JAMES COOK UNIVERSITY

REQUIRED SAFETY MONITORING AND REPORTING IN CLINICAL TRIALS

SPONSOR RESPONSIBILITIES **NOTE: Where the institution is also named as the trial sponsor, the institution will also assume the sponsor responsibilities.

Involving Investigational Medicinal Products (IMPs)

SPONSOR RESPONSIBILITIES

TYPE	Action	Time Frame
Fatal or Life Threatening Australian SUSARs	Notify TGA	Immediately notify TGA but no later than 7 calendar days after being made aware of the case, with any follow-up information within a further 8 calendar days.
All other Australian SUSARs	Notify TGA	No Later than 15 calendar days after being made aware of the case
Significant Safety Issues that adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial	Notify TGA Notify TGA	Urgent safety measures - within 72 hours Other significant safety issues within 15 calendar days
Submit safety report including a clear summary of the evolving safety of the trial	Notify HRECs	Annual

Urgent Safety Measure (USMs) Report – reasons for the USM, measures taken and further actions planned. (The HREC are not required to approve any proposed actions but will consider if proposed actions are appropriate and if an amendment is required.)	Notify TGA, Investigators and HREC	Strongly recommended contact TGA within 24 hours – initial contact by phone, follow up by email within 72 hours. Without undue delay and no later than 72 hours of the measure being taken.
Notification of amendment – details of the significant safety issue and further actions planned.	Notify TGA, Investigators and HREC	Without undue delay and no later than 15 calendar days of the sponsor becoming aware of the issue. Sponsors should submit to the HREC an amendment relating to any revised trial documentation without undue delay
Temporary halt of a trial for safety reasons – reasons for the halt, scope of the halt, measures taken and further actions planned	Notify TGA, Investigators and HREC	Without undue delay and no later than 15 calendar days of the sponsor's decision to halt the trial. Where it is necessary to seek ethical review of related actions, a letter describing these actions should be submitted to the HREC within 15 calendar days of the temporary halt.
Early termination of a trial for safety reasons Reasons for the early termination, measures taken, further actions planned	Notify TGA, Investigators and HREC	Without undue delay and no later than 15 calendar days of the sponsor's decision to terminate the trial. Where it is necessary to seek ethical review of related actions, a letter describing these actions should be submitted to the HREC within 15 calendar days of any termination.

INVESTIGATOR RESPONSIBILITIES

TYPE	**Action**

Safety Events	Investigators should assess all local safety events and should act on any events as clinical care dictates. The role of Investigator with regard to safety reporting is to provide the sponsor with all relevant information so that an appropriate safety analysis can be performed.
Capture and assess all AEs that occur at the site as required and in accordance with the protocol	
Report to the Sponsor: • All SAEs except those that are identified in the protocol as not needing immediate reporting • Any occurrences of congenital anomaly/birth defect arising from any pregnancy of a participant (or partner) • All urgent safety measure instigated at the site	Within 24 Hours of becoming aware of the event
Report to the Sponsor: • All safety critical events • Any additional requested information relating to reported deaths	
Report to the Institution: • All significant safety issues • SUSARs arising from the local site.	Within 72 hours of becoming aware of the event

HREC RESPONSIBILITIES

The approving HREC should:	
Assess the safety of proposed trials, including whether the evaluation of the anticipated benefits and risks is satisfactory and ensure that the sponsor has proportionate systems in place to mitigate and manage identified risks	Satisfy itself that the sponsor's on-going safety monitoring arrangements are adequate, including the justification for appointing/not appointing a Date Safety Monitoring Board and any "stopping rules" or criteria for withdrawing individual participants from the trial.
Keep under review the adequacy and completeness of the informed consent process and documentation in light of new information about risks and benefits.	Assess whether change to the risk-benefit ratio that are reported by the sponsor are compatible with continued ethical approval.

Advise the TGA, Investigators and their institutions of any decision to withdraw approval.	

INSTITUTION RESPONSIBILITIES

An Institution should:	
Assess whether any safety reports received, impact on medico-legal risk, the responsible conduct of research, adherence to contractual obligations or the trial's continued site authorization and, where applicable, facilitate the implementation of corrective and preventative action.	Develop clear guidance for investigators details the requirements of safety reporting and monitoring in clinical trials. This document should cover the requirements for externally sponsored clinical trials, and if applicable, internally sponsored investigator/initiated or collaborative group trials.

