Health
South Eastern Sydney
Local Health District

COVID-19: Clinical trials guidance for researchers and sponsors

Background

COVID-19 represents an unprecedented challenge to the conduct of clinical trials. Our response to this challenge needs to consider that:

- 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.
- Whilst the conduct of research related to COVID-19 will be a significant priority, the continuation and initiation of other research is also critical for the well-being of patients, participants, communities and research capacity in SESLHD.
- The conduct of a clinical trial is an ethically governed, contractual relationship between the sponsor and the investigator(s) and 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.
- It is critical that the HREC and support provided by the SESLHD Research Office remain able to respond to the needs of the research community, both those impacted by COVID-19 and in terms of regular workloads. This unprecedented crisis coincides with a period of significant understaffing, restructure and retraining of the Research Office that presents a unique operational challenge.
- COVID-19 is rapidly evolving in Australia and worldwide. Recommendations made today will require regular review and updates which need to be communicated widely to the clinical trials community throughout SESLHD. Decisions and actions in response to the crisis will be most effective if they are made in consultation with the key stakeholders in a clinical trial, however there may be times where this isn't possible. In such cases, all stakeholders will be informed of decisions and actions via:
    - The SESLHD Research website
    - Email communications distributed to research active staff.

Purpose

This document provides advice to clinical trial units and their sponsors in conducting clinical trials within SESLHD in the context of the COVID-19 pandemic. It is directed towards those involved in clinical trial research and other relevant clinical research. This document addresses:

- The anticipated effect of COVID-19 on the conduct of clinical trials in SESLHD
- Prioritisation of clinical trial research.
- Changes to SESLHD HREC and Research Office procedures in response to this crisis.

This advice draws upon and consolidates advice and recommendations contained in:

- NSW Health – COVID-19 Clinical Trial Guidance for Sponsors, Sites, Researchers, HRECs and RGOs
- Department of Health – COVID-19: Guidance on clinical trials for institutions, HRECs, researchers and sponsors

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- National Health and Medical Research Council – COVID-19 impacts
- Therapeutic Goods Administration – Coronavirus (COVID-19): Information on medicines and medical devices
- SESLHD Research Strategy 2017-2021
- SESLHD Journey to Excellence Strategy 2018-2021

1. Overview of risks associated with COVID-19 pertaining to Clinical Trials and clinical research

At present the only effective strategy for managing COVID-19 is adherence to policies of social distancing and self-isolation (SD&SI). Where those measures are impractical and unenforceable such as treating patients severely affected by the disease the principles of personal protection apply. These policies apply to Clinical Trials and clinical research because health and research *in* health are indivisible.

With a limited armamentarium against a virulent and exponentially expanding vector it is expected that "the crisis" is a period defined by containment and suppression until herd immunity builds to a level where the health service is not overwhelmed by its sudden appearance in a non-immune population. Therefore, while it is difficult to define the duration of a crisis, the inflection point is the time where the exponential rate of change of new diagnoses is no longer > 1 and is the "beginning of the end". However the COVID-19 crisis may only "end" with viral exposure to near full population penetration (with sustained immunity and resistance to repeat infection which is currently unknown), relaxation of public health SD&SI regulations or an effective treatment or vaccine, whichever comes first.

The safety and well-being of trial participants, patients, family members, researchers and other clinical and support staff is paramount. SD&SI has implications for these and sponsors of the trial.

2. Advice for participants, staff and sponsors

2.1 Clinical Trial Participants

- All participants in trials that proceed should explicitly be given the following options:
  - Ongoing participation in the trial with information about any modifications including, but not limited to:
    - alternative mechanisms for engagement such as remote visits,
    - changes to medical and trial procedures,
    - ongoing treatment,
    - additional tests (e.g. COVID-19 status)
    - data collection,
    - remote monitoring etc.
  - Suspending participation, 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 to participate in trial activities, 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. Standard withdrawal procedures must be followed and safety issues addressed.

- 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.
- Should a participant be unable to fulfil conditions of participation due to public health directives or government policy (such as restricted travel), sponsors and researchers are encouraged to facilitate participation within the limits of restrictions. For example by participating at a different trial site, or offsite. Data collected off-site may then be transmitted to the participant's usual trial site.

