COVID-19 Guidance on Clinical Trials

Guidance for clinical trial Sponsors, sites and researchers

COVID-19: Guidance for clinical trial Sponsors, sites and researchers

NSW Health is responding to an outbreak of a novel coronavirus (COVID-19), first diagnosed in China in December 2019.

General principles:

This guidance has been provided to minimise the adverse health impacts on clinical trial participants as well as site, sponsor and vendor staff involved in clinical trials. Emphasis is placed on managing burden and disruption to health-related services in NSW at this critical time. Safety of ongoing trial participants and risk reduction remains the priority for NSW Health.

Sponsors, sites and researchers are asked to consider the wider impact of COVID-19 on their clinical trials portfolio, participants and staff, as related to health system reprioritisation, restrictions on movement, and supply chain challenges.

Where possible all new clinical trial arrangements should be managed prospectively as a Protocol Amendment. However changes may need to be implemented as Urgent Safety Measures (NHMRC Safety Monitoring and Reporting in Clinical Trials 2016) and reported immediately. Sponsors are reminded of the need to obtain Participant Informed Consent for changes to trial conduct.

NSW Health also requests that any changes are designed to have minimal impact on the NSW Health system at this time including HREC, Research Governance and clinical trial unit staff.

Further information regarding HREC and RGO guidance follows below.

Active clinical trials

Sponsors, sites and researchers are asked to collaborate on all active clinical trials and consider:

- The risks to participant safety in either (i) continuing a clinical trial or (ii) discontinuing a clinical trial where there are no other treatment options. Where there is an unacceptable risk to participant safety in continuing a clinical trial, sponsors and sites should decide whether to temporarily suspend enrolment, suspend the trial or to discontinue the trial altogether.
- The availability of the Principal Investigator and delegation of responsibility should be considered in terms of current healthcare reprioritisation and the PIs primary responsibility of the trial under ICH-GCP. Availability of clinician investigators and research nurses will be impacted as resources are diverted to essential services and Sponsors should plan for this occurence.
- Changes to participant visits should be considered and may include reduction in visits, increase in visit windows, establishment of satellite sites, conduct of out-of-hospital visits, remote consultations, telephone calls, emails and postal questionnaires.
- Continuity of IP to participants – safety of participants and discontinuation of investigational product should be carefully considered, including the safety of abruptly interrupting study drug. Dispensing, shipping and storage arrangements should be reviewed:

  This may include;

  - dispensing to a third party where a trial participant is in self-isolation or practicing social distancing

    - dispensing an extended supply of study drug beyond protocol-mandated dispensing
    - couriering study drug to participants' homes,
    - chain of custody and temperature monitoring requirements.

- Protocol amendments and deviations – contact the reviewing HREC and Research Governance Office in accordance with the information below for protocol amendments, deviations and safety reports. Requested changes should be prioritised and managed to reduce the administrative burden on NSW Health staff.
- Changes to monitoring arrangements should be considered and may include reduction in frequency of monitoring and/or increased remote monitoring. The additional burden of remote monitoring on NSW Health staff should be considered in terms of healthcare reprioritisation.
- Quality of documentation practices at site and by Sponsors must be maintained.
- New trials of potential COVID-19 therapeutics must follow current TGA and NHMRC processes including HREC approval.

Clinical trials currently in start-up phase or planned for 2020

Sponsors, researchers and sites are requested to consider their planned clinical trial portfolio for 2020 and allocate according to health system capacity and risk assessment. Trials currently in start-up phase through Q2 2020 may require review and postponement depending on the developing COVID situation.

For further queries please contact: clinicaltrialsNSW@health.nsw.gov.au

For the most recent information on COVID-19, please refer to the NSW Health Website.

COVID-19: Clinical trial guidance for HRECs and RGOs

Modelled on UK NHS HRA COVID-19: Guidance for Sponsors, Sites and Researchers
Referenced from Bellberry https://bellberry.com.au/?cat=-1

General principles:

Human Research Ethics Committee (HREC) meetings:

- HRECs 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 or NSW Health policy for the HREC to meet face-to-face to conduct a quorate meeting. That is, remote attendance is possible and encouraged as circumstances determine. (NHMRC has released a statement to HRECs at Appendix 1 below.)
- 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.

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 amendments.

