CRDO RISK ASSESSMENT AND RISK MANAGEMENT TOOL
FOR CLINICAL TRIALS: Information and instructions for researchers

All sponsors and chief/principal investigators of clinical trials conducted in Australia must ensure that their trials are designed, managed and monitored to minimse risks, ensure that trial participants are protected and ensure that the trial data generated are reliable and robust ("Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2)" dated 9 November 2016 Annotated with TGA comments. This requirement applies to both investigator-initiated clinical trials and commercially funded clinical trials.

In clinical trials, major risks can be very broadly categorised into:

1. Risks to the safety and rights of the trial participants;
2. Risks to the successful conduct of the trial (e.g. inadequate funding, poor recruitment, poor quality data/samples).

The template Risk Assessment and Management Plan that follows is divided into 3 parts to guide you in identifying risks and documenting your plan to manage and monitor these risks. Part 3 also allows you to document areas where your risk assessment and management plan indicates that reduced / targeted safety oversight of your trial may be applicable.

1) WHAT IS RISK?

A risk is the possibility that harm might occur when exposed to a hazard (*https://www.safeworkaustralia.gov.au/risk*). Although risk is a continuum, it is useful to quantify risk (e.g. low, medium, high risk) to help focus management on the reduction of the most critical risks. To quantify risk, both the **likelihood** (*a*) of the hazard's occurrence and the **severity** (*b*) of the harm (i.e. the impact) need to be determined and multiplied (*a x b*).

Likelihood can be defined in various ways but the following is a guide:

Remote	- Almost never
Unlikely	- Occurs rarely
Possible	- Could occur but uncommon
Likely	- Recurrent but not frequent
Very likely	- Occurs frequently

Severity can also be defined in various ways but the following is a guide:

- Trivial
- Minor
- Moderate
- Serious
- Catastrophic

How the categories of severity are defined will depend on whether the harm is to the trial participant (e.g. harms related to the intervention, trial procedures, serious breaches) or to the conduct of the trial (e.g. trial inadequately powered, poor recruitment, inadequate system for safety monitoring or inadequate data collection & management systems).

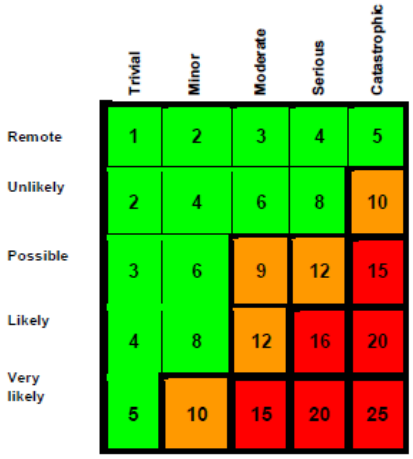
The guide given below* is relevant only for harms to participants:

- Trivial e.g. discomfort, slight bruising, no treatment required
- Minor e.g. small cut, abrasion, first aid needed
- Moderate e.g. strain, sprain, incapacitation > 3 days
- Serious e.g. fracture, hospitalisation > 24 hours, incapacitation > 4 weeks
- Catastrophic e.g. fatal event (single or multiple)

* Reference: University of Bath Risk Assessment template
http://www.bath.ac.uk/hr/stayingsafewell/hazard-risk-management/index.html

2) HOW IS RISK IN CLINICAL TRIALS ASSESSED AND MANAGED?

1) Identify potential hazards in the trial.
2) Assess the risk (e.g. low, medium, high) of each hazard by determining and multiplying:
   - The likelihood of the hazard's occurrence;
   - And the severity of the impact if the hazard occurs.



The risk rating (high, medium or low) indicates the level of response required to be taken when designing the action plan.

Rating Bands (a x b)		
LOW RISK (1 – 8)	MEDIUM RISK (9 - 12)	HIGH RISK (15 - 25)
Continue, but review periodically to ensure controls remain effective	Continue, but implement additional reasonably practicable controls where possible and monitor regularly	-STOP THE ACTIVITY- Identify new controls. Activity must not proceed until risks are reduced to a low or medium level

Reference: University of Bath Risk Assessment template
http://www.bath.ac.uk/hr/stayingsafewell/hazard-risk-management/index.html

Efforts to manage risk should be prioritised – they should focus on where they are most needed (i.e. critical data points and critical trial processes); this is known as risk-based management approach. Clearly, those deemed "high risk" are the most critical risks to manage and should be reduced to at least "medium risk".

