3 – CLINICAL TRIAL SPONSOR FOR NON-COMMERCIAL TRIALS

Clinical Trials

Background

The sponsor of a trial is defined as *an individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study*[1]. All clinical trials under the CTN/CTX scheme require a formal sponsor who should assume responsibility for the scientific, ethical, regulatory and legal aspects of the trial. The sponsor is often, but not always, the main funder of the research, particularly when it is a commercial company that will retain ownership of the intellectual property rights. In a non-commercial trial, the sponsor may be a Collaborative Research Group, or the employer of the coordinating principal investigator, such as a higher education institution, a research institute, or the public health organisation where the research is to take place. For non-commercial trials, it is the responsibility of the coordinating principal investigator (CPI) to ensure that a sponsor is identified for their research and that the sponsor agrees to this role.

Although the international definition allows an individual to be named as sponsor, it is rare in practice for this to occur, as the sponsor's responsibilities are extensive and investigators are not equipped to fulfil all those requirements[2]. It is common practice for this role to be reserved for institutions. In this respect, the Australian Code of Responsible Conduct aligns with international practice by placing the responsibility for developing a comprehensive framework for good research conduct and governance, with the institution. As HRECs approving research require transparent assurances that the necessary quality and safety systems are in place, research-active institutions should develop overarching sponsor quality systems and make adherence to these systems a condition of sponsorship.

Regulatory responsibilities

International sponsors, whether commercial or non-commercial, are subject to international laws in the jurisdictions where their trials are conducted. International legislative requirements also apply when the results of a trial are intended to be submitted for regulatory approval overseas. In addition, the requirement to work to internationally recognised principles of Good Clinical Practice[3] is often written into local regulation. In Australia, the Therapeutic Goods Regulations (1990) provides the legal framework for access to unapproved therapeutic goods.

Scope and purpose of this document

Most commercial sponsors work to global policies mandating the strict application of ICH GCP or ISO 14155 2011 Standards. These guidelines were developed specifically for commercial trials, to provide a unified standard to facilitate the mutual acceptance of clinical data submitted to regulatory authorities. As the responsibilities of commercial sponsors are already well defined (both in GCP Guidelines and within their global policies), they will not be considered further in this document.

The aim of this document is to summarise the key sponsor responsibilities outlined in the ICH GCP guidelines[4] in order to reduce overlap amongst parties involved in the conduct of clinical trials and so that non-commercial trial sponsors can determine the most appropriate mechanisms to operationalise these responsibilities, taking into account:

- the differing environment in which non-commercial trials are conducted, particularly in terms of infrastructure and availability of resources, and
- the differing objectives of non-commercial trials which are seldom conducted to provide data to support Marketing Authorisation applications.

[1] Definition adopted from the UK DOH Research Governance Framework for Health and Social Care to reflect that the trial sponsor and trial funder may be separate entities in a non-commercial trial.

[2] In order to mitigate the risk of vicarious liability, is it recommended that institutions put in place arrangements for sponsorship and do not rely on investigators to manage all sponsor responsibilities.

[3] The Note for Guidance for Good Clinical Practice (ICH GCP) for investigational medicinal product trials or ISO 14155 2011 for investigational medical device trials.

[4] As the majority of therapeutic goods trials are conducted with medicinal products, the ICH GCP guidelines have been used to illustrate sponsor responsibilities in this document.

Although this document illustrates the responsibilities for non-commercial trials involving investigational medicinal products, the majority of principles and responsibilities outlined in GCP guidelines are relevant to all types of clinical trial. Their application provides assurance that the rights, safety and well-being of participants are protected and that clinical trial data are reliable and robust.

