or **minor amendments*** that do not require HREC approval or Governance authorisation but can be noted or acknowledged to expedite the approval process.
- Sponsors and investigators should consult with the institution's clinical trial pharmacies about proposed alternative access mechanisms.

G. Temporarily halting a study or extending the duration due to COVID-19

- Temporarily halting a study is a serious consideration, as the successful completion of a study is an important ethical endpoint. A study should only be suspended if there is no practical way of allowing it to achieve its primary outcomes during the COVID-19 pandemic.
- The decision to temporarily halt a study should include detailed written consideration of how the study could be usefully brought to a conclusion post the COVID-19 pandemic.
- Where a study that involves an investigational product (drug, device, or procedural intervention) needs to be temporarily halted, sponsors must issue a major amendment to the HREC, who should expedite the process after assessing the submission against existing guidance.
- Where the study does not involve an investigational product, this may be made as an Administrative amendment and may not require HREC approval. Please confirm with reviewing HREC. It may be implemented at the site through communication with the study team.

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H. Closing a study

- Closing a study is a serious consideration, as the successful completion of a study is an important ethical endpoint. A study should only be stopped if there is no practical way of allowing it to achieve its primary outcomes during the COVID-19 pandemic, and/or if it will not be possible to complete the study within an appropriate timeframe after the COVID-19 pandemic.
- For any studies involving provision of treatment to participants, careful consideration should be given to post-study care. If this cannot be in line with the information provided in the participant-information sheet, a major amendment should be submitted to the HREC. Such amendments will be reviewed according to existing guidance, but the process will be expedited.
- For any studies not involving provision of treatment to participants, a notification to the HREC should be provided, and an end of study report should subsequently be provided.

I. Site-instigated changes due to clinical requirements needing to suspend recruitment

- Sites must raise such issues with the sponsor as early as possible if this is likely to occur. If the arrangements will affect the whole study.
- As always, participant safety is paramount: if continuing to conduct the trial according to the protocol is judged to pose an unacceptable risk to trial participants or research coordination staff, and any reasonable amendment to the protocol would compromise the study results or outcome, sites should consider the temporary suspension of participant recruitment.
- If sites and sponsors agree to suspend recruitment due to COVID-19 issues, Clinical Trial Research Agreements (CTRAs) should be amended through an exchange of letters to account for impacts on any applicable recruitment targets and contractual obligations.

J. Sites needing to terminate a study due to COVID-19:

- Sites whose studies are affected by COVID-19 are encouraged to work with trial sponsors to the greatest extent possible to come to an arrangement so trials can continue without posing an unacceptable risk to participants or trial staff.

Please contact QCTCU if you need trained clinical trial volunteer staff support to maintain your clinical trials essential to critical care at QCTCU@health.qld.gov.au

- Sites conducting their trial under the CTRA are reminded that termination provisions are contained in the Force Majeure clause of the agreements. Sites needing to invoke a force majeure provision are reminded that they must follow the process described in the clause.

K. Sites needing to move participant visits due to staff and resources reallocated to clinical care or limiting participant contact

- Sites must raise such issues with the sponsor as early as possible if this is likely to occur. Where possible such arrangements should be handled prospectively as an amendment. In cases where there is no time to arrange for such review, changes should be implemented as urgent safety measures and reported retrospectively. In any such situation the impact on participants should be considered and arrangements made to cover this, for example additional transport or another location.
- The options are to set up as a sub-contracted site of the existing site if oversight can be maintained by the existing site, or to set up new sites, or to implement direct home care arrangements by the sponsor. For study types where addition of new sites (with new PIs) is a

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substantial amendment, existing guidance for submitting a substantial amendment for new sites should be followed. In all other cases, existing guidance for non-substantial amendments and addition of new sites should be followed.

- Establishing subsidiary sites to accommodate moving away from the hospital setting is an amendment that does not require HREC approval.

L. Withdrawing participants

- Sites must raise such issues with the sponsor as early as possible if this is likely to occur. For any studies involving provision of treatment to participants, careful consideration should be given to post-study care. If this cannot be in line with the information provided in the participant-information sheet, an amendment should be submitted. Such amendments will be categorised and assessed according to existing guidance, but the process will be expedited. Studies where the Principal Investigator is taken off the study.
- Any existing arrangements covering a Principal Investigator's absence should be followed. HRECs may review and amend their own arrangements. Where no such arrangements are in place, Queensland Health guidance is that:
 - if the Principal Investigator's absence will be greater than one month the HREC should be notified.
 - if the Principal Investigator's absence will be greater than three months alternative arrangements should be put in place.

M. References

*Amendment Definitions

<https://www.research.nhg.com.sg/wps/wcm/connect/d3bf9f804b2e3afb8c44ce132c2b9a2e/QuaIite+Issue+2012-04.pdf?MOD=AJPERES>

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*** Electronic Signature References

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