3) Decide on the response to best manage and monitor each risk. Responses to a risk include:
   - Avoid/Eliminate the risk (if feasible) (e.g. decision not to undertake project or adjustment of the project to eliminate this risk);
   - Mitigate (where a risk cannot be eliminated but adjustment can reduce the likelihood that it will occur OR reduce the negative impact of the risk if it occurs);
   - Transfer (e.g. to another organisation with more expertise in managing the risk);
   - Accepted (i.e. actively deciding that you will accept the consequences [impact] of a risk if it occurs).
4) Document the risk assessment and management in a Risk Assessment and Management Plan.

3. RISK ASSESSMENT AND MANAGEMENT PLAN – A TEMPLATE

Sponsors (i.e. Chief/Principal Investigator for investigator-initiated trials) should implement a risk assessment and management plan to manage quality throughout all stages of the trial from trial design through to reporting. The focus should be on participant protection and data integrity. The plan should include identification of hazards, assessment of their risk and decisions on how to best manage and monitor risks.

The template Risk Assessment and Management Plan that follows is divided into 3 parts

- **Part 1: The risk category of the intervention** (e.g. investigational medicinal product/ investigational medical device) when compared with the standard of care product. This involves a simple risk categorisation based on the marketing (i.e. registration) status of the investigational product and comparison with standard medical care (Type A, B or C);
- **Part 2: Broader assessment of other hazards and risks involved in trial conduct** (e.g. the trial design, population and procedures) to identify specific areas of vulnerability and to determine how any risks can be mitigated;

- **Part 3: The implications for trial oversight.** The NHMRC 'Guidance: Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods' (2016) clarifies that there are **some areas where trial oversight may be reduced (or increased) according to the risks you identified in Parts 1-2. You should use this section of the document (Part 3) to document and justify any reduced oversight**

If you have already completed a Risk Assessment for the Campus Sponsorship Committee, you will not need to complete in this template those sections you previously covered previously (Sections 2.2 Points 3, 6, 7, 8, 14 and 15) - these are highlighted with a light grey background.

The plan should be written in parallel with the development of the trial protocol and before applying for funding (where applicable). It should be reviewed by other key stakeholders (e.g. sponsor, funders, other investigators) to ensure agreement on the main risks in the clinical trial and allow a risk-proportionate approach to be taken for all trial activities. The plan should be reviewed on an ongoing basis during the trial.

Acknowledgement
This assessment tool has been adapted in large part from wording on the UK's NHS NIHR's Clinical Trials Toolkit at http://www.ct-toolkit.ac.uk/routemap/risk-assessment/ and from example assessments placed on the UK MHRA GCP Inspectorate collaborative forum at http://forums.mhra.gov.uk/showthread.php?1678-Examples-of-risk-assessments.

The assessment tool also incorporates guidance from the following documents:

- NHMRC guidance "Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods" dated 2016
- NHMRC guidance "Risk-based Management and Monitoring of Clinical Trials Involving Therapeutic Goods" dated 2018
- "Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2)" dated 9 November 2016 Annotated with TGA comments

How to use this template?	**Throughout this document, explanations/instructions are given in** *purple italics* and suggested wording is given in *green italics*. Please delete these when using the tool as a template

CRDO RISK ASSESSMENT AND RISK MANAGEMENT TOOL FOR CLINICAL TRIALS

Protocol Name/No:	
Investigator:	Sponsor:

PART 1: RISK CATEGORY OF THE INTERVENTION [WHEN COMPARED WITH STANDARD OF CARE PRODUCT]

The risk associated with the investigational product (trial intervention) has implications for all the other risks, but does not determine them. In other words, where a trial will use as its investigational product a drug already registered by the TGA for Australian use and where the drug will be used within its current approved indication, the risk category will be Type A (the lowest risk). This does not take into account all other trial risks, which must be assessed independently of the risks related to the intervention product – see Part 2.