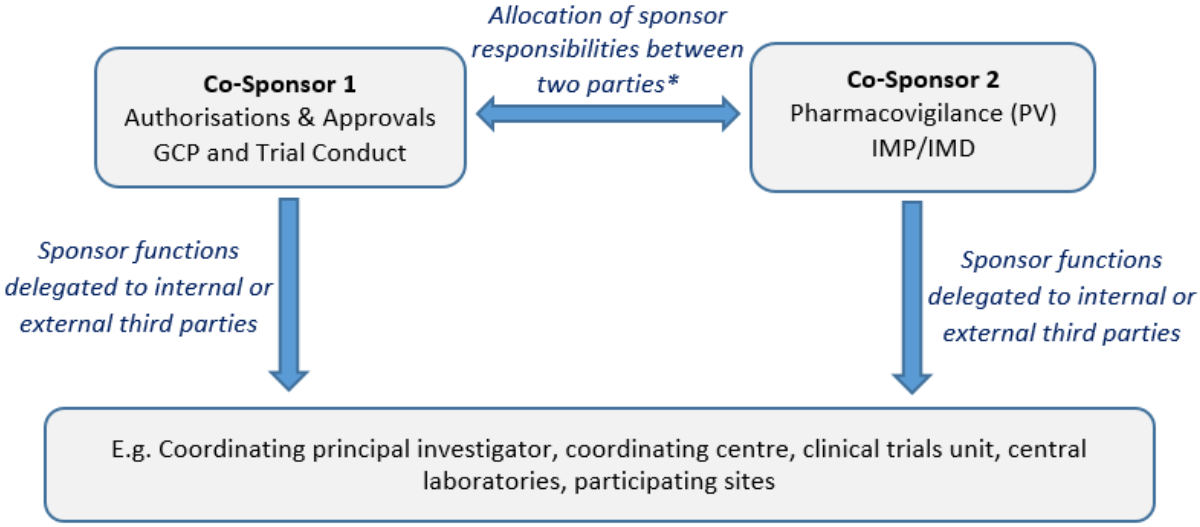
Allocation and delegation of sponsor responsibilities

Single sponsor model: Provided the sponsor keeps in place arrangements for oversight and audit, sponsor functions can be formally delegated to the coordinating principal investigator[5], clinical trial unit or another third party[6]. However, the sponsor remains accountable for all aspects of sponsorship whether delegated or not.

Co-sponsorship model: Where two or more organisations share a significant interest in a trial, for example, one as employer of the CPI and another as the principal host institution, they may elect to distribute sponsorship responsibilities amongst the members of the group provided that collectively, they make arrangements to allocate all responsibilities. Each co-sponsor is accountable only for their allocated responsibilities. In such circumstances, formal arrangements should be put in place:

- Between the co-sponsors: To clarify the allocation of responsibility for all sponsor responsibilities.
- Between co-sponsors and those delegated sponsor functions: To ensure all parties are aware of their delegated roles.

Figure 1: example of co-sponsorship model



** Co-sponsorship arrangements may be documented either on a trial-by-trial basis or, where two or more organisations are closely connected and frequently collaborate, in an overarching Master Agreement.*

All clinical trials should comply with the principles of Good Clinical Practice (GCP). Table 1 is an illustration of how key sponsor responsibilities for a non-commercial medicinal product trial may be grouped in order to allow for the unambiguous allocation of responsibilities within

[5] Institutions sponsoring clinical trials should ensure adequate support to enable CPIs to undertake the sponsor activities delegated to them (e.g. Access to expertise to facilitate grant applications and protocol design).

[6] As the person responsible for leading the team of researchers undertaking the design, conduct and reporting of a non-commercial trial, the CPI should also have oversight of a number of sponsor activities even when they are conducted by third parties.

contracts/agreements. Most of the good practice requirements in this table apply to all clinical trials and this document could be adapted as applicable. Please note the table does not represent all aspects/sections of GCP.

Table 1: Sponsor Functions and Responsibilities (IMP Trial)	**ICH GCP Reference**
1. Communication with approval bodies	
For trials conducted under the CTX/CTN Schemes, act as the point of contact for all communications with the Therapeutic Goods Administration	5.10
Ensure all approvals/authorisations are obtained (ethical approval, site-specific authorisation(s) and where applicable, TGA notification) before releasing investigational medicinal product to site	5.10, 5.11, 5.14.2, 8.2.7
Keep records of all amendments to the protocol and obtain approval/authorisations where required	5.4.2, 8.2.7
Notify all relevant bodies of the conclusion or termination of the trial, including a final report	4.13, 5.21, 5.22
Register trial in a publicly accessible clinical trial registry	N/A
2. GCP and trial conduct	
Ensure trials are well designed and a high quality protocol[7] and other key study documents, are developed	4.8, 6.0, 7.0
Implement and maintain quality assurance and quality control systems including appropriate SOPs for the conduct and management of trials	5.1
Implement a system to manage quality throughout the design, conduct, recording, evaluation, reporting and archiving of trials	5.0
Document in writing how all sponsor responsibilities have been allocated or delegated	5.2
Ensure that the principles of Good Clinical Practice (GCP) are satisfied and adhered to by implementing appropriate trial management and monitoring plans[8]	5.5, 5.18 6.0
Select investigators that are qualified by education, training and experience and with adequate resources to conduct the trial. Ensure written agreements are in place with investigators/institutions	5.1.2, 5.1.4, 5.6, 5.9, 5.18.4 (b), 8.2.6
Ensure provisions are in place for insurance/indemnity and compensation of trial subjects	5.8
Set up and maintain a Trial Master File (TMF) to hold all essential documents relating	8.0

