



Trans Tasman Radiation Oncology  
Group Limited  
ACN 132 672 292

## TROG POLICY AND PROCEDURES

# Quality Assurance Statement of Minimum Requirements for Clinical Trials

**TPP E6**

**Version 2: 24<sup>th</sup> September 2008**

(Always refer to the TROG website to check for the current version of this policy)

### **TROG Central Operations Office**

Level 5, Building 7  
Calvary Mater Newcastle  
Locked Bag 7 HRMC NSW 2310  
Tel: + 61 2 49 211 466  
Fax: + 61 2 49 211 465  
Email: [trog@trog.com.au](mailto:trog@trog.com.au)  
Website: [www.trog.com.au](http://www.trog.com.au)

## Contents

1.	Introduction .....	5
1.1	Definitions of Quality Assurance.....	5
1.2	Definition of Audit.....	6
1.2.1	Definition of Source Data Verification .....	7
1.2.2	Definitions of Deviations/Variations .....	7
1.3	Definition of Monitoring.....	8
1.3.1	On-site Monitoring .....	9
1.3.2	Central/Remote/Off-Site Monitoring.....	10
2.	TROG QA Structure.....	11
2.1	TROG C.O.O. Support .....	11
2.1.1	Role and Duties .....	12
2.2	Trial coordinating centre.....	13
2.2.1	Minimum Standards.....	13
2.2.2	Roles and Duties .....	14
2.3	Local Sites.....	19
2.3.1	Minimum Standards.....	19
2.3.2	Roles and Duties .....	20
2.4	Minimum Standards of QA .....	20
2.4.1	QA for TROG-led Trials .....	21
2.4.2	QA for TROG Collaborating Trials .....	21
3.	TROG QA Process .....	22
3.1	Protocol, CRF and Trial Database .....	22
3.2	QA Procedures.....	22
3.2.1	Review Sampling.....	23
3.2.2	Variables/Classifications of Deviations .....	24
3.2.3	Checklists for Source Documentation.....	25
3.2.4	Audit Forms .....	25
3.2.5	Reporting of QA Reviews .....	26
4.	QA Reporting .....	26
4.1	QA Progress Reports .....	26
4.2	QA Case Reports .....	26
4.3	Suspension of Delinquent Sites.....	27
5.	QA Review Categories.....	27
5.1	Ethics and Regulatory Approval Quality Assurance.....	27

5.1.1	Introduction.....	27
5.1.2	Examples of Major Deviations <sup>32</sup> .....	28
5.2	Eligibility Quality Assurance .....	29
5.2.1	Introduction.....	29
5.2.2	Examples of Major Deviations .....	29
5.2.3	Example of Minor Deviations .....	30
5.3	Informed Consent Quality Assurance .....	30
5.3.1	Introduction.....	30
5.3.2	Examples of Major Deviations .....	30
5.3.3	Examples of Minor Deviations .....	31
5.4	Pathology Quality Assurance .....	31
5.4.1	Introduction.....	31
5.4.2	Examples of Deviations .....	31
5.4.3	Central Review Discrepancy Procedure.....	32
5.5	Radiotherapy Quality Assurance .....	32
5.5.1	Introduction.....	32
5.5.2	Dummy Runs/Benchmarks .....	32
5.5.3	Treatment Verification .....	33
5.5.4	Site Dosimetry Confirmation .....	34
5.5.5	Examples of Major Deviations .....	34
5.5.6	Examples of Minor Deviations .....	35
5.6	Chemotherapy Quality Assurance .....	35
5.6.1	Introduction.....	35
5.6.2	Examples of Major Deviations .....	35
5.6.3	Examples of Minor Deviations .....	36
5.7	Pharmaceutical Products Quality Assurance .....	36
5.7.1	Introduction.....	36
5.7.2	Examples of Major Deviations <sup>32</sup> .....	36
5.7.3	Examples of Minor Deviations <sup>32</sup> .....	36
5.8	Medical Devices Quality Assurance.....	37
5.8.1	Introduction.....	37
5.8.2	Examples of Major Deviations <sup>32</sup> .....	37
5.9	Surgical Oncology Quality Assurance .....	37
5.9.1	Introduction.....	37
5.9.2	Examples of Major Deviations .....	38
5.10	Response Assessment Quality Assurance .....	39

