Clinical Oncological Society of Australia

Risk minimisation and liability issues in clinical trials

A Clinical Oncological Society of Australia workshop

19 May 2010

Stamford Plaza Hotel, Sydney Airport

WORKSHOP SUMMARY

Workshop report prepared for COSA by ZEST Health Strategies

INTRODUCTION

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 Trial Groups (CCTGs). These collaborative trial networks undertake rigorous clinical research studies designed to address clinically important questions that are directly related to improving patient outcomes. 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 key areas:

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

In 2006, the Enabling Project Steering Committee identified insurance for CCTGs as a significant barrier to initiating investigator-initiated clinical trials. With the agreement of this Committee, COSA commissioned Healthcare Risk Resources International (HRRI) to prepare a report on issues related to insurance for investigator-initiated trials. The report[1] concluded that:

- the risk of litigation for investigator-initiated trials is low/negligible
- CCTGs conducting these trials have a number of options regarding clinical trials insurance, including:
    1. do not insure (not recommended by HHRI)
    2. maintain the status quo (each CCTG to source its own clinical trials insurance)
    3. consider a collective arrangement (Umbrella Policy; ***recommended by HHRI***).

The Enabling Project Steering Committee elected to pursue option 3, and nine CCTGs agreed to participate in the COSA Umbrella Insurance Scheme, which commenced on 1 June 2009.

The inception of the COSA Umbrella Insurance Scheme represents a significant step forward in providing a cost-effective, simplified and streamlined approach to the management of insurance for clinical trials within Australia. The aim of the Scheme is to develop a well-managed, high-quality scheme for participating trials groups. A further objective of the Enabling Project is to develop risk-management and quality-assurance strategies and to educate members of the participating CCTGs about these strategies.

In May 2010, COSA and the CCTGs Enabling Project held a workshop for CCTG representatives about liability issues in clinical trials. The half-day workshop was developed and delivered on a pro-bono basis by Dr Teresa Schafer of commercial law firm Piper Alderman. The purpose of the workshop was to train junior clinicians involved in CCTGs about the rules, regulations, processes and rigor required for the conduct of clinical trials as well as

[1] COSA and Cooperative Group Enabling Project and Clinical Oncological Society of Australia. Analysis of issues behind insurance options and indemnity for clinical trials in Australia. August 2008. http://www.cosa.org.au//Groups/Enabling/ClinicalTrialsInsurance/COSAReport.htm

factors to be considered in the management of a business that entails risk and associated mitigation of that risk.

This report provides an overview of the key messages and recommendations from the workshop, which was attended by 39 participants from the CCTGs (see Appendix I for a list of workshop participants).

ABOUT DR TERESA SCHAFER

Dr Teresa Schafer is a partner in Piper Alderman's corporate group. She is both a lawyer and scientist with more than 17 years experience in the pharmaceutical and medical device industry in Australia and New Zealand.

Teresa's practice provides strategic legal and regulatory advice to clients in drug registration; clinical research; reimbursement; product supply and distribution; contractual arrangements; promotion and advertising; patent law, product safety and pharmacovigilance. She has worked extensively in the industry, both at senior management level and in a consultancy capacity. The value-added advice Teresa provides to clients draws upon her legal, regulatory and scientific expertise, combined with practical commercial knowledge and strong business acumen.

In addition to Piper Alderman, Teresa is a part-time member of the Administrative Appeals Tribunal, a position which she has held since August 2006. She is also a Director of the Board of the Association of Regulatory & Clinical Scientists and a member of the Association of Therapeutic Goods Consultants.

KEY POINTS

This Clinical Oncological Society of Australia (COSA) and Cancer Cooperative Trial Groups (CCTGs) Enabling Project workshop highlighted a number of issues relating to the identification, minimisation and management of risks associated with the conduct of cancer clinical trials.

The risks discussed related to a case study involving a phase I trial. Most of the trials undertaken by CCTGs are typically phase II and III trials or do not involve an intervention, and as such tend to carry a lower level of risk than that discussed during the workshop. However, the workshop illustrated the importance of all those involved in the planning and conduct of a clinical trial being aware of and taking steps to mitigate the level of risk involved.

Key points and recommendations relating to liability and risk minimisation in clinical trials identified during the workshop are outlined below.