1. RISK CATEGORISATION BY INVESTIGATIONAL MEDICINAL PRODUCT* *Prepared for Investigational Medicinal Products (IMPs) – adapt where the intervention is an Investigational Medical Device [IMD] or investigational procedure])*		
Type of Clinical Trial	**Risk Category**	**Justification** *(Briefly explain the selection of category)*
1a) Trials involving a drug entered onto the Australian Register of Therapeutic Goods (ARTG) if: • The use of the drug is within the conditions of its marketing approval or; • The trial involves off-label use of a registered drug - if this use is established practice and supported by sufficient published evidence and/or guidelines (e.g.in paediatrics or oncology)	**TYPE A** Risk comparable to standard medical care	
2) Trials involving a drug entered onto the ARTG if: • Such products are used for a new indication (different patient population/disease group) or; • Substantial dosage modifications are made or; • Drugs are used in combinations for which interactions are suspected 3) Trials involving a drug NOT entered onto the ARTG if: • The active substance is part of a drug that is entered onto the ARTG *Note: A 'TYPE A' grading may be justified if there is extensive use/clinical experience with the product and no reason to suspect a different safety profile in the trial population.*	**TYPE B** Risk associated with modified use of an existing product	
4) Trials involving a drug NOT entered onto the ARTG *Note: A grading other than 'TYPE C' may be justified for drugs not on the ARTG but which have been approved in other jurisdictions and for which there is extensive clinical data*	**TYPE C** Risk associated with use of an unlicensed product	
Other Interventional Clinical Trials		
For other interventional clinical trials, similar principles should be used to identify the risks associated with the trial intervention(s). Risks should be assessed relative to the standard of care for the relevant clinical condition (i.e. use of the intervention meets local or national protocols) and the level of clinical experience with the intervention rather than the patients' underlying condition or the recognised adverse effects of the intervention.		

PART 2: BROADER ASSESSMENT OF HAZARDS AND RISKS INVOLVED IN THE TRIAL

2. HAZARDS AND RISKS OF THE INTERVENTION (IMP) AND STUDY PROCEDURES							
Hazard ID	**Hazard**	**Concerns identified** **Provide details of trial-specific considerations / risk concerns**	**Hazard LIKELIHOOD of Occurrence** **1 Remote** **2 Unlikely** **3 Possible** **4 Likely** **5 Very Likely**	**Hazard SEVERITY** **1 Trivial** **2 Minor** **3 Moderate** **4 Serious** **5 Catastrophic**	**RISK** **Low (1-8)** **Medium (9-12)** **High (15-25)**	**How will these risks be managed?** **Address all concerns identified**	**Monitoring strategies** **Discuss how you will monitor the management of the risk**
2.1 HAZARDS AND RISKS – PARTICIPANT							
2	**Expected hazards related to study intervention (i.e. Investigational Medicinal Product [IMP]) and/or its administration.**	*Include in this category (for example):* *IMP risks* • *side effects* • *Interactions with concomitant/permitted medications* • *Potential harm in reproduction* • *Precautions and impact on eligibility* *IMP administration risks* • *high risk dosing procedure e.g. cohort, maximum tolerated dose (MTD)* • *high level of treatment interception e.g. frequent PKs* *Other known or anticipated safety issues* ***Example text – customise*** *IMP & administration risks:* • *Minor side effects where the impact would be relatively*				*For example: Build into the protocol* • *Written documentation of Investigator's review of participant eligibility (to minimise ineligible participants being entered and exposed to the IMP).* • *Additional participant monitoring of <insert> (e.g. additional blood glucose monitoring for a product with hyperglycaemia as a hazard).* • *Exclusion of those taking medications with a known interaction to the IMP or other agents used in the trial.* • *Dose adjustment or stopping rules*	***Example text – customise for your trial:*** *On-site monitoring of trial conduct:* • *Eligibility (inclusion/exclusion criteria) – verification will be performed for all/xx% of enrolled participants.* • *For those participants selected for monitoring, all safety events will be reviewed.* *Safety monitoring* • *Independent data and safety monitoring will be conducted by <insert> (e.g. an independent Medical Monitor or a Data Safety Monitoring Board)*

		non-substantial in this participant group: <insert where applicable> • *Side-effects that could have a substantial impact in this group: <insert where applicable>* • *Risk of interactions of the IMPs causing harm to a foetus: <insert where applicable>*				• *Exclusion of women of child-bearing potential (WOCBP). Or, if included, build in (i) requirement for contraception plus (ii) pregnancy testing before, during and after (e.g. for XX half-lives after last dose) and (iii) follow up of any pregnancy (in participant or partner) until post-birth or otherwise (i.e. spontaneous termination) to allow information on the status of the mother and child to be reported to the sponsor pregnancy.*	