5.10.1 Introduction.....	39
5.10.2 Examples of Major Deviations .....	39
5.11 Adverse Event Reporting.....	40
5.11.1 Introduction.....	40
5.11.2 Examples of Major Deviations <sup>32</sup> .....	40
5.11.3 Examples of Minor Deviations <sup>32</sup> .....	41
5.12 Data Quality.....	41
5.12.1 Introduction.....	41
5.12.2 Examples of Major Deviations <sup>32</sup> .....	41
5.12.3 Examples of Minor Deficiencies <sup>32</sup> .....	41
6. References.....	42

## 1. Introduction

The National Health and Medical Research Council (NHMRC) describes quality assurance (QA) in health care as an activity where the primary purpose is to monitor, evaluate or improve the quality of health care delivered by a health care professional (an individual, a service or an organisation)<sup>1</sup>.

In order for trial results to be published and adopted into practice the data generated must be reliable. Quality assurance provides the framework to allow verification of data accuracy and protocol compliance via the review of source documentation. It also ensures that any safety issues for patients on a trial are identified as soon as possible, and highlights issues which may require a protocol amendment to facilitate smooth running of a trial.

Quality assurance is not only a required feature of clinical trials but is a part of standard clinical practice, for example in radiotherapy. The World Health Organisation (WHO) describes quality assurance in radiotherapy as those procedures in place to ensure consistency and safe fulfilment of the medical prescription with the aim of determining the end result of treatment<sup>2</sup>.

In addition to ensuring verification of data accuracy, protocol compliance and ultimate patient evaluability, quality control processes serve a valuable role in educating all participating investigators and data managers involved in these trials.

The purpose of this statement is to define TROG's minimum QA requirements to achieve and maintain a level of international credibility.

### 1.1 Definitions of Quality Assurance

ICH GCP defines quality assurance as 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<sup>3</sup>.

NCI CTEP describes a process of change and actions in response to findings in the following definition of quality assurance. The goal of a quality assurance program is to prevent and detect problems, to take appropriate action and to provide an appropriate feedback and educational mechanism<sup>4</sup>.

## 1.2 Definition of Audit

Audit is defined as 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)<sup>3</sup>.

NCI CTEP describes auditing as one component of a monitoring program. An audit program is designed to specifically verify key variables relating to data accuracy and protocol compliance that could affect the interpretation of the primary trial endpoints.

Audits are undertaken through independent verification of source documents, including review and evaluation of the following categories:

- IRB documentation and regulatory/contractual requirements
- Investigational agents and pharmacy operations: accountability, security and storage
- Individual patient case records: eligibility, treatment, outcome/response and general data quality

The following activities are recommended for clinical trial audit:

- Progress of the trial: including determination of recruitment/accrual status and number of withdrawals (including types and reasons).
- Trial site verification: review of the activities of the trial site's Principal Investigator and their staff and the continuing ability of the trial site to participate in the trial, including:
  - GCP compliance: that the investigator retains all necessary trial documentation in compliance with GCP
  - Regulatory/Contractual compliance: that the trial site maintains up to date regulatory/contractual requirements
- Case source data verification: conformity of the data presented in the case report forms with that in medical records and adherence to the protocol (in particular an effort should be made to obtain maximum information on any missing data), including:

- Eligibility details: including conduct of the informed consent process and that written informed consent has been obtained for every trial patient, and confirmation of diagnosis.
- Treatment/intervention details: such as delivery of radiotherapy and trial drug treatment, and if applicable - that full dispensing records of any investigational drugs are maintained.
- Outcome/Response details: including verification of endpoints and adverse event reporting - and that expedited reporting guidelines were adhered to for serious adverse events.