Protocol Breaches

With thanks to Alfred Health, Melbourne's guidance document: Contingency Plan for COVID19 Interruption to Clinical Trials

- As this situation is unprecedented, it is acknowledged that protocol and GCP breaches are inevitable. There is no suitable guidance covering reporting currently available. NSW 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.
- With respect to non-serious breaches, in lieu of reporting individual events, a post COVID-19 deviation report should be submitted after the situation has resolved.
- The 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)
    - missing data

New studies relating to COVID-19

- HRECs should proactively liaise with their research communities (esp. those in COVID-relevant areas (eg respiratory medicine, virology, etc), to horizon-scan projects that are

being developed and proposed to be submitted and the volume of those projects. This liaison does not have to be overly burdensome and could constitute email correspondence.
- HRECs should use that knowledge to advertise extraordinary full HREC meeting dates, if possible, and prepare members to be able to attend.
- HRECs should use their current SOPs to determine whether a proposed study meets the relevant threshold to hold 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.
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Amendments to existing studies:

- 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 highly likely to dramatically 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.
- 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.
- The NSW Health Consent Toolkit contains a number of consent materials including a range of sample consent forms that cover all essential areas for sample testing, including issues such as return of incidental findings.

Studies adding new COVID-19 related elements

- 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.

Amendments to existing studies impacted by the wider COVID-19 response:

(Largely adopted from NHS HRA Guidance)

Where a study needs to be amended, with no COVID 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 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.

Sponsor-instigated changes

In no case may a sponsor 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.

Monitoring arrangements

- Site monitoring or administrative arrangements to reduce the burden or physical contact with sites may be made as non-substantial amendments and do not require HREC approval. They may be implemented at the site through communication with the study team.
- Any remote monitoring amendments must still maintain all 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.

Participant visit arrangements

- Sponsor-proposed changes to avoid exposing patients or to reduce the burden on clinical services may be made as non-substantial amendments and do not require HREC approval. They may be implemented at the site through communication with the study team.
- Where an amendment may potentially increase the risk to participants (eg, resulting in fewer participant checks), the HREC must be notified and the amendment processed through the expedited pathway.
- 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.

Study product sent directly to participants

- Sponsors must assess the risks relating to the product 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. Any such temporary arrangements should be handled as a non-substantial amendment that does not require HREC Approval.
- Sponsors and investigators should consult with the institution's clinical trial pharmacies about proposes alternative access mechanisms.

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 in the COVID-19 world.
- The decision to temporarily halt a study should include detailed written consideration of how the study could be usefully brought to a conclusion in the post-COVID-19 world.
- Where a study that involves an investigational product (drug, device, or procedural intervention) should be temporarily halted, sponsors must issue a substantial 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 a non-substantial amendment and does not require HREC approval. It may be implemented at the site through communication with the study team.

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 in the COVID-19 world.
- 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 substantial amendment should be submitted to the HREC. Such amendments will be categorised and assessed 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.

Site-instigated changes due to clinical requirements

Sites 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, NSW encourages sponsors follow the instructions contained in this guidance (above).
- 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, CTRAs should be amended through an exchange of letters to minimise any applicable recruitment targets.

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.
- Sites conducting their trial under the Clinical Trial Research Agreements (CTRAs) 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.

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.
- 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 is a 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 is a non-substantial amendment. These should be handled as a non-substantial amendment that does not require HREC approval.

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, a substantial 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, NSW Health guidance is that:
    - if the absence will be greater than one month the HREC should be notified.
    - if the Principal Investigator will be absent for greater than three months alternative arrangements should be put in place.

Sources consulted:

- UK NHS HRA COVID-19: Guidance for Sponsors, Sites and Researchers
- Bellberry Ltd – Clinical trials and COVID-19 https://bellberry.com.au/?cat=-1
- Alfred Health, Melbourne: Contingency Plan for COVID19 Interruption to Clinical Trials

Appendix 1:

From: HREC.admin <HREC.admin@nhmrc.gov.au>
Sent: Monday, 16 March 2020 4:32 PM
Subject: HREC meetings by video or phone conference [SEC=OFFICIAL]

Dear HREC Chairs and administration officers

We have had a few queries about the suitability of holding ethics committee meetings by means other than face-to-face (i.e. video or phone conferencing).

While the *National Statement on Ethical Conduct in Human Research* doesn't address this matter specifically, we would like to assure you that meetings by video or phone are fine (so long as they meet the requirements of 5.2.30) and are encouraged at this time. We would also like to assure you that as per paragraphs 5.2.31 and 5.2.32, the views of and opinions of those in the minimum membership categories need to be provided. While this is ideally at a meeting, if this is not possible, then the views of those absent should be received and considered before a decision is reached.

We would like to take this opportunity to thank you for your valuable work and contribution to progressing the research effort in Australia, particularly with the challenges around us at this present moment.

Please email HREC.admin@nhmrc.gov.au if you have any further queries.

Kind regards

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Australian Government
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BUILDING A HEALTHY AUSTRALIA

Appendix 2

TGA response to coronavirus (COVID-19) (issued 13 March 2020)

As part of the Department of Health, 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 the novel coronavirus (COVID-19).
https://www.tga.gov.au/media-release/tga-response-coronavirus-covid-19