3	**Hazards related to study procedures/ investigations**
	
	(Not req'd if you have already completed the Campus Sponsorship Committee risk assessment)
		Include in this category (for example):
		• *Frequent blood sampling*
		• *Invasive assessments*
		Other known or anticipated safety issues
		
		Example text – customise
		
		Trial procedure risks:
		• *Minor side effects where the impact would be relatively non-substantial in this participant group: <insert where applicable>*
		• *Side-effects that could have a substantial impact in this group: <insert where applicable>*
		• *Risk of interactions of the IMPs causing harm to*
						For example:
						• *For an invasive procedure consider*
						  ○ *limiting trial sites to those experienced in the procedure*
						  ○ *Including contact details of a clinical advisor in protocol*
						• *Limit samples to remain within blood volume guidance by age*
						• *For frequent blood sampling ensure skilled, qualified staff available.*
						• *Limit participation by participants to one study at a time*
						• *Independent data & safety monitoring as in section 2*
							Example text – customise for your trial:
							
							On-site monitoring of trial conduct:
							• *For those participants selected for monitoring, all safety events will be reviewed.*
							• *Safety monitoring Independent data and safety monitoring will be conducted by <insert> (e.g. an independent Medical Monitor or a Data Safety Monitoring Board)*

		participants: <insert where applicable>				*above (i.e. an independent Medical Monitor or a Data Safety Monitoring Board)*	
4	**Non-compliance with consent process**	*In this category, outline potential difficulties in consenting or sources of non-compliance with the informed consent process. Review factors such as language difficulties, consenting in an emergency situation, consenting remotely, consent in vulnerable populations, coercion, risk that the informed consent process is not undertaken as per the protocol/GCP/HREC approval (e.g. due to inadequate or lack of appropriate staff, time difficulties where trial treatment is time-critical).*				***Example text – customise for your trial:*** *Consent will only be obtained by trial-specific personnel, who have been delegated this task by the PI.*	***Example text – customise for your trial:*** *Monitoring* • *All/xx% of participant consent forms will be reviewed.* • *The Signature and Delegation of Duties Log will be checked (to confirm only delegated personnel obtained consent)*
5	**Serious breach of protocol, ethical requirements, confidentiality**	*In this category detail:* • *What is the potential for failure to protect participants' privacy?* • *Will only key study personnel have access to identifiable participant data?* • *How will data and samples be identified during trial / during archiving?* • *How will data be identified for export to Sponsor / Trial coordinating centre etc* • *Will sensitive data be collected (e.g. data on ethnic origins, sexual or religious orientation)*					

		• *Will identifiers will be collected indirectly (place of work, Medicare number etc)* • *Will a secure web-based system with secure transfer of data to/from sites be used?*					
6	**Hazards to participant well-being** *(Not req'd if you have already completed the Campus Sponsorship Committee risk assessment)*	*Outline concerns for example:* • *Burden of study visits* • *Lifestyle restrictions* • *Study specific procedures which carry risk additional to standard care* • *Risk-benefit balance*					
7	**Hazards arising from complexity of study procedures** *(Not req'd if you have already completed the Campus Sponsorship Committee risk assessment)*	*Does the protocol require any complex or uncommon procedures beyond the usual standard of care?* *Consider the impact for both study sites and participants of the number of visits, the duration of the study, diagnostic testing that is not common for this population, strict timing for certain procedures in the protocol, complex trial designs (crossover design, dose escalation, structured therapeutic interruption).* *Are there procedures that will be performed at the participant's home and/or by themselves and how does this impact risk?*					

		How burdensome are the follow up visits and investigations compared with standard of care? *Does the protocol have any/multiple sub studies?*					
2.2 HAZARDS AND RISKS – TRIAL DESIGN, SYSTEMS, PERSONNEL & FACILITIES							
8	**Trial inadequately powered / Poor recruitment** *(Not req'd if you have already completed the Campus Sponsorship Committee risk assessment)*	*Outline concerns, for example:* *Trial level (Coordinating Centre):* • *Insufficient power due to lower than anticipated incidence of disease* • *Poorly-recruiting participating sites* *Site level:* • *Little experience in recruiting the target population* • *Insufficient suitable patients to enrol*				***Example text – customise for your trial:*** *Trial level* • *Reliable disease incidence estimates will be based on 'x' years of data collected by <insert>.* • *Sample size calculation accounts for conservative estimates of missed assessments/ withdrawals/ losses to follow-up.* • *Selection of participating sites is based on evidence of their past performance.* • *Additional sites will be opened if needed.* *Site-level* • *The site has experience in recruiting the target population.* • *Recruitment feasibility for the trial and site's enrolment target is based on known, robust clinical department activity data.*	