TGA RESPONSIBILITIES

Clinical trials of unapproved therapeutic goods are conducted in Australia under either the Clinical Trial Notification (CTN) Scheme or the Clinical Trial Exemption (CTX) Scheme. Responsibility for the regulatory control of therapeutic goods in Australia lies with the Therapeutic Good Administration (TGA. The TGA may:	
Conduct an audit of a clinical trial where necessary on safety grounds	Stop a trial where that action is in the public's interest

#In compliance with *Safety monitoring and reporting in clinical trials involving therapeutic goods. TGA November 2016*

Summary of Main Changes to Reporting Requirements TGA Position

Change from 2009 TGA Position Statement	Rationale
Removing the requirement to submit individual reports of adverse events (AEs), serious adverse events (SAEs), suspected unexpected serious adverse reactions (SUSARs), unanticipated serious adverse device effects (USADEs) and six monthly line listings to HRECs.	HREC are often not best placed to perform an analysis of these reports. The outcomes of the sponsor's analyses of accumulating safety data provides the HREC with more useful and useable information.
Removing the requirement to submit individual reports of AEs, SAEs, SUSARs/USADEs and six monthly line listings to investigators to align with EU Regulation.6	Updated/addended investigator's brochures and spontaneous reports of significant safety issues provide investigators with the most relevant information on the use of the medicinal product or medical device.
Removing the requirement to submit individual reports of AEs, SAEs, *external* SUSARs/USADEs and six monthly line listings to institutions.	Institutions are often not best placed to perform an analysis of these reports. The outcomes of the sponsor's analyses of accumulating safety data provides the institution with more useful and useable information.
Including the requirement for sponsors to provide HRECs with an annual safety report.	Provides HRECs with a report that supports trial oversight, including a clear summary of the evolving safety profile of the trial and also evidence that the sponsor is conducting its ongoing safety monitoring appropriately.
Clarifying requirements and terminology for the reporting of significant safety issues.	Ensures that significant safety issues are communicated to all parties in a consistent manner and timeframe.

DEFINITIONS (IMPs)

Term	Description
Investigational Medicinal Product (IMP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, a new patient group or when used to gain further information about an approved use. Note: This definition includes biologicals used as investigational medicinal products.
Biological[7]	An item made from, or containing, human cells or human tissues, and that is used to treat or prevent disease or injury, diagnose a condition of a person, alter the physiological processes of a person, test the susceptibility of a person to disease, replace or modify a person's body part(s). Examples include: human tissue therapy products (e.g. skin, tissues, bone for grafting) processed human tissues (e.g. demineralised bone, collagen) human cellular therapy products (e.g. cartilage cells, cultured skin cells) immunotherapy products containing human cells genetically modified human cellular products.
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and that does not necessarily have a causal relationship with this treatment.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered. Comment: All adverse events judged by either the reporting investigator or the sponsor as having a reasonable possibility of a causal relationship to an investigational medicinal product would qualify as adverse reactions. The expression 'reasonable causal relationship' means to convey, in general, that there is evidence or argument to suggest a causal relationship. Note[8]: The following are examples of types of evidence that would suggest a causal relationship between the investigational product and the adverse event: A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)

	One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture). An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.
Investigator's Brochure (IB)	The document containing a summary of the clinical and non-clinical data relating to an investigational medicinal product that are relevant to the study of the product in humans.
Product Information (PI)	The approved Australian summary of the scientific information relevant to the safe and effective use of a prescription medicine. Note: In a trial in which the IMP is an approved product, the Product Information may replace the investigator's brochure. If the conditions of use differ from those authorised, the PI should be supplemented with a summary of relevant clinical and non-clinical data that supports the use of the IMP in the trial. The Australian Product Information should be used where available for each trial IMP adopted across Australian sites.
Reference Safety Information (RSI)	The information contained in either an investigator's brochure or an approved Australian Product Information (or another country's equivalent) that contains the information used to determine what adverse reactions are to be considered expected adverse reactions and on the frequency and nature of those adverse reactions.
Safety Critical Adverse Events	Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations that should be reported to the sponsor according to the reporting requirements specified in the protocol.
Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)	Any adverse event/adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. Note: Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe. Note: Medical and scientific judgement should be exercised in deciding whether an adverse event/ reaction should be classified as serious in other situations. Important medical events that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

Significant Safety Issue (SSI)	A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	An adverse reaction that is both serious and unexpected.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the Reference Safety Information (RSI). Note: The RSI should be contained in the investigator's brochure for an unapproved medicinal product or Product Information (or another country's equivalent of the Product Information) for an approved medicinal product.
Urgent Safety Measure (USM)	A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety. Note: This type of significant safety issue can be instigated by either the investigator or sponsor and can be implemented before seeking approval from HRECs or institutions.