#### 1.2.1 Definition of Source Data Verification

Source data are all records of original observations/assessments. In clinical trials, source data can include (but is not restricted to) medical records, reports, scans and images. All data required on a trial case report form (CRF) should be primarily recorded in the original source data at the trial site and transposed onto the CRF. For the purpose of trial QA data verification, source data verification (SDV) documents may be the original copy or a certified copy (photocopy). In the event of central remote/off-site source data verification, all SDV documents should be copies of the original with personal identifiers such as name and medical record number removed and replaced with patient initials and trial registration number). This is a mandatory requirement to ensure trial sites comply with the Privacy Act (1988) by de-identifying documents (removing any personal identifiers) before they leave the boundaries of the hospital at which the patient consented to their information being collected and held.

#### 1.2.2 Definitions of Deviations/Variations

Each component of audit is assigned a deviation classification. The total number of type of deviation category must be included in each QA case review report and the total number of cases with major deviations and total number of patient cases reviewed should be listed in each QA trial progress report. TROG has standardized templates for the reporting of case and trial QA review results (copies are available from the TROG Central Operations Office on request).

Deviations can be defined as follows:

- Acceptable: no variation or variation within tolerance limits

- Minor/Lesser Deviation: variation that will not have a significant impact on the outcome or interpretation of the trial but may require follow-up or education to prevent recurrence in subsequent cases or progression to major deviations
- Major Deviation: variation from protocol-specified procedures that is deemed 'significant' in that it may make the resulting trial data questionable, [safety] and may affect the interpretation or validity of the endpoints<sup>4</sup>.

### 1.3 Definition of Monitoring

Monitoring is defined as 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)<sup>3</sup>.

The NCI CTEP has expanded the GCP definition to provide a practical basis to describe monitoring in the context of co-operative clinical trials groups. A summary of their 'Guidelines for Monitoring of Clinical Trials for Co-operative Groups' is provided below:

Routine monitoring procedures should be implemented from the beginning of data collection through to publication of results to ensure optimal therapy for participating patients and optimal conduct of the research so that the patients' participation is meaningful.

The purpose of the monitoring program is to provide ongoing reports on compliance (protocol and regulatory) and accuracy (data). These reports are designed to monitor progress of the trial over a period of time to allow for the identification of any ongoing or developing quality issues and to facilitate intervention and improvement. The monitoring program also facilitates the provision of information to trial sites on good clinical practices related to data collection and data management.

Ongoing monitoring of a clinical trial's progress includes tracking the progress of the following quality-related elements:

- Accrual, eligibility and evaluability
- Submission of trial data
- Medical assessment of individual patients' data

- Rapid reporting of treatment-related morbidity information, and
- Interim evaluation of outcome measures and patient safety information<sup>4</sup>

Credentialing of trial sites in relation to their ability to conduct clinical trials (facilities, resources and expertise) can also be evaluated during monitoring activities.

TROG requires periodic progress reports on trial QA activities. QA case review results must be presented in the QA trial progress report format (as per section 1.2.1). Results of other trial QA activities (such as credentialing, trial site compliance with GCP, regulatory/contractual reviews and data quality) must either be included in these reports, or reported in a separate 'trial site QA' trial progress report document. The purpose of these reports is to provide formal notification of issues identified during audit and to track ongoing trial quality (particularly in relation to major deviations) to the Trial Management Committee, Data Monitoring Committees (if applicable) and the TROG Scientific Committee. If the TROG Central QA Office (TROG Central Operations Office) does not compile these trial reports then they must be provided with a copy of the report at the time of submission to the TMC.

Comprehensive monitoring programs are essential to add to the reliability and credibility of the trial results in the scientific community. TROG's aim is to incorporate both on-site (trial site visits) and off-site (centralised remote) monitoring activities into trial QA programs. Off-site monitoring will be utilised when it is feasible for source data verification documentation to be sent to a centralised location for remote review.

### 1.3.1 On-site Monitoring

On-site monitoring is defined as a visit to a centre in a trial made by personnel from outside that centre for the purpose of conducting trial audits (reviews of source documentation) and for conducting trial monitoring activities (credentialing, evaluating trial site compliance, evaluating trial progress and tracking of QA issues). Integral to the on-site method are local trial site data managers who obtain and collate the source documents, then provide access to the documents and suitable trial site facilities for review to a monitor/reviewer appointed by the Trial Management Committee. Trial site visits should include contact with the Principal Investigator, Co-investigators, the Data Manager and the Pharmacist, if applicable.

