Clinical Oncological Society of Australia

How to manage clinical trial agreements more effectively

A joint Clinical Oncological Society of Australia and ARCS Australia workshop

28 May 2010

Workshop held during the ARCS Australia Scientific Congress
Australian Jockey Club, Randwick, Sydney

WORKSHOP SUMMARY

Workshop report prepared for COSA by ZEST Health Strategies

INTRODUCTION

Clinical research in Australia is undertaken by three main sectors: (i) the pharmaceutical and biotechnology industry; (ii) contract research organisations (CROs); (iii) cooperative or collaborative clinical trial groups (CCTGs). Each of these sectors must adhere to strict protocols and guidelines for the conduct of clinical trials. This requires that appropriate agreements are in place between the trial sponsor and the institution(s) in which the trial is being conducted.

Historically, trial sponsors each had their own clinical trial agreement (CTRA), each institution had their own requirements, and sponsors and institutions had their own legal representation. Negotiation of a new CTRA for each trial resulted in significant inefficiencies in trial approval and duplication of effort, often contributing to a delay in initiation and start-up. In recent years, efforts have been made by all three sectors and government agencies to simplify and streamline this process through the development of Standard CTRAs that are mutually acceptable for sponsors, institutions and jurisdictional bodies responsible for research governance and ethics.

Establishment of Standard CTRAs has been complicated by a range of factors, including:

- variation in legislation relating to clinical trial conduct between jurisdictions
- variation in legislation relating to clinical trials conducted in public and private institutions
- variation in legislation and expectations relating to clinical trials conducted in Australia on behalf of overseas sponsors
- the increasing focus in Australia and internationally on risk aversion, privacy and intellectual property.

In 2007, Medicines Australia, NSW, Victoria and Queensland approved a Standard CTRA for commercially sponsored trials. Since then, Standard CTRAs have also been developed for trials conducted by CROs and CRGs. Use of these agreements is recommended by some jurisdictions but is not typically mandated and, while considerable progress has been made, confusion still remains about how and when they can and should be used.

In May 2010, the Clinical Oncological Society of Australia (COSA) and ARCS Australia held a joint workshop for clinical trial professionals from all sectors of clinical research with the aim of highlighting the benefits of Standard CTRAs and clarifying how such agreements can be used more effectively. The workshop was attended by around 90 participants from industry, CROs, CTGs and trial sites across Australia. This report summarises key workshop messages and recommendations, together with issues that may require further consideration in this area.

ABOUT THE WORKSHOP SPONSORS

The **Clinical Oncological Society of Australia (COSA)** is Australia's peak multidisciplinary organisation representing health professionals working in cancer. COSA's mission is to develop and maintain high-quality clinical care for cancer patients in Australia. A critical component of this mission is the promotion and facilitation of cancer research. COSA provides support for Australia's 13 national Cancer Cooperative Clinical Trial Groups (CCTGs).

In 2005, COSA and the CCTGs successfully applied for a National Health and Medical Research Council (NHMRC) Enabling Grant. This national grant scheme is designed to assist Australian researchers in undertaking high-quality, world-class research by providing support for specific facilities and/or activities. Through the Enabling Project, COSA enhances the capacity of all member CCTGs to conduct high-quality clinical research by developing and providing fundamental resources in three areas:

- protocol development from concept outline to externally approved protocols
- web-based randomisation and data collection
- independent, comprehensive quality assurance program.

A significant recent initiative involving the senior operations staff from COSA and the CCTGs has been the development of a *Standard clinical trial research agreement template for collaborative or cooperative research group (CRG) studies* in cooperation with members of NSW Health and the Victorian Managed Insurance Authority (VMIA).

ARCS Australia Ltd (ARCS) (previously the Association of Regulatory and Clinical Scientists) is the professional development association representing individuals involved in the development of therapeutic products. ARCS is the leading provider of education and information to members and to all therapeutics goods personnel, and a forum for the exchange of ideas.