[7] Where required, non-commercial sponsors should provide access to proportionate independent peer review.

[8] Where applicable, a non-commercial sponsor should ensure the CPI has access to staff with appropriate qualifications and experience to advise on/undertake key study management activities for clinical trials, such as protocol design, safety monitoring, randomisation, allocation concealment, data management and analysis.

to that trial	
Monitor/audit the trial to ensure that it is conducted in accordance with the current protocol, GCP and all regulatory requirements. If non-compliance is identified, act appropriately to secure compliance	5.1.2, 5.18, 5.19, 5.20.1, 8.3
Ensure electronic data processing systems are validated and meet the GCP expectations for source data, including the ability to maintain an audit/edit trail and adequate back-up of data	5.5
Ensure all trial-related duties and functions are defined, established and allocated	5.7
Utilise qualified individuals throughout all stages of the trial management process (trial design, data collection, study monitoring, data monitoring, analysis and reporting)	5.3, 5.4.1, 5.5.1, 5.5.2
Capture and notify to appropriate bodies, any serious breaches of GCP or the protocol/clinical investigation plan.	5.16, 5.18.4 (q)
Ensure trial essential documents including all research data and primary materials, are managed and archived appropriately	5.5
All findings (including negative findings) are disseminated/published (to both the scientific community and the public) and dissemination plans are made clear	6.15

3. Pharmacovigilance	
Ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied	5.12.1
Set up appropriate safety monitoring systems and perform an ongoing safety evaluation of the clinical trial	5.16.1
Ensure an investigator's brochure/product information exists for the trial and that it is reviewed at least annually and updated as significant new information becomes available	5.12, 7.0
Ensure that all adverse events relating to the trial are appropriately reported by investigators, as required in the protocol	5.18.4 (o)
Report to all relevant bodies, suspected unexpected serious adverse reactions (SUSARs)	5.17.1
Inform all relevant bodies and investigators of any significant safety issues[9] including any significant safety issues that were implemented as an urgent safety measure[10].	5.16.2, 3.3.7, 3.3.8, 4.5.2, 4.5.4

[9] A 'significant safety issue' is a term used to describe a safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.

[10] An urgent safety measure is a measure taken in order to eliminate an immediate hazard to a participant's health or safety. 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.

Provide an annual safety report to appropriate bodies	5.17.3

4. Investigational Medicinal Product (IMP)	
Ensure IMP is manufactured/imported in accordance with Good Manufacturing Practices (PIC/S Guide to Good Manufacturing Practice for medicinal products: Annex 13)	5.13.1
Ensure IMP is packaged and labelled in accordance with Good Manufacturing Practices (PIC/S Guide to Good Manufacturing Practice for medicinal products: Annex 13) and used in accordance with the protocol	5.13.2, 5.13.3, 5.15.18.4.(c ii)
In blinded trials, ensure that the coding system for IMP allows rapid identification of the product in case of a medical emergency but does not permit undetectable breaks of the blinding	5.13.4
Ensure appropriate records of IMP accountability, destruction/return are kept and investigational sites store, handle and supply IMP in accordance with the protocol	8.3.8, 8.3.9 5.14, 5.18.4 (c)

5. Generic
Ensure trials are conducted to all relevant Australian guidance and national and jurisdictional law
Ensure that sufficient resources are planned for full compliance with ethical, scientific and GCP requirements
Ensure agreements consider any funding, indemnities, insurances, confidential information or intellectual property ownership and authorship related to the trial