This type of QA activity is labour and cost intensive, therefore these reviews are primarily implemented in TROG trials when central remote audits are not feasible or appropriate and/or if required due to safety issues in a high risk trial.

In addition to fulfilling an audit and monitoring role, trial site visits also provide educational benefits for all staff involved as they are an opportunity to discuss specific organisational aspects of the trial, including GCP compliance, trial site resources and trial centre expectations.

The frequency of the trial site visits will depend on the nature of the trial, ie number of patients entered and complexity of data collected, and the available funding (eg. monitors travel costs).

A written report of the trial site visit must be provided to indicate the areas of activities reviewed and a list of specific recommendations if applicable. Review of source documentation for case reviews must be reported in the TROG QA case report format (as per section 1.2.1). The trial site visit report should be sent to the Principal Investigator of the centre visited, the Trial Management Committee of the trial reviewed and the TROG Central Operations Office.

### 1.3.2 Central/Remote/Off-Site Monitoring

The major focus of TROG's quality assurance program has been the implementation of off-site monitoring procedures by incorporating centralised remote audits/reviews. Centralised monitoring is noted in ICH GCP as acceptable in exceptional circumstances. As TROG trials are primarily non-commercial, clinician-led research with limited budgets it is appropriate to establish a monitoring program whose activities are co-ordinated and conducted centrally. This enables robust review, audit and reporting of trials activities in a cost-effective manner whilst providing assurance that integrity of results will be maintained.

The TROG central quality assurance facilities were primarily established to enable remote ('off-site') case reviews of radiotherapy treatment and planning data by independent experts (clinicians). The review process employs the same method of source data verification as on-site visits to ensure protocol compliance and data accuracy. Integral to the centralised method are local trial site data managers who obtain and collate the source documents, as requested in a QA checklist, and forward them to a central location for review. Results of these reviews are reported to trial sites through QA case reports and additional feedback and education is provided to all trial personnel through specific QA activities, trial newsletter QA reports and at annual meetings.

In addition to central remote monitoring, additional on-site monitoring visits may be required at a particular trial site in the following circumstances:

- no source documentation is received for central review, despite repeated requests;
- high level of major variations despite educational/interventions;
- to ensure other aspects of the monitoring program as listed above are verified.

## **2. TROG QA Structure**

### **2.1 TROG C.O.O. Support**

The TROG Central QA Office is part of the Central Operations Office and was initially established to act in an advisory role to develop and implement trial QA procedures in partnership with the Trial Chairperson and Trial Centre Co-ordinator. The office also co-ordinates a strategic approach to development of new TROG QA resources, including activation of working groups and access to expert advisors as required and facilitation of collaboration with other international groups involved in clinical trial QA activities.

An important component of the TROG Central QA Office role is the provision of support and assistance with the set-up and facilitation of the trial-specific QA process for new TROG trials and ensuring once recruitment has commenced that timely reports and feedback are provided to the TMC and local trial sites. Reporting of QA case reviews and QA trial progress reports must now be in accordance with the TROG QA templates.

The TROG Central QA Office must be involved with the development of trial protocols (and the QA section must follow the TROG protocol template format) and CRF design to ensure they are amenable to QA review procedures.

A primary role of the TROG Central QA Office is the administration of QA case reviews for TROG trials. As such, the office provides a central facility for the conduct of remote 'off-site' reviews, including receiving and checking QA SDV documents, liaising with reviewers and sites, tracking QA review progress, entering QA review data into the QA database, compiling and analysing results and reporting regularly to trial sites, trial chairpersons, TMCs and the Scientific Committee. TROG has developed specialised trial QA case review facilities including

the CQMS (Central Quality Management System) which is a unique programmed database designed specifically for the management of trial QA activities including remote access to the system to ensure ongoing communication with trial sites, reviewers and TMCs regarding trial QA case reviews and automated functionalities for tracking progress and generating reports. Central resources for on-site monitoring are a priority for new developments.

The TROG QA Manager is a member of the TROG Scientific Committee and also reports to the TROG Board. The TROG Scientific Committee is informed of trial QA progress and any arising trial or operational issues. Specialist advice is also provided by a physicist, radiation therapist and a medical oncologist as members of the Scientific Committee.