9	**Unreliable outcome assessments of primary and main secondary outcomes**	*Is the assessment of outcomes objective or subjective? If any assessments are subjective how will this be managed? Will an independent outcomes assessor be used? What trial-specific training will they require? How will you ensure standardisation amongst multiple assessors?*				*In the protocol and/or trial standard operating procedures (SOPs), address all arrangements and potential issues.* *Ensure staff roles are clear – and that delegation is appropriate.*	*Build into trial conduct monitoring:* • *Review of appropriate delegation and evidence that trial-specific training was undertaken (where required)* • *Evidence that outcomes were assessed by delegated assessors (where applicable)*
10	**Lack of robust procedure for assignment to intervention (and randomisation and blinding where applicable***)*	*Outline* • *Randomisation / blinding and any associated concerns.* • *How will participants be randomised?* • *When and how will blinding be done?* *Who will be aware of trial treatment assignment and who will be blinded? (e.g. study team, outcome assessors, statisticians?) What is the potential for accidental unblinding?*				*In the protocol and/or trial standard operating procedures (SOPs), address all arrangements and potential issues.* *Ensure staff roles are clear.*	*Build into trial conduct monitoring:* • *Was randomisation done by appropriate personnel?* • *Has the blind been maintained?*
11	**Inadequate pharmacovigilance system**	*Outline when and how safety events (e.g. AEs, SAEs, SUSARs, SSIs, USMs) will be identified and reported.* *Indicate whether the protocol specifies:* • *The time period for collecting adverse events e.g. (i) From Screening or randomisation/ administration of investigational product (IP) (ii) End 30 days or 5 half-lives after last administration of IP*				***Example text – customise for your trial:*** • *The protocol will specify the safety monitoring procedures and a trial-specific SOP will be provided.* • *A safety monitoring plan/SOP will be in place* • *Stated events will be recorded in the CRF, thus will be available to the sponsor to review via the CRF. Stated events will*	

		(iii) End after completion of all study-related procedures • *Events that do not need to be documented on the CRF (e.g. expected SAEs)* • *Events that need to be recorded on the CRF but not reported (e.g. specified SAEs).* *Outline who will be responsible for event:* • *Identification* • *Reporting to Sponsor & Research Governance* *Outline Sponsor responsibility for event reporting to HRECs & regulatory bodies* *Provide justification for having / not having a DSMB.*				*also be reviewed by the DSMB. It is anticipated that liver abnormality and renal impairment may be an outcome for patients as a result of paracetamol toxicity as opposed to a reaction to study treatment.*	
12	**Deficiencies in IMP manufacture and/or distribution** *(applicable where this will be undertaken by the trial organisers / the Coordinating Centre)*	*In this category, outline where/by whom the IMP will be:* • *Manufactured (if not a registered product)* • *Packaged (a/a)* • *Labelled* • *Distributed* *Outline any associated risks (e.g. distribution by a 3rd party).*				*For example, for external contractors build in:* • *Pre-agreement checks (e.g. certification and license checks, facility audit)* • *site visits, license checks)* ***Example text – customise for your trial:*** *Agreement will be put in place describing arrangements and responsibilities (and where applicable re-auditing of facilities)*	

13	**Poor IMP management system at Site(S)**	*Consider potential issues concerning:* • *Shipping and receipt of product* • *Storage conditions – and monitoring of these* • *Monitoring of expiry date* • *Clinical trial re-labelling (e.g. of ward stock)* • *Accountability - dispensing & returns* *Robustness of dose calculation*				***Example text – customise for your trial:*** *Storage conditions* • *Temperature will be monitored <insert frequency> by <insert>.* • *Reporting of temperature excursions (i.e. out of range temperatures) to sponsor/manufacturer /trial coordinating centre will be as follows…* • *Affected products may/will be quarantined…*	*Build into the trial conduct monitoring plan for review of:* • *Staff delegation and training logs* • *Temperature logs (where applicable) and storage areas* • *Accountability of xx% of records (shipment receipts, participant dispensing & return records etc.)*
14	**Poor data collection & management system** *(Not req'd if you have already completed the Campus Sponsorship Committee risk assessment)*	*Consider:* • *Trial data and source data privacy - how will data be identified? Stored?* • *Use of devices (ePRO, iPad, vital signs collection devices, other devices) to collect participant data - how difficult will they be to use and how much training will be require? Is the new device being used to capture a primary/secondary endpoint – consider experience with the device* • *Data collection and management* ○ *Data quality – Quality control checks*				• *Sponsor SOPs and/or a trial procedure manual will cover data collection and management procedures and also tissue/sample collection and storage.*	