1. The clinical trial environment is becoming increasingly risk averse.
2. The clinical trial subject should remain the primary focus at all times.
3. Clinical trial sponsors, investigators, Human Research Ethics Committees (HRECs) and the institutions in which trials are being conducted have a responsibility to ensure that appropriate resources and agreements are in place and that informed consent, compensation, indemnity, insurance cover and protection of information are appropriate to ensure that the interests of all parties are protected.
4. It is essential that clinical trial sponsors, institutions and investigators understand their responsibilities in relation to the trial conduct, the potential risks associated with the trial and that they carry a level of indemnity and insurance appropriate to this level of risk.
5. A sponsor, investigator or clinical research staff member involved in a clinical trial should make no assumptions about the adequacy of the trial design to account for all situations that may arise; all parties should check the protocol before initiation.
6. Full disclosure of potential risks is paramount in ensuring informed consent for clinical trial subjects.
7. Financial compensation for clinical trial subjects should not subvert the need to obtain proper informed consent.
8. Risk minimisation for the conduct of clinical trials includes ensuring that:
    - all parties involved understand and commit to their role and responsibilities and have adequate insurance
    - all parties comply fully with the protocol
    - appropriate governance mechanisms are in place.
9. In the case of multi-centre ethical review, the insurer must be informed that ethical review will be used by multiple institutions.
10. Adequate disclosure of risk does not avoid liability for the negligent conduct of a clinical trial.

WORKSHOP OVERVIEW

The COSA and CCTGs Enabling Project workshop involved a series of small group discussions based around a real case study about a phase I clinical trial and covered questions around:

- who could be at fault in the case of a compensation claim?
- legal and regulatory issues associated with the conduct of clinical trials
- how to minimise risk to all parties involved in a clinical trial
- how to achieve informed consent for trial participants.

Although the majority of trials conducted by the CCTGs are phase II and III trials, the issues around risk management relating to the phase I trial discussed were considered highly relevant to all phases of clinical trials.

In discussing these issues, participants were reminded of the legislative basis for the conduct of clinical trials in Australia, in particular, Section 19 of the *Therapeutic Goods Act 1989*,[2] which states that clinical trials must comply with the *Therapeutic Goods Regulations 1990*.[3] Specifically, Regulation 12AD provides that clinical trials must:

- comply with ICH Guidelines for Good Clinical Practice (GCP)[4]
- be in accordance with the protocol that has been approved by a human research ethics committee (HREC)
- comply with the NHMRC *Australian Code for the Responsible Conduct of Research*[5]
- cease if an ethics committee notifies the principal investigator (PI) that use of the study drug/therapy is inconsistent with the protocol or conditions of use.

It was emphasised that in the case of non-compliance, legal action could be taken regardless of whether the Therapeutic Goods Administration (TGA) has reviewed trial data through the Clinical Trials Exemption Scheme (CTX) or has only been notified of the trial through the Clinical Trials Notification Scheme (CTN).[6]

Key messages arising from each of the discussion sessions are summarised below.

WHO IS AT FAULT?

Clinical trials involve a range of parties, and may include the company supplying the drug/entity being tested, the trial sponsor (in the case of this workshop, the CCTG), the institution(s) in which the trial is being conducted, the investigator and staff conducting the trial and ultimately the trial subjects. Agreements between each of these parties outline the responsibilities of each party.

In the case of a compensation claim, a trial subject could make a claim against any of these parties. Moreover, the HREC or any consultants providing advice to the HREC could also be at risk. Workshop participants discussed the obligations of each of these parties and the steps that should be taken to mitigate risk.

[2] http://www.comlaw.gov.au/ComLaw/Legislation/ActCompilation1.nsf/0/840CB0162B421D54CA256FBF00121547/$file/TherapeuticGoods1989_WD02.pdf (accessed 21 May 2010)
[3] http://www.comlaw.gov.au/comlaw/Legislation/LegislativeInstrumentCompilation1.nsf/0/602B7B69ABC23B16CA2576DD0005B478/$file/TherapeuticGoodsRegs1990.pdf (accessed 21 May 2010)
[4] http://www.tga.gov.au/docs/html/ich13595.htm (accessed 21 May 2010)
[5] http://www.nhmrc.gov.au/publications/synopses/r39syn.htm (accessed 21 May 2010)
[6] http://www.tga.gov.au/ct/index.htm (accessed 21 May 2010)

Trial sponsor

The **trial sponsor** carries primary responsibility in relation to the safety and conduct of the trial. This means that they must:

- ensure that the trial protocol is scientifically sound and minimises exposure to subjects
- ensure that the trial complies with legislative and regulatory requirements
- ensure that the trial complies with state and territory legislation
- obtain HREC approval and comply with the conditions of this approval
- report all serious and unexpected adverse events to the TGA
- ensure that legal and financial arrangements are clearly set out with the institution through a governance agreement
- establish appropriate insurance and indemnity arrangements.

