Ingham Institute
Applied Medical Research

NSW GOVERNMENT Health
South Western Sydney Local Health District

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Risk Assessment for Clinical Trials

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1.0 Introduction / Background

The National Clinical Trials Governance Framework released by the Australian Commission on Safety and Quality in Health Care defines the responsibilities of Australian Hospitals in assessing and managing risk of clinical trials in Australian hospitals. The health service organisation identifies risks, develops mitigation strategies, analyses and evaluates the risk associated with the potential hazard and uses risk assessment to set priorities for and improve the quality of clinical trial service provision.

International Council for Harmonisation (ICH) Good Clinical Practice (GCP) E6 (R2), requires clinical trial teams to implement a robust risk management process before starting clinical trial activities. Before a clinical trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual clinical trial subject and society. A clinical trial should be initiated and continued only if the anticipated benefits justify the risks.

ICH GCP E6 (R2) reinforces the responsibility that Principal Investigators (PI) have for ensuring adequately skilled/trained personnel and quality process management as part of their oversight of the clinical trial. The PI should undertake a clinical trial risk assessment that is well-balanced between applying critical thinking and implementing lessons learned from previous clinical trials.

Experienced sites encounter clinical trials that underperform for a variety of reasons including complex protocol procedures, difficult inclusion and exclusion criteria, and over-estimated recruitment rate expectations. Sites must do an initial and ongoing assessment to assess risks and have the opportunity to provide feedback to Sponsors and Contract Research Organisations (CROs) about these and other potential issues. This can be provided in the follow manner: protocol risk assessment feedback on the site information forms (i.e., feasibility questionnaire), at Investigator Meetings, during meetings between the Sponsor, sites and advocacy groups, and during site monitoring visits.

2.0 Objective

To describe the risk assessment and management for overall clinical trials activities for South Western Sydney Local Health District (SWSLHD) and the Ingham Institute through the Clinical Trials Support Unit.

To describe the procedure for assessing the risk of any clinical trial being considered to be conducted within the SWSLHD and Ingham Institute for commercially sponsored, collaborative group sponsored or Investigator initiated clinical trials.

This risk assessment will include: the risks to participant safety in relation to the Investigational Product (IP); all other risks related to the design and methods of the clinical trial (including risks to participant safety and rights, as well as reliability of results) and a risk assessment of the resources required to conduct the clinical trials.

3.0 Scope

This SOP applies to all staff involved in clinical trials at SWSLHD and the Ingham Institute.

4.0 Ownership and Responsibility

The SWSLHD facilities have risk management strategies and processes to management risks and incidence in accordance with the NSW Policy PD2020_047 Incidence Management Policy. The Clinical Trials Support Team (CTSU) will work with the facilities to ensure that the National Clinical Trials Governance Framework is implemented across the SWSLHD and Ingham Institute.

ICH GCP clearly defines the responsibility of the Human Research Ethics Committee (HREC), Investigator and Sponsor's role in assessing and managing risk.

The PI is responsible for assessing the overall risk, protocol risks, risk to participants and ongoing risks throughout the clinical trial. The feasibility process is the initial assessment of risk conducted by the PI and any risks should be documented and discussed with the clinical trials teams and mitigations put into place prior to submitting the protocol to the HREC for review.

The PI must inform the HREC of any change in risk (particularly increased risk) for the clinical trial. And the PI must notifying the Sponsor of any unforeseen or ongoing risks.

5.0 Associate Documents

SOP_CTSU_02 Investigator Responsibilities

SOP_CTSU_03 Communication with Human Research Ethics Committee, Research Governance Office, Trial Sponsor and Insurer

SOP_CTSU_04 Clinical Trial Start Up

SOP_CTSU_09 Investigator Site File and Essential Documents

SOP_CTSU_20 Non-Compliance

SOP_CTSU_22 Corrective and Preventative Action Plans (CAPA)

6.0 Procedure

6.1 Organisational Level

The CTSU has a Business Continuity Plan for clinical trials across SWSLHD and the Ingham Institute in accordance with PD2018_045 Business Continuity Management.

The Risk Assessment & Risk Log (FM_ 032_Risk Assessment & Risk Log) must be submitted to the CTSU for review prior to HREC submission:

- If SWSLHD or the Ingham Institute are to be the Sponsor of the clinical trial
- For phase I clinical trials

The CTSU will review the level of risk and discuss risk mitigation plans with the Principal Investigator where applicable. For clinical trials that don't fit the above criteria the Risk Assessment & Risk Log should be completed and discussed during the Department level and risk mitigation implemented.