#### 2.1.1 Role and Duties

The primary responsibility for the design, conduct and recording of QA activities is with the Trial Chairman/person and the Trial Management Committee (TMC). The TROG Central QA Office is available to advise and assist with QA procedures for all trials. Prior to trial activation and throughout the trial ongoing consultation with the TROG Central QA Office is required to ensure that the trial complies with TROG QA policy. The Trial Chairman/person and TMC are responsible for ensuring that the trial is appropriately resourced (including the establishment of a Trial coordinating centre and provision of funding) that will facilitate effective QA.

The TROG Central QA Office through the Scientific Committee has a broader role of standardising the approach across all trials, prioritising policy, accountability, monitoring QA activities across all trials, monitoring and advising on QA issues at individual participating centres, reporting to and advising the Scientific Committee and members at the Annual Meeting and ensuring comprehensive data integrity.

Responsibilities include:

- supervise the QA conduct of all trials;
- ensure accountability of the Trial Chairman/person;
- co-ordinate QA activities;
- standardise QA activities;
- assist the Trial Chairman/person to appoint independent QA reviewers;
- disperse resources for QA;
- ensure, through the Trial Chairman/person, the reporting of QA summaries (internal and external) regularly;

- direct secondary storage (off site) – storage of all QA data and documents at a designated QA centre;
- presenting educational sessions on QA, such as at the Annual Meeting
- identify institutional resource shortfalls and delinquency issues. Advise institutions accordingly.

## **2.2 Trial coordinating centre**

### **2.2.1 Minimum Standards**

An acceptable level of data management skills is required at each trial coordinating centre to ensure a high level of data quality for a TROG trial. In addition, to undertake appropriate trial QA procedures requires a high level of communication and co-ordination between the trial coordinating centre and the TROG Central QA Office. Therefore, trial centres that are responsible for the central co-ordination of TROG trials are required to adhere to minimum standards. When establishing a trial coordinating centre for a new trial, the Trial Chairperson and TMC must be able to demonstrate that the trial centre has the capacity and ability to match these requirements.

#### **Essential Requirements:**

- Knowledge and experience of participating in or centrally co-ordinating multi-centre clinical trials from the design and development phase through to publication in a peer reviewed journal, including facilitation of database, protocol and CRF development.
- Multi-disciplinary core trial team of experienced staff will be in regular communication with the trial coordinating centre, including the trial chairman/person, statisticians, expert clinical consultants and IT staff.
- Adequate infrastructure to support trial activity (administrative staff, work area, IT equipment – software and hardware, storage space).
- Core funding to provide adequate infrastructure and staff.
- Good multi-disciplinary working relationships with clinicians, TROG and other trial experts.
- Ability to provide timely information and reports to TROG as required.
- Systems in place (such as standard operating procedures) to ensure that staff work to appropriate guidelines and standards.
- Systems in place to provide staff training and continued professional development.

- Ability to ensure long-term continuity, or adequate cover, for all core staff – particularly for trial centres providing randomisation services.
- Ability to archive and retrieve trial data for at least 15 years after the end of a trial.
- Ability to work within ethical and legal frameworks such as ICH GCP, TGA Guidelines, NZ Medsafe Guidelines and confidentiality legislation.

Desirable Requirements:

- Knowledge and experience of the trial-related site-specific disease, treatment modality or methodological approach<sup>5</sup>.

### 2.2.2 Roles and Responsibilities

#### Regulatory Documents:

The trial coordinating centre must maintain filed copies of all required regulatory documents relevant for each trial. Regulatory documents may include copies of ethics approval letters for each trial site (for each protocol version), letters confirming submission of CTN documents for each trial site, records of pharmaceutical drug provision and documentation relating to the use of copyrighted trial material such as quality-of-life questionnaires. Records should be kept up to date and accessible as trial coordinating centre maintenance of regulatory documents may be audited by the TROG Central Operations Office or external auditors eg TGA.

#### Trial site Contact Details:

A central register of the name and contact details for the trial team actively involved in the trial management at each trial site should be maintained and kept up-to-date eg investigators, data managers/trial co-ordinators, physicists, radiation therapists.