Management of risk by the trial sponsor includes ensuring that:

- a clinical trial agreement (CTA) is in place with the institution(s) conducting the trial that minimises risk and mitigates exposure
- an agreement is in place, if relevant, with the company supplying the drug or entity being tested stating clearly that the sponsor will be indemnified if an issue arises because of the drug/entity (this is less of an issue with phase III and IV trials in which drug safety data are already available).

Institution

The institution carries 'vicarious liability', which means it is responsible for the actions of its employees. This includes the clinical investigator(s) and the clinical research staff employed to coordinate the trial. The institution is linked to the investigator and research staff through their employment contracts and therefore if the investigator or another staff member is found liable for an issue, the institution will also be liable.

Management of risk by the institution includes:

- ensuring that the investigator(s) and staff involved in the trial have the appropriate expertise to conduct the trial
- ensuring that the facilities at the institution are appropriate for the conduct of the trial (for example, provision of acute care facilities in the case of a phase I trial)
- reviewing the CTA to ensure that it mitigates risk and minimises exposure.

Investigator

The PI has overall responsibility for the conduct of a trial at the trial site, in particular when delegating responsibility to other trial staff. The PI has a duty of care to the subjects enrolled on the trial and must ensure that the trial protocol is scientifically sound and minimises any potential risk to the trial subjects. If any responsibility for the conduct of the trial is delegated to other staff members, those individuals should also review the protocol to ensure their satisfaction with the adequacy and appropriateness of the trial design.

Ethics committee

Each member of an HREC will be indemnified by the institution in which the HREC operates. Although the HREC would be likely to defer to the relevant scientific sub-committee in the event of a compensation claim, there should be sufficient informed discussion to identify any major issues with the protocol design.

LEGAL AND REGULATORY ISSUES

The risks associated with the conduct of a clinical trial are highest at the transition point from a pre-clinical study to a phase I (first in man (FIM)) trial. The advent of biological therapies is also contributing to increased risk, given that such therapies carry more species-specific activity than many chemical entities.

Although the focus of CCTG trials is typically phase II and III trials, the concepts and issues discussed in relation to the phase I trial were highly relevant to participants. Key issues for consideration included:

- the need to ensure adequate insurance for the conduct of trials
- the importance of calculating an appropriate starting dose for use in FIM trials (typically a maximum of 1/100th of the dose used in animal models)
- the importance of ensuring adequate time between administration of doses to subjects to allow time to identify and act on any unexpected reactions/side effects
- the need to consider the safety of trial subjects, including whether it is appropriate to use healthy volunteers or patients (see Table 1 below).

Table 1: Comparison of benefits of using healthy volunteers vs patients in dose-finding studies

Justification for using healthy volunteers	Justification for using patients
Interpretation of data is easier	No therapeutic benefit for healthy subjects
More homogeneous population	Use of cytotoxic agents cannot be justified in healthy subjects
More able to tolerate pharmacological insult	May provide preliminary information about efficacy
Similar expression of target antigen	

Financial compensation

Participants discussed the difference between financial compensation for trial subjects and inducement to participate in trials. While there are no objective criteria to determine what is appropriate, participants were reminded of the need for appropriate checks to ensure that the level of compensation could not be seen as influencing the judgement of a subject about whether to participate. Appropriate examples included reimbursement for transport costs to attend a study visit, and, depending on the timing of required tests or procedures, reimbursement of small costs for a meal.

RISK MINIMISATION

Workshop participants discussed a range of issues related to insurance and indemnity provisions for clinical trials. The need for sponsors to provide insurance or indemnify investigators/institutions against claims arising from clinical trials (with the exception of claims arising from malpractice/negligence) is mandated in the ICH Guidelines for Good Clinical Practice (GCP)[7] and supported by the NHMRC *National Statement on Ethical Conduct for Human Research*.[8] In addition, according to the NHMRC Statement, institutions must compensate subjects for harm resulting from research negligence.

