



1. Background

The total budget included in the original COSA and Co-Operative Groups Enabling Grant application was \$3.13 million over 5 years; the amount awarded was \$1.84 million. Initial co-funding was to be \$959,836; co-funding required to complete all of proposed work of original grant is \$1.299 million. Quality Assurance and SOPs were 18% of original application budget. It is recommended that the Subcommittee works with proportion of 15% of total budget; which is approximately \$55,200 p.a. (\$276,000 over 5 yrs).

Preliminary terms of reference for the QA Subcommittee were to conduct a scoping exercise to assess existing QA programs and collect the member groups' views on how to proceed, recommend a model for distributing funds to support QA activities, and recommend a process for oversight of QA activities. In discussing the report resulting from the scoping exercise, the QA Working Party agreed that due to the ambiguity of responses and lack of consistent application of definitions the conclusions of the scoping exercise are unclear. There was need for clarification in regard to:

- Standardised interpretation and implementation of definitions
- Risk assessment for trials to determine the appropriate level and scale of quality assurance activities, particularly with regard to use of resource intensive on-site monitoring and audits

The Working Party recommended that the Enabling Grant support a QA workshop involving 2 representatives of each co-operative group, a representative of the clinical trial coordinating centres (CTC, Peter Mac, VCOG, others as appropriate), site staff, industry, Cancer Institute NSW, and the QA Working Party. This workshop aims to progress this component of the grant.

2. Workshop

2.1 Workshop purpose

The purpose of the workshop are to:

- reach consensus regarding interpretation of standard terminology
- identify existing QA programs and their components
- define/assess benchmarks for QA in clinical research
- define the optimal model(s) and state principles of such a model taking into consideration resources available

2.2 Workshop attendees

The workshop was facilitated by Marie Malica, Manager of the Strategic Research Unit, The Cancer Council NSW. A broad range of people were invited to attend the meeting, including representatives from all cancer cooperative groups, Trial Coordinating Centre, Participating Sites, and other stakeholders. The full list of attendees and apologies are provided in Appendix 1.

3. Content

Agenda for the workshop is included in Appendix 2.

3.1 Goals of QA program

- To demonstrate that a study has been done to an appropriate level of quality, in particular:
 - credible outcomes and adequate precision
 - patient safety

- regulatory compliance; noted in discussion that regulatory compliance is a secondary goal to ensure that the first two goals are met, it is an external check.
- To minimize the risk that:
 - a patient will be harmed
 - the study will not be completed satisfactorily
 - the study will give erroneous results and conclusions
 - the study is not credible in the academic world

NHMRC CTC Quality Management System

Goal of this QA program is to provide support to ensure data quality and compliance with the regulations. Specific issues to be addressed may include:

- Protocol quality and feasibility
- Adequate study organisation and accountabilities, including site SOPs
- Training support for clinicians and site staff
- Outcomes assessment
- Governance/oversight through monitoring at the collaborative group level and possibly an audit program.

Phillipa Smith, Acting Head of QA, NHMRC Clinical Trial Centre, presented the CTC's approach to designing and implementing a QA program based on risk assessment (Appendix 3). The effectiveness of any QMS is only as good as its ongoing maintenance.

There was some discussion about the error rates in monitored versus unmonitored studies, experience indicates that unmonitored studies have a higher rate of data errors. A review by the VCOG Clinical trials Group found 7% variability in key data points collected at the time of randomisation. There was a sense that a data quality standard needs to be articulated, including the trial data points that this should relate to.

3.2 Terminology

Phillipa Smith clarified the regulatory status of ICH GCP at the commencement of her presentation. GCP has not been written into the Therapeutic Goods Regulations, BUT it has been adopted by the TGA as policy. The two ICH guidelines that the TGA has formally adopted are E6 (GCP Guidelines) and E2A (Expedited Reporting of Serious Adverse Events). When an investigator signs the CTN form, they are agreeing to comply with GCP and the CTN form is a legally-binding agreement. GCP is also required by the Clinical Trials Directive in the European Union and the GCP-equivalent sections of the US Federal Code of Regulations.