#### Screening Logs:

The trial centre may request that trial sites maintain screening logs for each trial. If screening logs are utilised they must be regularly reviewed by the trial coordinating centre and any patterns or trends discussed with the Trial Chairman/person.

#### Randomisation:

For randomised trials, the trial coordinating centre must facilitate the design and testing of the randomisation system prior to commencement of accrual. A randomisation table by stratification variables should be produced on a frequent basis to check for accurate allocation and the results reported to the Trial Chairman/person. Randomisation procedures may be

audited as part of the TROG central QA program. Numbers of cases allocated to each trial arm should be reported in any trial progress reports. Each trial's randomisation program must be available if required for assessment by a nominated representative of the Scientific Committee.

Randomisation procedures must be documented for all trials in both the protocol and trial procedure notes. The recommended procedure is for the trial site to fax the required CRFs to the trial coordinating centre. The eligibility details are verified by phone before the trial coordinating centre performs the randomisation. Written verification of randomisation must be provided to the trial site by return fax or email. On-site audits may check that the trial site has a randomisation verification on file for each case.

Co-ordination of Data Collection:

The trial coordinating centre is responsible for the collection and checking of case report forms (CRFs). Trial coordinating centre procedures should include a system for tracking all CRFs including the estimated due date, date of receipt and notification of missing CRFs for all registered trial cases. Minimum standards (see section 4.12) include the ability to provide data reports at set time points.

A recommended system for data reporting includes the regular assessment of:

- percentage of CRFs received (number of CRFs received / estimated number of CRFs due)
- percentage of CRFs 0-3, 3-6, >6 months overdue (current date – estimated due date for forms not received after the estimated due date)
- percentage of missing CRFs (trial site has notified the CRF will not be available eg scheduled follow-up not conducted).

**CRF Edit Checks:**

The following table provides a minimum list of edit checks that should be performed by the Central Data Manager upon receipt of the CRFs:

<i>Type</i>	<i>Edit Check</i>
◆ Patient identification and record linkage	<ul style="list-style-type: none"> <li>◆ Check ID (trial registration) number for transposition errors;</li> <li>◆ Check all CRF pages display the same ID number.</li> </ul>
◆ Legibility	<ul style="list-style-type: none"> <li>◆ Check for illegible handwritten replies, spelling errors, etc.</li> </ul>
◆ Form admissibility	<ul style="list-style-type: none"> <li>◆ Check to determine if the CRF was completed within the specified time frame (as per CRF schedule).</li> <li>◆ Check to make certain the correct CRF has been completed for the indicated examination and/or time point.</li> </ul>
◆ Missing information	<ul style="list-style-type: none"> <li>◆ Check for unanswered variables of an otherwise completed CRF.</li> <li>◆ Check to make certain all required CRFs have been completed.</li> </ul>
◆ Consistency	<ul style="list-style-type: none"> <li>◆ Check information supplied in one section against another section on the same CRF for inconsistencies.</li> <li>◆ Check information supplied on the same patient on one CRF with that from another CRF completed at the same or a different examination as a check for possible data inconsistencies.</li> </ul>
◆ Range and inadmissible codes	<ul style="list-style-type: none"> <li>◆ Check to identify items with values that exceed specified ranges.</li> <li>◆ Check for undefined alphabetic or numerical codes.</li> </ul>

Important examples of checks for consistency and protocol compliance would include recalculation of BSA from height and weight and a check that correct drug doses and schedules were given. A check that modification of doses occurred, if applicable, is vital. Otherwise, this would be classed as a major protocol violation.

Some of the above can be computerised with range and logic checks as a function of the trial database. All date variables should be checked for appropriate temporal sequencing eg end of radiotherapy minus start of radiotherapy = overall treatment duration. Other computerised data quality assurance procedures should include a summary of data on an ongoing basis in terms of frequency, mean, median and range for all important quantitative variables. Outliers can therefore be identified and corrected or confirmed.