[7] http://www.tga.gov.au/docs/html/ich13595.htm (accessed 21 May 2010)
[8] http://www.nhmrc.gov.au/publications/synopses/e72syn.htm (accessed 16 August 2010)

Sponsors should agree to compensation in accordance with the Medicines Australia *Guidelines for compensation for injury for participants injured in a company-sponsored clinical trial.*[9] These guidelines provide a minimum standard for compensation in which the sponsor agrees to compensate subjects who '*suffer personal injury (including death)*' on a no-fault basis. The guideline states that compensation will only be paid for '*the more serious injury of an enduring and disabling character*' and not for '*temporary pain or discomfort or less serious or readily curable complaints'.*

Given that the Medicines Australia guideline does not clearly define '*personal injury*', workshop participants were reminded of the need to ensure that any insurance/indemnity agreement is not open ended. It was suggested that any agreement should clearly state the scope of cover, such as:

- medical expenses
- pain and suffering
- loss of earnings/earning capacity/potential earnings
- other financial loss/expenses
- funeral costs
- dependents' allowances.

Participants were also reminded that use of the Medicines Australia Guidelines does not affect an individual's right to pursue their claim through the courts.

Standard Clinical Trial Agreements

There are 3 types of standard CTAs:[10]

- 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*.

Use of the *Standard Clinical Trials Agreement for Collaborative (or Cooperative) Research Group (CRG) Studies* has been adopted widely in Australia to standardise agreements between sponsors and the institutions in which a trial is being conducted. Adopting this agreement can help to avoid delays in ethics approval. While amendments can be sought, the extent to which this is accepted varies by jurisdiction, with little scope for amendment in Victoria and NSW for trials conducted in public institutions. Institutions that do accept a varied agreement may request additional funds from the sponsor to support having the varied agreement checked from a legal perspective.

Insurance provisions for investigators

According to the *Medical Indemnity (Prudential Supervision and Product Standards) Act, 2003*,[11] health professionals must have at least $5 million in professional indemnity cover. While some HRECs accept this level of cover for investigators involved in clinical trials, some hospitals, especially public institutions in Victoria, currently require a higher level of cover and a specific policy that extends coverage to clinical trials.

[9] http://www.medicinesaustralia.com.au/pages/images/Clnical%20Trials%20Compensation%20Guidelines.pdf (accessed 24 May 2010)
[10] http://www.medicinesaustralia.com.au/pages/page39.asp (accessed 16 August 2010)
[11] http://www.comlaw.gov.au/comlaw/management.nsf/lookupindexpagesbyid/IP200401881?OpenDocument (accessed 24 May 2010)

Other specific insurance provisions

There is some discretion for variation in insurance provisions, especially in the case of lower risk studies. Where a trial is being conducted in Australia but the sponsor has an overseas 'parent', the parent must provide confirmation that the Australian corporate entity acting as the sponsor is a wholly owned, operated and controlled subsidiary of the parent, and the subsidiary must be a named insured on the policy.

PROTECTION OF INFORMATION

Participants were reminded of the need for institutions who are participating in a clinical trial to have established procedures for the retention of trial data and records as outlined in the ICH Guidelines for GCP. The requirements for document retention should be captured in the CTA. From a privacy perspective, personal and sensitive information should be protected according to the Commonwealth's *Privacy Act (1988)*[12] and the ten National Privacy Principles (NPPs; see Table 2).[13]

Table 2: National Privacy Principles

The National Privacy Principles are the base line privacy standards which some private sector organisations need to comply with in relation to personal information they hold. All health service providers in the private sector need to comply with these principles.

1. Collection
2. Use and disclosure
3. Data quality
4. Data security
5. Openness
6. Access and correction
7. Identifiers
8. Anonymity
9. Transborder data flows
10. Sensitive information

Although the *Privacy Act (1988)* does not expressly address confidentiality, unauthorised disclosure of information may breach NPP 2. Confidentiality should be included as part of the CTA.

Every CTA should specify how personal and sensitive information will be used and protected. According to the NPPs, sensitive information can only be collected: (i) following individual consent; (ii) if the requires collection; or (iii) if collection of the information is necessary to prevent or lessen the threat to life or health.

INFORMED CONSENT

Participants discussed the minimum requirements for a patient information sheet and informed consent form, in the context of current privacy and confidentiality principles and the need for full disclosure of information. In discussing the requirements for informed consent, participants were encouraged to consider the balance between providing sufficient information to ensure full

[12] http://www.comlaw.gov.au/ComLaw/Management.nsf/current/bytitle/32AA97DFE9AA8326CA256F7100071D25?OpenDocument&mostrecent=1 (accessed 24 May 2010)
[13] http://www.privacy.gov.au/materials/types/infosheets/view/6583 (accessed 24 May 2010)

disclosure and the risk of overloading subjects with too much information, which may reduce the clarity of the information provided.