		○ *Use of electronic Case Report Forms (eCRF) (i.e. data collection forms)* ○ *Time to entry of data from paper to database* ○ *Security of data entry - secured websites, user permissions and passwords* • *Sample collection and storage* • *Archiving- retention period to be specified in protocol*					
15	**Inexperienced and/or poorly trained personnel** *(Not req'd if you have already completed the Campus Sponsorship Committee risk assessment)*	*For your site, consider:* • *Experience in the study phase and disease/therapeutic area.* • *GCP certification mandatory for PI (strongly recommended for trial coordinator also)* • *GCP procedures, informed consent, data confidentiality, safety event reporting, data query management* • *Adequate resources available for the duration of the study* • *Knowledge of study procedures: trial interventions, trial investigations* • *Awareness of sponsor SOPs* *For multi-site trials, the coordinating centre should consider the above for each trial but also consider:*				***Example text – customise for your trial:*** • *GCP training (TransCelerate-recognised) will be/has been completed by Principal Investigator and <insert>.* • *Sponsor SOPs and/or a trial procedure manual will be provided to research site teams.* • *Site initiation training will include training in study specific procedures including essential document management (Investigator Site File), all aspects of IMP handling, serious breach and protocol deviation identification and reporting, safety event reporting, data collection,*	***Example text – customise for your trial:*** *For sites new to research and/or new site staff:* • *Monitors will verify that new staff trained in study procedures (per training logs) and delegated appropriate tasks.* • *Support will be provided, particularly in the early stages, to new sites to identify and rectify any problem.* • *Ongoing review of Signature and Delegation Log, CVs, site staff training logs*

		• *Are there new sites/principal investigators (i.e. that the coordinating centre has not previously worked with)?* • *Have there been previous negative audit/inspection observations or other issues with the principal investigators or sites?*				*archiving and (where applicable) sponsor SOPs.* ○ *Training will include any staff who may be involved in study procedures.* ○ *Initiation procedures will also determine if adequate resources are available.* • *In addition for multi-site trials:* ○ *On-site initiation visits will be conducted at those sites new to research or with inexperienced staff.* ○ *GCP training (TransCelerate-recognised) will be/has been completed by each Site Principal Investigator and will be strongly recommended for trial coordinators.*	
16	**Lack of clarity regarding personnel responsibilities**	*For example, are roles clear?* *Site team - Are all delegated tasks listed on the Signature and Delegation Log and signed by delegate and Site PI?* *Are the Sponsor responsibilities clearly defined between the institution and Coordinating PI?*					*Build into the trial conduct monitoring plan for review of:* • *Completed delegation logs* • *Training logs (for evidence of trial team training)*
17	**Inadequate facilities**	*Consider*					***Example text – customise for your trial:*** *Monitoring*

		• *Sufficient clinical area and required facilities (e.g. resuscitation)* • *Clinical equipment maintenance* • *Laboratories*					• *Monitors will verify that safety equipment has an appropriate maintenance schedule and correct equipment for the study is always available.* • *QA: Pre-qualification audit of the laboratory will be conducted to examine if facilities and equipment are adequate and to examine if methods are robust with descriptive procedures and lab staff are suitably trained and qualified.*

PART 3: OUTCOME OF HAZARD AND RISK ASSESSMENT – IMPLICATIONS FOR THE OVERSIGHT OF YOUR TRIAL

The NHMRC 'Guidance: Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods' (2016) clarifies that there are **some areas where trial oversight can be reduced (or of course increased) according to the risks you identified above in Part 2**.

You should use this section of the document (Part 3) to document and justify decisions taken regarding reduced trial oversight (as outlined below).