Data queries should be issued to the trial site on a trial CRF query form and require a written reply. Query form templates are available from the TROG Central QA Office on request. Trial coordinating centre procedures should include a system for CRF edits. A recommended procedure is for each trial CRF query to be allocated an individual query number and tracked in a trial query log. When the query has been resolved and changes are required to the CRF, if the trial centre holds the original CRF on file the recommended edit may be documented on a copy of the CRF and the original CRF sent back to the trial site requesting the changes. Alternatively, the trial procedures may authorise the trial co-ordinator to write the query number beside the variable on the CRF, document the change, then initial and date the edit. The query log should then be updated and should also verify that changes have also been amended in the trial database if required. Trial coordinating centre audits may check that audit trails are evident for any CRF queries and amendments.

The trial coordinating centre should regularly assess the query log for any trends or recurring data queries. Consideration should be given to modifying the trial CRFs if required or providing feedback and clarification to the trial sites eg in trial newsletters and data management workshop presentations.

#### Serious Adverse Event Reporting:

The trial coordinating centre should maintain a log of all SAEs and ensure that adequate information is provided by the trial site for review by a nominated representative of the TMC. Failure of a trial site to provide sufficient information for the reviewer's assessment of SAEs should be notified immediately to the Trial Chairman/person. The TROG Central Operations Office requires a copy of all trial SAEs. The trial coordinating centre procedures should document the procedures for SAE monitoring.

Data Entry:

Regular entry of CRF data into the main trial database should be undertaken so that up to date information can be provided to the Trial Chairman/person or TMC on request. Trial coordinating centre procedures should include a system of database quality assurance, such as double data entry and/or independent database/CRF sampled audits. The primary purpose of database QA is to ensure that the data has been accurately entered eg transposition errors have not occurred. Trial coordinating centres should be able to provide documentation of QA procedures undertaken to verify database data accuracy if requested by the TROG Central QA Office or Scientific Committee.

Reporting:

The trial coordinating centre should undertake ongoing monitoring of central trial records and progress and regularly discuss the results with the Trial Chairman/person. Action should be undertaken as requested by the Trial Chairman/person and TMC. Periodic reporting and updates will be also required by the TROG Central Operations Office eg accrual, data quality, ethics approvals, trial site details.

Ongoing QA reports may be produced jointly by the trial coordinating centre and TROG Central QA Office to report the results of all trial QA activities. The TROG Central QA Office has templates available for reporting QA results. The following are recommended minimum standards for monitoring trial progress and trial centres should ensure that adequate reporting is undertaken:

[a] *Patient recruitment*

- Number of patients screened for enrolment; proportion and tabulation of reasons for rejection.
- Current rate of recruitment compared with that required to achieve the target accrual.

[b] *Patient follow-up*

- Number of withdrawals (extent of withdrawal eg no further data collection or no further treatment but follow-up data may be collected).
- Number of patients who cannot be located for follow-up.
- Completeness of late outcome data.
- Completeness of cause of death data

[c] *Data quantity and quality*

- Percentage of CRFs received, overdue and missing
- Number of forms completed since last report and number that generated data queries.
- Number of unanswered data queries.

[d] *Protocol adherence*

- Number of ineligible patients enrolled.
- Number of patients who did not accept the assigned treatment.
- Number of patients who received a treatment other than the one assigned.
- Summary of data on trial drug treatment and other compliance tests (ie dose reductions) by treatment group.
- Number of departures from the treatment protocol.
- Summary of other treatment or data collection protocol violations.

## **2.3 Local Trial Sites**

### **2.3.1 Minimum Standards**

Multi-disciplinary research teams should be established at local trial sites prior to participation in a clinical trial. Initial consultation and inclusion of multi-disciplinary staff at the feasibility phase of a trial should provide support to encourage trials activity. This core research team may include Radiation Oncologists, Radiation Therapists, Physicists, Medical Oncologists, Surgeons, Pharmacy staff, Nurses and Data Managers. The following minimum standards should be adhered to by local trial sites participating in clinical trials.