Disclosure of risk

According to the Declaration of Helsinki,[14] which provides ethical guidelines for the conduct of research involving human subjects, every trial subject must be informed of any '*potential risks of the study and the discomfort it may entail'.* This includes providing information about any procedures and their associated risks.

The patient information sheet and informed consent form should adequately disclose the risk to the patient. Disclosure should include a description of the magnitude and severity of potential harms including:

- physical harm (eg pain, side effects)
- psychological harm (eg depression, anxiety)
- harms associated with breaches or infringements of confidentiality
- social harm (eg discrimination)
- economic harm (eg financial cost of participation).

Descriptions should be explicit about what is known or not known about a treatment or procedure and should include all information that is in the public domain. Inclusion of a statement relating to additional unknown or unforeseen risks would be prudent. However, such disclosure does not mitigate liability for negligence or misconduct.

Use of information

The patient information sheet and informed consent form should specify how information collected as part of the trial will be collated and used, how confidentiality will be protected and the circumstances in which a patient identification code may need to be broken (eg in the case of particular serious adverse events). According to the NPPs, data collected must be relevant to the trial. For example, if information about ethnicity is collected, this must be because ethnicity may affect the pharmacokinetics of the treatment under study.

The patient information sheet should also specify how a trial subject can access information collected as part of the trial if required.

Other information

In addition to the information about risk and use of information, participants discussed a range of other inclusions for a patient information sheet/informed consent form, including:

- whether there is/is not a potential health benefit associated with trial participation (eg dose finding study vs comparison of therapeutic benefit)
- the chance of receiving the experimental agent and whether the trial is randomised
- contact details, including details of the ethics committee and emergency contact details
- a clear description of what the subject can expect to happen during the trial
- a clear description of what will happen if something goes wrong, including compensation details.

Participants were cautioned against being too aggressive in the patient information sheet and consent form about the requirements of the individual.

[14] http://www.wma.net/en/30publications/10policies/b3/index.html (accessed 24 May 2010)

MULTI-CENTRE RESEARCH

HoMER Initiative

The Harmonisation of Multi-centre Ethical Review (HoMER) is a system in development by designed by the NHMRC to enable the outcome of an ethical review by a single HREC to be accepted by all institutions participating in a multi-centre research project. The aim of the HoMER initiative is to avoid duplication of effort by streamlining the ethical review process.

According to the NHMRC National Statement on Ethical Conduct in Human Research:

> *'Wherever more than one institution has a responsibility to ensure that a human research project is subject to ethical review, each institution has the further responsibility to adopt a review process that eliminates any unnecessary duplication of ethical review.'*[15]

Each institution participating in a multi-centre study conducted under the HoMER initiative must have appropriate research governance procedures and adequate insurance arrangements in place. Commercial insurers will cover multi-centre research but must be informed that ethics approval will be used at multiple sites. State and territory insurance allows for insurance arrangements to be adapted according to local governance and administrative requirements. Private institutions should clarify insurance arrangements with their insurer.

Liability issues and ethical review

Consideration of liability issues within a clinical trial will relate to whether there is evidence of negligent behaviour.

If a researcher is found to have been negligent, there will typically be no grounds for a claim against the HREC. In this instance, a claim may be made against the researcher/investigator, and against the institution (through vicarious liability).

A HREC would only be found negligent if a trial was conducted according to the protocol and if there was a direct connection between the conduct of ethical review and the alleged harm. In such circumstances, the institution that established the HREC (rather than the accepting institution) would most likely be a co-defendant and, in the case of a public health organisation, the state/territory insurer may be involved.

It is important for HREC members to ensure that appropriate and adequate indemnity is in place for the trial. According to the NHMRC National Statement on Ethical Conduct in Human Research:

> 'Institutions should provide an assurance of legal protection to all those involved in the ethical review of research, for liabilities may arise in the course of bona fide conduct of their duties in this capacity.'[16]

The institution accepting the ethical review from an external HREC should inform their insurer that this is the case. The accepting institution does not need to indemnify the HREC and may claim against the HREC in the case of negligence.

[15] http://www.nhmrc.gov.au/publications/ethics/2007_humans/section5.3.htm (accessed 25 May 2010)
[16] http://www.nhmrc.gov.au/publications/ethics/2007_humans/section5.1.htm (accessed 25 May 2010)

APPENDIX I: WORKSHOP PARTICIPANTS

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