Within GCP there is no distinction between commercial and non-commercial sponsors, and it is applicable to marketed and unmarketed drugs and devices. Increasingly we are seeing statements of GCP compliance in published peer-reviewed journal articles. The question is no longer does GCP apply? Rather, how will we interpret GCP in an affordable way?

The relevant definitions from ICH GCP are listed below.

1.46 Quality Assurance

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded) and reported in compliance with GCP and the applicable regulatory requirements.

1.38 Monitoring

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

1.6 Audit

A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately

reported according to the protocol, sponsor's standard operating Procedures (SOP's), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

1.55 Standard Operating Procedures (SOPs)

Detailed, written instructions to achieve uniformity of the performance of a specific function.

Reference:

TGA Note For Guidance On Good Clinical Practice (CPMP/ICH/135/95) <http://www.tga.gov.au/docs/html/ich13595.htm>

The subsequent discussion highlighted the need for a comprehensive QA program to incorporate:

- Training for coordinating centre and site staff
- Need for a philosophy of continuous improvement that includes two-way feedback, so the improvements at sites and coordinating centres are considered.
- Both audit and monitoring (the experience is that no monitoring is equivalent to no training).
- An Annual training workshop on GCP.

The concept of a cooperative trial group accreditation and training program including standard operating procedures could be feasible. However, there is a clear need to fund the infrastructure which could possibly be done by building QA into trial budgets.

3.4 *What exists now?*

6 groups discussed the QA programs and structures that exist at the moment. Copies of the presentations are included in Appendix 3.

The following points were common across all 6 groups:

- The aim is to ensure accurate and timely data on trials
- Ensure patient safety, appropriate drug handling processes and adherence to protocols
- Review of regulatory documents (Investigator Site File)
- Assessment of trial management processes (recruitment, enrolment, etc)
- Audit of each participating site once every 3 years.
- Centralised QA functions such as checking eligibility criteria at the time of registration/randomisation
- QA processes are evolving within groups.
- Reporting and review process.
- Incorporation of good ideas, tools and strategies into trial processes and communication to all sites.

Individual features.

TROG: Radiotherapy quality assurance process

ALLG: Histopathology/morphology review

AGITG/ANZGOG: Piloting the audit program to assess feasibility of the schedule and methodology used in the audit program.

ANZGOG: Trained and operated to fulfill the requirements of participation in NCI-funded studies
Trained clinicians as part of the audit program development

ANZBCTG: Coordinating Centre has had external review.

Conducted more than 270 audits and audited more than 900 cases since 1991.

CTNZ: Audit of Coordinating Centre undertaken and prospective planning ahead.

There are varying levels of documentation (Standard Operating Procedures, Policies, etc) and processes and opportunities for staff training. Several groups are doing both monitoring and auditing themselves, other groups out source monitoring when it is required.

3.5 *What can we afford*

There are a range of activities that could be undertaken, at a variety of costs. There was general agreement that establishing a minimum set of principles is a key task; collating and evaluating data from the NCI, EORTC, NCIC CTG, NCRN-UK will contribute to this process. Minimum standards need to incorporate the minimum training standards for all staff (Investigators, Coordinators). Subsidising staff to attend annual meetings of the trials groups will provide greater opportunities for training to be made available. Duplication needs to be avoided where possible.

A summary of low cost strategies includes:

- Generic SOP adoption: Where possible adopt common SOPs or a common index of SOPs across groups and participating sites. It is highly desirable that common SOPs be adopted across participating sites.
- Minimum training deliverable in a variety of ways (web-based, seminar, courses)
- More comprehensive study manuals that include reference material
- Effective start-up meetings and dry-runs of protocols
- Quality control within sites; i.e. internal QA at the site level. For example: having SOPs in place, one study coordinator checking data and processes followed on a colleagues trial.
- Timely feedback from Coordinating Centres available for use by other groups.
- Make templates, key variables, and logical checks public

Medium cost strategies include:

- A mentoring program
- 1 extra patient monitored on a different trial per monitoring visit.
- Audit program across cooperative groups, coordinating centres, and trials (eg. the AGITG and ANZGOG pilot program)

The high cost strategy is the pharmaceutical model of QA and QC.