The NHMRC document provides extensive guidance on when and how trial oversight can be varied to reflect risk in the areas listed above. A brief summary only is provided here and researchers should review the full NHMRC document when completing this section. The areas where reduced oversight may be justified are:

1. Targeted collection of safety data **reduced oversight**
2. Reduced requirement for expedited (time-critical) reporting of certain Serious Adverse Events
3. Trial monitoring – a focus on risk-based monitoring
4. Investigational Medicinal Products (IMP) - traceability and accountability

1. Targeted collection of safety data

As a general rule, all clinical trial adverse events should be collected and reported unless there is justification in a risk assessment for not doing so. Collection and reporting of all adverse events in a clinical trial is standard practice in the early development of the IMP, but **once IMPs have been registered and marketed, international agencies support a more risk-based approach**, detailed below. All non-serious adverse reactions still need to be captured in the participant's medical or study record.

<u>When registered IMPs are used within their marketing approval</u>

Where supported by data from use of the IMP - and where the number of participants exposed is sufficient to adequately characterise the IMP's safety profile - reduced (i.e. targeted) safety data collection may be appropriate. If the occurrence of common, non-serious adverse events has been generally similar across multiple trials, it is reasonable to conclude that their occurrence in the population to be studied will be similar to rates observed in previously conducted trials. Therefore, the need to report these adverse events on the Case Report Form (CRF) may be waived (meaning that they are not reported to the sponsor). Any selective safety reporting processes should be clearly described and justified in the protocol and/or ethics application as well as in this risk assessment.

<u>When IMPs are used differently from the conditions of their marketing approval or in the later stages of premarket development</u>

Where IMPs are used differently from the conditions of their registration and marketing approval (i.e. as listed in the Australian Product Information), the researchers must assess whether this different use* in the proposed clinical trial may lead to new, more severe or more frequent adverse reactions or new drug-drug interactions. If it is reasonable to conclude that the occurrence of common, non-serious adverse events in the population to be studied will be similar to rates observed in previously conducted trials, the need to report these adverse events on the Case Report Form (CRF) may be waived. Any selective safety reporting processes should be clearly described and justified in the protocol and/or ethics application as well as in this risk assessment.

* The changed conditions may be a new population (e.g. in terms of age, gender or other patient characteristics), a new combination therapy, a different concomitant medication, a different dose or dosage regime or a different route of administration.

2. Reduced requirement for expedited (time-critical) reporting of certain Serious Adverse Events

Within the protocol, it is possible to define those serious adverse events (SAEs) that do not require immediate reporting by the investigator to the sponsor despite meeting the definition of an SAE. Examples include: trial outcomes (otherwise known as endpoints) that will be captured and monitored by the trial's Data and Safety Monitoring Board (e.g. death in a stroke trial); and pre-planned events (e.g. elective surgeries).

3. Trial monitoring – a focus on risk-based monitoring

The **purpose** of trial monitoring is to oversee the progress of a trial to protect the rights and well-being of trial participants and to give reassurance that the trial protocol and procedures are being followed, that legal/governance requirements are being complied with, and that the critical data collected are reliable. (**Trial monitoring focuses on quality control and is undertaken by a representative of the sponsor; it differs from the functions of those undertaking safety monitoring but there may be some overlap**.)

The trial risk assessment should be used to determine the intensity, focus and type of trial monitoring undertaken. There are a number of **different approaches and techniques that are used for trial monitoring** – these can be categorised into two main types:

- **Central monitoring** involves the review of centralised data, for example, by trial oversight committees, data management staff or statisticians. This may include:
    - Central review by the coordinating trial team of
        - Data from sites (e.g. a review of the Case Report Form for inconsistent, missing or invalid data, late or poor CRF completion, confirmation that CRFs have been completed by authorised personnel);
        - Statistical monitoring (for large or multicentre trials) includes, for example, examining patterns of accumulating data using statistical approaches or modelling. Some examples of this would be checking for unusual data patterns or a between-sites comparison of adverse event reporting rates.
- **On-site monitoring** (called **remote monitoring** when this is done from an off-site location) involves visits to the site to verify the existence of trial documents and source data and to verify site staff understanding of, and compliance with, the protocol and trial procedures. Some examples are: targeted source data verification (SDV) where critical data elements such as key eligibility and outcome (endpoint) data are prioritised; checks for understanding and adherence to trial protocol, GCP and regulatory requirements; review of trial procedures (e.g. informed consent and safety reporting procedures, data capture, CRF completion); and verification that resources and facilities remain adequate. Some of these activities can be completed off-site ("remote monitoring").

Trial monitoring efforts should focus on where they are most needed (i.e. critical data points and critical trial processes); this is known as '**risk-based monitoring'**, it is also increasingly used to describe 'adaptive' monitoring, where the focus of monitoring is on those sites that appear to need it most.