The NSW Health Incident Management Process must be followed and the CTSU must be notified if Incidence Information Management System (IIMS) report is made related to a clinical trial or a clinical trial participant. A quarterly report will be presented to the Research and Ethics Steering Committee and discussed at the meetings.

The PI must notify the CTSU if they are notified of a Sponsor or Regulatory audit. Audit report findings must be forwarded to the CTSU. Any Corrective and Preventative Action (CAPA) will be discussed with the CTSU to ensure the recommendations are implemented across the SWSLHD and Ingham Institute where applicable.

Risk assessment and management training will be provided by the CTSU during the on boarding of new clinical trial team members. Ongoing education and training will be provided.

Email CTSU: swslhd-clinicaltrialssupportunit@health.nsw.gov.au

6.2 Department Level

The Department will review the risk of each of the clinical trials on an ongoing basis and determine how best to mitigate and manage the risk. The PI will be the risk owner for the management and monitoring of the risk and ensuring that appropriate delegation and accountability is in place.

The Department will ensure that their clinical trial projects are entered into the Clinical Trial Management System (CTMS) within the first 3 months of activation or earlier. This is in line with NSW Health directive to ensure accurate oversight and management of clinical trial activities.

6.3 Clinical Trial Level

This risk assessment should be conducted on all clinical trials as early as possible, before a trial is submitted to a HREC for review and before a Clinical Trial Research Agreement (CTRA) is finalised with the sponsor.

The PI and the clinical trials team must consider:

- The nature of the medicinal product(s)/device(s)/
- The potential for known or anticipated toxicities/adverse consequences
- Which body systems may be affected
- Phase of development
- Study population: healthy volunteers or patients. Do you require community input?
- What are the known/anticipated safety issues and are they all addressed within the normal clinical practice?
- If unknown, what are the anticipated risks/other effects based on preclinical data or knowledge of class of drugs?
- Is the duration of use compatible with previous experience?
- Is there a potential risk of dosing errors?
- Might concomitant medications increase the risk (i.e., drug interactions)?

The Clinical Trials Team should assess whether a Data Safety Monitoring Board (DSMB) is required for the clinical trial and whether this has been established by the Sponsor. According to the National Statement a DSMB is one of a range of mechanisms available to sponsors to mitigate these risks and every trial must identify the most appropriate mix of monitoring activities. Things to consider for why a DSMB should be established:

- The study endpoint is such that a highly favourable or unfavourable result, or even a finding of futility, at an interim analysis might ethically require termination of the study before its planned completion;
- There are reasons for a particular safety concern, as, for example, if the procedure for administering the treatment is particularly invasive;
- There is prior information suggesting the possibility of serious toxicity with the study treatment;
- The study is being performed in a potentially fragile population such as children, pregnant women or the very elderly, or other vulnerable populations, such as those who are terminally ill or of diminished mental capacity;
- The study is being performed in a population at elevated risk of death or other serious outcomes, even when the study objective addresses a lesser endpoint;
- The study is large, of long duration, and multi-centre.

While a DSMB might not always be warranted the Clinical Trials Team should assess the oversight measures in place to protect participants such as Medical Monitor oversight, safety data analysis on an ongoing basis, stopping rules and monitoring plans. These

measures must be defined in the protocol and an ongoing assessment made for participant safety.

Assessment of the risk should be documented by completing the Risk Assessment and Risk Log (FM_ 032_Risk Assessment & Risk Log). This Log should be updated on a regular basis throughout the study if risks change. If risks are identified the PI should discuss these with the Sponsor and agree on risk mitigation strategies. And report the risks as required to the HREC.

The Risk Assessment and Risk Log must be filed in the Investigator Site File (ISF). See SOP_CTSU_09 Investigator Site File and Essential Documents for more information.

Any non-compliance should be clearly documented in accordance with SOP_CTSU_20 Non-compliance and corrective and preventative action plans established as per SOP_CTSU_22 Corrective and Preventative Actions Plans (CAPA).

The PI will also determine if the incident needs to be documented in the Incidence Information Management System (PD2020_047 Incidence Management Policy).

7.0 References

ICH GCP (E6 R2): Good Clinical Practice Guidelines - Annotated by TGA

National Statement on Ethical Conduct in Human Research (2018)

Australian Code for the Responsible Conduct of Research (2018)

PD2018_045 Business Continuity Management

PD2020_047 Incidence Management Policy

8.0 Amendment History

Version	Date	Amended by	Details of Amendment
1.0	01-Sep-2020	Erfan Jaberiyanfar	• Updated reference to incident management policy. • 6.2 – Updating of study registry via CTMS. • Update of reference links

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