3.6 Optimal Model

The Optimal QA model will cover both coordinating centres and participating sites. It will involve standardisation across groups, Standard Operating Procedures, training for staff at all levels and possibly accreditation. Training and professional development are key factors in retaining staff, minimum training standards should be defined and shared modular training would be feasible.

Audits should be conducted preferably within a model that involves sharing across groups, based on common processes and defined minimum standards. A reasonable target would be to audit 80% of sites within 3 years of their last audit. It should incorporate feedback to groups about audit and monitoring. Source data verification should be less than 100% and we should develop “smart” monitoring strategies.

It was noted that at the time of the workshop recommending optimal ranges for SDV, audit or QA targets in an evidence-based manner was not possible. One of the objectives of this working group will be to identify and recommend standards regarding SDV, audits and other QA/QC processes.

4. Recommendations

Q1 2007

- Collect and collate SOP indexes and any specific SOPs that Coordinating Centres and Groups are comfortable sharing
- Agree Standard Operating Procedure Index for the Coordinating Centres.
- Establish subgroup to review and recommend minimum SOP index for Coordinating Centres.
- Establish a Subgroup to investigate and develop standards for optimal QA models
- Establish subgroup to develop a standardised training program
- Review COSA SOPs for Investigational Sites, in conjunction with Cancer Institute NSW SOPs to recommend minimum set of SOPs for cooperative group participating sites.

Q2 2007

- Identify, review and recommend a uniform SOP regarding “how Coordinating Centres interact with sites”
- Work with Cancer Institute NSW to evaluate the participating site SOPs they are developing.
- Develop a comprehensive training plan for cooperative trials group staff and members based around ICH GCP and the generic SOPs
- Develop core training modules for ICH GCP
- Commence detailed review of QA programs (structure, processes, reporting, outcomes) across groups to determine feasibility of cross-group audits

Q3 2007

- Pilot core training modules for ICH GCP at one or more Cooperative Group Data Management/Study Coordinator Fora.
- Complete detailed review of QA programs (structure, processes, reporting, outcomes) across groups to determine feasibility of cross-group audits
- Promote SOPs to all groups and participating sites.

Q4 2007

- Continue work on training modules
- Develop and run a “train the trainer” workshop to ensure that training can be delivered around the country
- Develop standardised audit tools and processes for consideration and adoption by trials groups

2008

- Develop oncology related biology and clinical training module.
- Pilot cross-group audits, including the radiation therapy component of a non-TROG trial
- Evaluate the training delivered in 2007
- Translate training modules into e-learning course
- Evaluate the pilot audit program



COSA & Cooperative Groups Enabling Grant

Quality Assurance Workshop
Rydgcs, Missenden Rd, Camperdown
25 August 2006

10am.	Welcome Overview of the enabling grant and aims of QA component of grant	Marie Malica Steve Ackland
10.15	Introductions	Marie Malica
10.25am	Establishing a QA program – what needs to be considered & how has NHMRC CTC done it?	Phillipa Smith
11.00am	Clarifying interpretation of standard terminology	Facilitated discussion
11.30	Goals of a QA program	Facilitated discussion
12.00pm	What is in place now? TROG, ALLG, ANZBCTG, ANZGOG, AGITG/ANZGOG, CTNZ	
12.45 to 1.15 Lunch		
1.15	Other issues <ul style="list-style-type: none"> · Minimum standard to ensure quality data · How much QA can we afford? · Monitoring vs audit only · Onsite vs offsite monitoring or audit · How does e-CRF impact on QA? 	Facilitated discussion
2.15	What is the optimal QA model(s) for ANZ Cancer Cooperative Trials Groups & what can we afford?	Small groups & facilitated discussion
3.20-3.30 Afternoon tea		
3.30.	Summary and next steps	facilitated discussion
	4pm Close	