ARCS is a 'not-for-profit' organisation and is a Company Limited by Guarantee, which is governed by an elected Board. ARCS Australia has been endorsed as a Charitable Institution by the Australian Taxation Office. Founded in 1984, ARCS has approximately 2500 members who are involved in regulatory affairs, clinical research, health economics, medical devices, diagnostics, data management, statistics, medical writing, pharmacovigilance and the provision of medical information in the Australian therapeutics industry.

KEY POINTS

Key points and recommendations relating to the effective use of Standard Clinical Trial Research Agreements (CTRAs) identified during this joint ARCS and COSA workshop are outlined below.

1. The Standard CTRAs for commercially sponsored trials, contract research organisations (CROs) and collaborative or cooperative trial group (CTG) studies have helped to streamline approvals for clinical trials in Australia.

2. Work is underway to develop Standard CTRAs for trials of new medical devices, investigator-initiated studies involving a commercial sponsor, and observational studies. The CTRA for medical devices has been accepted by Victoria and Queensland and New South Wales is in the process of accepting its use.

3. The Standard CTRAs relate primarily to clinical trials undertaken in public institutions in Australia.

4. Use of the Standard CTRAs is recommended by some jurisdictions but is not currently mandated in Australia and jurisdictional variation in acceptance of the Agreements remains.

5. Operational or site-specific variations in the Standard CTRAs can be requested and incorporated through Schedule 7 (for commercially sponsored clinical trials and trials conducted by CROs) and Schedule 4 (for trials conducted by CRGs).

6. Variations in the Standard CTRAs through Schedule 7 and 4 amendments should not seek to change the terms and conditions in the body of the agreement or alter the overall intent of the agreement.

7. Use of Standard CTRAs raises issues for trials involving an overseas sponsor. Agreements for trials conducted in Australia must be between an institution and an Australian entity – either an Australian company, CRO or CTG or an Australian subsidiary of an overseas company, CRO or CTG.

8. Further clarification is required regarding what constitutes a ‘satellite site’ and whether such sites should be listed on a CTRA.

9. Efforts to further streamline trial approvals through standardisation of other trial processes would be welcomed. Suggestions included standardising indemnity agreements and standardising the nature and maximum fees associated with trial-related activities.

WORKSHOP OVERVIEW

PRESENTATION SUMMARY

The workshop opened with a series of presentations by a panel of experts, who provided an update on progress and issues with Standard CTRAs from the perspective of:

- the pharmaceutical and biotechnology industry (Carlo Maccarrone, Associate Director, Clinical Research, GlaxoSmithKline Australia)
- clinical research organisations (CROs) (Mathew Palmer, Senior Project Manager, Trident Clinical Research)
- cooperative and collaborative clinical trial groups (CTGs) (Kathy Hall, Research Manager, Trans-Tasman Radiation Oncology Group (TROG))
- research governance (Naho Yamazaki, Research, Ethics and Public Health Training Branch, NSW Health).

Key issues arising from the expert presentations are summarised below.

Background and context

There are currently three types of Standard CTRAs available for clinical trials conducted in Australia:[1]

- Medicines Australia *Standard Clinical Trials Agreement for Commercially Sponsored Trials*
- Medicines Australia *Standard Clinical Trials Agreement for Contract Research Organisations*
- *Standard Clinical Trials Agreement for Collaborative (or Cooperative) Research Group (CRG) Studies*.

These Standard CTRAs are designed primarily for clinical trial agreements conducted in public health institutions. They have been accepted by New South Wales, Victoria and Queensland. The Standard CTRAs for commercially sponsored trials and CROs have not been accepted by other states/territories. However, the Standard CTRA for CTGs has also been endorsed in the Australian Capital Territory, has provisional endorsement in South Australia and a modified version has been accepted in WA.

In addition to these Agreements, Standard CTRAs are also in development for:

- trials of medical devices
- investigator-initiated trials with commercial support
- observational trials.

[1] http://www.medicinesaustralia.com.au/pages/page39.asp (accessed 16 August 2010)

Differences in CTRAs between sectors

In the case of trials conducted by **CROs** on behalf of a commercial company, the institution and investigator are responsible to the CRO (as local sponsor of the trial) not the company. Requests for changes through Schedule 7 are common (see Table 1).