2.2 Clinical Trials and Research Staff

Clinical trials and research staff should continue to adhere to the study protocol and:

- Inform all participants in a clinical trial, with or without modification, of the ongoing conditions of the trial and confirm continued participation including an offer to suspend or withdraw participation in the trial.
- Ensure training and compliance with social distancing and the correct PPE where appropriate for studies or procedures that carry a higher aerosolised risk.
- Screen participants in advance of attending any on site trial visits for:
  - Symptoms suggestive of COVID-19 infection
  - Recent return (within 14 days) from overseas and close contact with someone known to have contracted COVID-19 or with symptoms suggestive of COVID-19 infection
  - Symptoms not suggestive of COVID-19 infection, but suggestive of influenza or other infectious disease or condition with respiratory symptoms.

2.3 Investigators

Investigators should:

- Review their register of ongoing and upcoming clinical trials and determine their capacity to start or continue the clinical trial. Decisions to recruit new participants to ongoing trials should take into account:
  - The potential benefits and burdens on SESLHD clinical service priorities
  - Individual trial factors
  - The capacity of the HREC and Research Office to process applications at this time
  - Current public health advice on social distancing

  The focus should remain on the safety and well-being of those most at risk in our institutions and communities.
- Assess the ability of participants to participate in the trial in accordance with protocol requirements and consider alternative models for participation that would not compromise the integrity of the trial.
- Arrange the appropriate follow-up of COVID-19 symptomatic participants. This may involve advising the participant to present to another site or service for assessment, testing and/or further investigation.
- Assess the resources available for continuing the trial, including research staff, clinical support staff, pharmacy and uninterrupted access to the study drug, space, equipment, PPE and other supplies. Consideration should be given to the reallocation of staff and equipment to clinical care activities.
- Notify the Research Office of modifications that do or do not comply with the information provided by the HREC for acknowledgement.

- Protocol modification can be reported to the HREC in the usual manner or collected and submitted in bulk form at the "end" of the crisis. Only the sub-set of modification known as "serious breaches" 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.

- Confirm their sponsor's willingness to start or continue the trial, with or without modification.
  - All modifications must to be reported to the trial sponsor.

2.4 Sponsors

Sponsors should:

- Review their register of ongoing and new clinical trials and determine their capacity (including insurance) to start or continue clinical trials.
- Familiarise themselves with novel approaches to conduct clinical trials, such as decentralised trials (i.e. teletrials) and hybrid models in which participants can be recruited and can participate remotely with data captured remotely.
- Confirm with their investigators their willingness to start or continue the trial, with or without modification.
- Consider their capacity to support remote monitoring visits. Sponsors and institutions must ensure that these are facilitated without burdening institutional resources. These arrangements must adhere to patient confidentiality protocols already in place. Remote source data verification may be done electronically provided the appropriate security arrangements exist.
  - Where remote monitoring visits are not feasible, then clinical research associates may continue to undertake on-site monitoring visits provided they adhere to the same criteria as study participants in accordance with the most current public health guidance and advice from NSW Health (i.e. they are not symptomatic, have not returned from overseas in the last 14 days or had contact with a known case of COVID-19).
- Investigator meetings to plan, conduct or monitor a clinical trial should employ the use of remote technology wherever possible. Face to face interaction will be subject to current public health advice.

3. Prioritisation of Clinical Research including Clinical Trials

Prioritisation is a balance between risk and benefit. This guidance draws on principles directing other medical services within SESLHD, recognising that categorisation of medical services unaffected by COVID-19 still need to be delivered according to levels of emergency and criticality. It confirms the importance of Research as a pillar in our Journey to Excellence and a centrepiece of learning and a culture of continuous improvement.

All research activity must maintain compliance with existing requirements, including availability of the study team to conduct research activities and sponsor approval.

The following categories should be considered by investigators in determining the priority of current and planned research.

3.1 Category 1: Research that works toward greater understanding of the disease or a treatment or vaccine for COVID-19.

Research that contributes towards greater understanding of COVID-19, treatments and vaccines should be prioritised by research teams, the Research Office and the HREC.

Category 1 studies must comply with existing requirements but will be expedited for HREC and governance review. Research teams are advised to consult with the SESLHD Research Office, the OHMR and/or the HREC Chair for more information.