In multi-site investigator-initiated clinical trials, central monitoring activities are being used to complement, reduce or sometimes replace on-site / remote monitoring (particularly the focus on verifying source data). There are many different approaches to quality control in a clinical trial; the most appropriate modalities will depend on the number of sites and logistical issues as well as the risk. **When determining the intensity, type and focus of trial monitoring**, consider the principles outlined in the table overleaf (extracted from 'NHMRC Guidance: Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods' (2016).

The sponsor's approach to monitoring should be documented in a plan that describes their monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used, and the rationale for their use. Note that CRDO has recently developed a **Clinical Monitoring Plan** template, which is available on the CRDO website along with the CRDO SOP "Monitoring Visit Activities" which provides guidance.

Table 3: Overall Risk Category to Determine the Intensity, Type and Focus of Monitoring

Risk associated with the trial intervention (IMP)		
Type A	**Type B**	**Type C**
Low intensity Central monitoring of key data, protocol adherence and data quality. Site visits not planned but may be triggered by concerns identified from central monitoring that cannot be addressed by other means.	**Moderate intensity** Central monitoring of key data, protocol adherence and data quality. Targeted site visits may be planned with frequency guided by central monitoring outputs.	**Higher intensity** Likely to require more intense monitoring involving both central and on-site activities in order to have confidence in the completeness and reliability of data, particularly safety data.
Additional monitoring to mitigate risks associated with other factors		
If the risk assessment has identified specific vulnerabilities associated with the factors other than the IMP, (e.g. the design, methods or conduct of the trial), add appropriate monitoring to address these issues. Examples* include: • Additional monitoring visits to provide extra support and training to new or inexperienced site staff. • Additional monitoring checks/visits when the sensitivity of sample analysis is highly dependent on how the samples are taken, processed, stored and transported, (i.e. in order to provide assurance that sample integrity has been maintained). • Additional monitoring checks/visits to verify that any equipment used to make primary end-point assessments or to calculate doses or dose adjustments is suitable for use and being used correctly. • Additional monitoring checks/visits to confirm understanding and adherence with the protocol when trial procedures or requirements are particularly complex.		

4. Investigational Medicinal Products (IMP) - traceability and accountability

IMP (drug) accountability refers to maintaining documentation that ensures traceability of the IMP used in a clinical trial. The level of IMP accountability should correspond to what is necessary for the scientific validity of the trial outcome or the safety to the trial participants. Therefore, when proposing reduced drug accountability, the impact should be taken into account. The level of accountability needed may vary. It depends on several factors, such as whether the IMP has marketing approval, the trial design (e.g. blinding or the complexity of the dosing regimen), who is administering the IMP, the toxicity of the IMP and its supply chain. A higher intensity of monitoring would be appropriate when compliance or storage of the IMP is critical to the trial outcomes. The risk assessment and management plan should include justifications for the planned documentation.

In some trials, IMPs may be sourced from normal stock (e.g. from a community/hospital pharmacy) and normal prescribing practice and documentation would apply. In these trials, it may be possible to maintain simplified accountability records (e.g. the batch number of the product dispensed may be captured on a trial specific or standard prescription form and filed in a trial folder to permit retrospective verification). Note that, **even for Type A trials, where changes to the IMP preparation are required (e.g. additional encapsulation in order to blind the trial), a full chain of custody from manufacture to destruction applies**.

In cases where the trial sponsor provides the IMP to the sites, accountability records of bulk receipt and destruction/return are required along with records that allow reconciliation of the bulk supply against individual participant use.

PART 3: OUTCOME OF HAZARD AND RISK ASSESSMENT – IMPLICATIONS FOR TRIAL OVERSIGHT

OUTCOME OF HAZARD AND RISK ASSESSMENT – IMPLICATIONS FOR REDUCTION/INCREASE IN SAFETY MONITORING			
#	**Category**	**Safety monitoring change**	**Justification**
	Targeted collection of safety data		
	Reduced requirement for expedited (time-critical) reporting of certain Serious Adverse Events		
	Trial monitoring – a focus on risk-based monitoring		
	Investigational Medicinal Products (IMP) - traceability and accountability		

PART 4: AUTHORISATION OF TRIAL RISK ASSESSMENT

	Name	Signature	Date of signature
Sponsor representative: Trial Chief Principal Investigator / Sponsor-Investigator			