Table 1: Common requests for changes to Schedule 7 of Medicines Australia clinical trial agreements for trials conducted by a CRO

Common changes requested	Issues related to changes
Intellectual property/information	1. CROs manage trials from phase I to phase IV across a wide range of therapeutic areas and study requirements vary considerably 2. Requests for changes potentially delay start-up of studies especially where legal review is required. These can vary widely amongst the different organisations 3. Changes that restrict rights and ownership relating to intellectual property are frequently strongly contested by all affected parties to the agreement 4. Changes that affect the risk profile of parties to the agreement will often be rejected by governance or require additional negotiation
Publication restrictions	
Request for payment to come through overseas company rather than local sponsor	
Minor wording changes	
How breaches to the agreement will be handled	
Where institutional responsibility lies (to the company vs to the local sponsor)	

The Standard CTRA for trials conducted by **CTGs** differs from the agreement for commercially sponsored trials in a number of respects, primarily related to the fact that the trials conducted by CTGs are not undertaken for commercial reasons (see Table 2).

Table 2: Differences between Standard CTRAs for commercially sponsored trials and trials conducted by CTGs

Commercially sponsored trials	Collaborative/cooperative group trials
Commercial focus	Non-commercial focus
Minor interpretive differences relating to operative provisions	
Financial disclosure required for Principal Investigator	Financial disclosure not required for Principal Investigator
Costs for audit by regulatory authorities borne by sponsor	Costs for audit by regulatory authorities shared by institution and CRG
Company acts as sponsor	CRG acts as sponsor
Sponsor indemnifies institution and maintains insurance with respect to its activities	Each party must maintain appropriate insurance to provide indemnity in relation to any liability it may incur
Responsibility for investigational product lies with the company	
Can subcontract activities	No specific clause that clarifies the party's right to subcontract (although not prohibited)
Differing responsibilities regarding payments and provision of equipment to sites	
Institution and PI have the right to publish	Institution and PI cannot publish without approval from CRG
Intellectual property lies with the company	Intellectual property lies with the CRG except that relating to investigational product or equipment

Variations in CTRAs

The Standard CTRAs have been developed as fair and reasonable agreements and therefore significant changes are not warranted. Operational or site specific variations in the Standard CTRAs can be incorporated through Schedule 7 (for commercially sponsored and CRO trials) and Schedule 4 (for trials conducted by CTGs). Requests for changes should be limited to 'must have' inclusions.

Variations made through Schedules 7 and 4 are not intended to be used for substantial changes to the terms and conditions in the body of the agreement or to change the overall intent of the agreement. They should not be used for:

- drafting amendments
- clauses that seek to override the applicability of the Standard CTRA
- clauses that are contrary to government insurance arrangements
- clauses seeking to impose additional indemnities on parties or to lessen an existing indemnity
- clauses that are clearly contrary to the core provisions of the Standard CTRA (eg publication, confidentiality, IP and termination provisions, and compliance with foreign legal requirements).

Requests for variations to Schedules 7 and 4 should not merely be a variation on the same theme and should not introduce onerous demands to institutions.

Currently, around 35 companies have pre-approved Schedule 7 provisions for ongoing use and one-off multicentre trials. The pre-approval of sponsor-specific clauses are designed to reduce the number of reviews required. They do not relate to one-off site-specific trials. Institutions can still retain the right to reject these pre-approved clauses for operational reasons.

Current issues

Ongoing issues relating to use of Standard CTRAs include:

- the need for communication and education to encourage a greater understanding of the intent of the agreements and to limit the type and number of changes requested.
- the need to achieve agreement on the Standard CTRAs from remaining states and territories (COSA and the cancer CTGs have been seeking endorsement from all states/territories of their Standard CTRA for CTGs. The agreement has been approved with no amendments by the Australian Capital Territory and with amendments by Western Australia. Provisional approval from South Australia has been obtained and negotiations are underway with the Northern Territory and Tasmania. An agreement for studies conducted in New Zealand is also in train).
- how to promote the relevance of Standard CTRAs and encourage their use for trials conducted through private institutions.