Participant recruitment should open for these studies.

3.2 Category 2: Research potentially affected by SD&SI where suspension or cessation presents a material risk to the participant.

Studies that may be affected by SD&SI but would present a risk to participants if suspended or ceased should be continued during the COVID-19 crisis, so long as they are adequately staffed and have approval from the sponsor to continue.

These studies may involve life-extending or life-saving treatment with no readily available, alternative treatments for the participant population. Although there are risks associated with continuing the study, the benefits to participants outweigh those risks.

Participant recruitment may remain open or may close at the discretion of the Principal Investigator.

3.3 Category 3: Research unaffected by SD&SI.
Research that is unaffected by SD&SI requirements may include:

- Retrospective or prospective medical record reviews
- Studies involving off-site or electronic/remote recruitment and participation
- Studies unaffected by quarantine or drug supply issues
- Studies not requiring protocol amendments
- Studies with research staff available to continue.

The capacity and potential benefit of commencing and continuing Category 3 studies outweighs the negligible risk and may commence or continue during the COVID-19 crisis.

Participant recruitment may remain open or may close at the discretion of the Principal Investigator.

3.4 Category 4: Research affected by SD&SI where suspension or cessation does not present a material risk to the participant.

Research that is affected by SD&SI requirements and where suspension or cessation poses no material risk to participants may be continued, suspended, modified or ceased at the Investigator's discretion.

Participant recruitment may remain open or may close at the discretion of the Principal Investigator.

3.5 Category 5: Research affected by unmitigated SD&SI risk.
Research that is affected by COVID-19 in such a way that it:

- Is affected by SD&SI requirements
- Cannot be modified in a way that achieves the research objectives
- Involves a treatment for which there are available alternatives
- Affected by staff redeployment and no longer adequately resourced
- No longer approved by the sponsor

Should be suspended or closed.

Decisions 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

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 investigational product or an unregistered device, diagnostic or biological is being provided, careful consideration should be given to any post-trial care or access to the product, device or biological that is planned, or not planned, for relevant participants.

4. Changes to SESLHD HREC and Research Office procedures

4.1 Ethics

The SESLHD HREC will facilitate reasonable risk mitigation measures relating to COVID19 and recommend that these changes should be implemented without delay, provided that there is no additional risk introduced to the participants and no increased burdens to the health district.

Such modifications must be communicated to the HREC as soon as convenient. The process for submitting is currently under development. The SESLHD Research Office can be contacted via SESLHD-RSO@health.nsw.gov.au.

For studies approved by the SESLHD HREC the following information must be provided with the amendment:

- The email subject line is to include the ethics reference number and "COVID-19 Modification"
- Confirmation of ethics approval from the SESLHD HREC.
- Confirmation that all changes are specific to managing risk due to COVID-19.
- Details of the changes must be attached to the protocol while the changes remain in effect.
- Advice as to whether the changes are likely to continue after COVID-19.
- Confirmation that no additional risks to participants or researchers or staff are created.
- Confirmation that no additional burden/expense to the hospital or health district is created, or if there is additional expense, your research budget will be cover this.

Modifications reported to the HREC in this way must be limited to those related to COVID-19 risk mitigation only. They will be considered 'Urgent Safety Measures' which do not need ethics approval to implement. These measures will be 'acknowledged' rather than 'approved'.

The arrangements above are only for amendments required to mitigate COVID-19 related risk. All other amendments to research must still be submitted in the usual way.

Researchers considering submitting any new studies for ethics review, are asked to consider if the application can wait until after the COVID-19 response measures are concluded.

4.2 Governance

Amendments to studies at SESLHD sites must be notified to Research Governance via existing processes (i.e. via SESLHD-RSO@health.nsw.gov.au).

All significant safety issues must be reported as per standard practice however non-serious breaches may be reported retrospectively in a single post COVID-19 modification report.

The modification report will require a summary to be provided to the site Research Governance Officer on:

- The number of patients impacted
- Changes to medication dispensing
- Dose interruptions

- Changes to visit schedules and activities
- Use of external services (e.g. pathology, imaging)
- Missing data.

Please contact the Research Office via SESLHD-RSO@health.nsw.gov.au for further information.