Opportunities for further streamlining of CTRAs

Opportunities for further streamlining of clinical trial processes exist through:

- consideration of precedents from previous trials conducted by the sponsor that may be useful in informing proposed Schedule 7/4 variations (sponsors only have access to the outcome of their own clauses submitted for pre-approval; these clauses are treated as commercial in confidence; CROs working for a number of sponsors may come across a range of issues over time and may be able to advise future clients of what may be considered acceptable or not)

- provision of all contextual information to support CTRAs and any requested amendments
- ensuring that all requests for Schedule 7/4 changes are submitted to the relevant body using the standard template, highlighting the original and proposed clause and appropriate justification to support the request.

CASE STUDY DISCUSSION OUTCOMES

Small group discussions focused around a series of case studies designed to highlight a range of issues related to use of a Standard CTRA, including:

- considerations for clinical trials in which procedures are undertaken at multiple sites (subcontracted and satellite sites)
- issues and potential risks of making changes to Standard CTRAs for trials conducted by a CRO on behalf of an overseas sponsor
- considerations when making changes to clauses of a Standard CTRA that affect intellectual property and confidentiality
- general views on the benefits of a Standard CTRA, lessons learned and opportunities for improvement.

Participants were given the opportunity to share their ideas on each of the case studies with the plenary group and to direct specific questions to the expert panel, which comprised the presenters together with Elizabeth Wilkinson from Trident Clinical Research.

The discussions highlighted a number of considerations as outlined below.

Acceptability of Schedule 7 amendments

Participants discussed a range of potential Schedule 7 amendments for a trial conducted by a CRO on behalf of an overseas sponsor. In discussing these amendments, it was highlighted that agreements for trials conducted in Australia must be between an institution and an Australian entity – either an Australian company, CRO or CTG or an Australian subsidiary of an overseas company, CRO or CTG.

In reviewing these amendments, participants identified a range of issues relating to Schedule 7 amendments, including the need to avoid:

- the use of subjective statements such as ‘reasonable endeavours’ or ‘commercially reasonable’ in a CTRA
- changes that merely restate an existing clause within the agreement
- changes that seek to impose additional indemnities on parties to the agreement.

Participants also discussed the issue of overseas sponsors who request the inclusion of clauses that require payment to be made directly from them to an institution. Such agreements add an additional level of complexity, raising the risk that sites will be financially compromised because of fluctuations in the exchange rate over the course of the trial and that trial initiation will be delayed while financial negotiations are underway. Payment from an overseas sponsor also raises the issue of how additional funds will be accessed if an issue arises with the trial once it has started. Payment through a local sponsor helps to mitigate the risk that sites will be financially compromised.

Potential solutions discussed by participants and the panel to address situations in which this was not acceptable to the overseas sponsor included:

- an upfront agreement to fix the currency exchange rate for the duration of the trial
- an agreement between the overseas sponsor and a local sponsor (Australian subsidiary or Australian CRO) with site payment then made between the local sponsor and the institution.

Suggestions made by the panel in relation to streamlining the CTRA process for trials conducted by a CRO on behalf of an overseas sponsor included:

- managing expectations of the global sponsor from the outset with the aim of limiting the number of amendments requested
- emphasising the requirement of making CTRAs between the institution and a local Australian entity
- highlighting the potential delay to trial initiation that may occur if multiple revisions to the CTRA are requested
- drawing on precedent from previous trials about variations to CTRAs that have/have not been accepted.

Issues of intellectual property and confidentiality

Participants reviewed some potential Schedule 7 amendments that related to issues of intellectual property and confidentiality. The discussion raised a number of issues including the need to avoid:

- changes that pose a potential increase in the level of risk associated with the conduct of a trial
- changes that seek to alter the core provision of the Standard CTRA.

Suggestions made by the panel to address requests to vary clauses relating to intellectual property and confidentiality included the addition of a statement to the effect that common law will prevail in the case of intentional breaches of confidentiality or intellectual property.

Conduct of trial procedures at multiple sites

The Therapeutic Goods Administration (TGA) Clinical Trial Notification (CTN) Scheme form[2] states that trial site details should be submitted for '*each site at which the trial will be conducted*'. The TGA defines a trial site as '*the location where trial-related activities are conducted.*'[3] Participants agreed that, typically, a subcontracted site provides services to a trial site without assessment or interpretation of trial data. Such sites would have a service-level agreement with the main site.

Discussions highlighted a level of confusion about whether all sites should be listed on the CTN form, regardless of the level of trial involvement, or whether the sites listed should be limited to those at which investigational product is administered. Participants described different experiences in relation to advice received from the TGA in relation to this issue.

The view from the panel was that:

- the sponsor will usually enter into an agreement with the institution that takes on the study – this is typically the institution at which the Principal Investigator is based
- at a practical level, the question of whether to list a site on the CTN depends on the extent of trial-related activity performed at that site

[2] http://www.tga.gov.au/docs/pdf/unapproved/ctnform.pdf (accessed 31 May 2010)
[3] http://www.tga.gov.au/docs/pdf/unapproved/clintrials.pdf (accessed 31 May 2010)

- regardless of which sites are listed on the CTN, the study protocol and relevant CTRAs should list all sites involved for the purposes of maintaining an audit trail.

Clarification may be useful from the TGA regarding which sites should be listed on the CTN.

Satellite sites

Discussions about which sites should be included within a CTRA or CTN generated considerable discussion about the definition of a 'satellite site'. Participants and panel members agreed that there is no one correct definition. A number of examples were given, including:

- sites where only certain activities are performed, such as screening or dialysis
- trials involving one Principal Investigator with multiple primary care sites where procedures are performed
- institutions with one central Human Research Ethics Committee (HREC) and multiple campuses
- trials undertaken by a health service with multiple hospitals involved.

The examples discussed raised a number of considerations in relation to CTRAs for trials involving satellite sites, including:

- ethics approval – because HRECs are responsible for monitoring the trial at sites listed in the CTN form, it is important that there is clarity on what constitutes a site and that all relevant locations are listed in CTN and CTRA
- payment – if a site is performing any trial activity for which it is being paid, a CTRA needs to be in place between the sponsor and the site
- insurance and indemnity – all satellite sites should be covered by appropriate insurance/indemnity relevant to the tasks being performed by the satellite site
- investigational product issues – robust procedures for dispensing and management of investigational product are needed for studies in which patient recruitment (and therefore randomisation) occur separately from dispensing of investigational product
- addition of satellite sites after trial initiation – addenda should be used to add additional satellite sites to a CTRA if required after a trial has started.

Further clarification from the TGA about what constitutes a 'satellite' and 'secondary' site would be valuable.

Impact of Standard CTRAs

There was general agreement from participants that Standard CTRAs have helped to streamline processes and have shortened the approval process for clinical trials. However, a number of participants commented on the lengthy timeframe that still exists for contract negotiations and emphasised the need for further efforts to be made, within reason, to standardise other elements of trial agreements, such as indemnity and budgets.

One area that generated considerable discussion was standardisation of clinical trial fees. Participants highlighted the considerable variation that exists in Australia between jurisdictions

and between upfront and variable trial costs, with some people raising concern that Australia will 'outprice' itself unless some form of fee capping is put in place.

Issues relating to standardisation of trial fees included:

- the fact that standardised fees, if agreed, could not be mandated
- the potential for institutions to charge an overhead in addition to the standardised fee.

One potential solution discussed was to agree on a set schedule of clinical trial activities for which a fee can be charged with an associated cap for each activity.

Panel feedback indicated that the Medicines Australia Clinical Working Group has discussed this issue but that so far no agreement on an approach has been reached, given restrictions on price fixing imposed by the Australian Competition and Consumer Commission (ACCC).

Further effort to standardise clinical trial procedures, in particular, clinical trial budgets, would be welcomed.