Essential Requirements:

- Knowledge and experience of conducting, and managing patients in a clinical trial.
- Adequate funding and infrastructure to support trials activity, particularly with the appointment of a local data manager, file storage space and technology requirements.
- Systems in place to ensure that staff work to appropriate guidelines and standards.
- Systems in place to provide training, education and development.
- Ability to work within ethical and legal frameworks such as ICH GCP, TGA Guidelines, NZ Medsafe Guidelines and confidentiality legislation<sup>5</sup>.

### 2.3.2 Roles and Duties

Timely data collection and recording has a major impact on the quality of data. Institutional data managers and investigators should record data on the case report forms (CRFs) as it is collected and should follow the schedule of when forms are due as closely as possible. Some data can be collected retrospectively, but this can be very time consuming, is inefficient and increases the likelihood of errors. Other data may be lost forever or will be unobtainable if it is not collected at a designated time point.

The following quality assurance procedures should be followed at the institution –

- visual check by the data manager / Principal Investigator after a CRF is completed for legibility and for unanswered or incorrectly answered items;
- once recorded on a CRF, data should not be erased or obliterated. Entries that are incorrect should be crossed out and the new entries added to the form. Any change, regardless of when it was made, should be dated and should carry the initials of the person making the change.
- Blank fields - do not leave any boxes/sections/variables blank, [add instructions for CRF completion to this section?]
- the original CRFs should be forwarded to the Central Data Manager as soon as each trial visit is completed so that any errors can be picked up as soon as possible and rectified. A copy of the CRF should be kept at the participating institution.
- adhere to QA Checklist requests and ensure all data is submitted for central review in the specified timeframe.

## 2.4 **Minimum Standards of QA**

A quality assurance program should be developed on a trial-by-trial basis in order to reflect the particular requirements of each trial. The TROG Central QA Office will provide advice on the appropriate QA activities that should be conducted for each trial. A risk assessment during the development phase of a trial will identify any issues which may require robust analysis and reporting to reduce the incidence of errors. For example, an experimental radiotherapy technique, a high-risk group of patients or a centre that is new to clinical trials may require higher levels of inspection to provide assurance that quality levels are acceptable.

A trial which poses a low level risk should set the following standards as a minimum in their quality assurance program:

- Review of all centre's ethics and regulatory approvals
- Review of all patient's eligibility and consent
- Review of sampled patient's treatment
- Review of sampled patient's response/endpoint assessments
- Review of all SAE reporting
- Review of all data accuracy and timing

Trials which are assessed to pose possible risks may incorporate additional safeguards and analysis into their quality assurance program as well as adhering to the minimum standards set out above. 'Specialised' quality assurance programs may utilise techniques such as credentialing including a 'dummy' runs/benchmarking activity), real-time reviews and increased sampling rates of patients to be reviewed.

These standards are discussed in further detail in the following sections.

#### 2.4.1 QA for TROG-led Trials

Trials which are co-ordinated by TROG must ensure minimum standards of quality assurance are addressed in their monitoring program. The TROG Central QA Office must be utilised as a resource in the development of a quality assurance program in order to ensure appropriate processes and procedures are included. To reduce the duplication of resource utilisation across new trials, the TROG Central QA Office provides facilities to co-ordinate the case review central QA program (eligibility, treatment and response/endpoint assessments) once the trial has been activated by facilitating requests for source data from local trial sites, forwarding case review material to assigned reviewers, collating and analysing audit responses, and reporting on outcomes and recommended actions. In the current model, the Co-ordinating Trial Centre co-ordinates the QA reviews of regulatory/contractual approvals, SAE reporting and data quality.

#### 2.4.2 QA for TROG Collaborating Trials

A robust process for quality assurance regarding all aspects of trial function should be implemented and monitored by the lead trials groups for studies in which TROG is a collaborative partner. It is expected that TROG will be provided with reports on the QA performance of Australasian trial sites participating in the trial in respect to the overall QA results for the trial. The results will be reported twice yearly and trial sites must reach a minimum standard for performance. These reports will be presented to the TMC and TSC as required.

### **3. TROG QA Process**

#### **3.1 Protocol, CRF and Trial Database**

The TROG Central QA Office review draft protocols during the development phase of a trial. The TROG protocol template format must be used for all TROG protocols. The TROG Central QA Office assists in adapting the template to suit the trial-specific needs of each new trial under development. Protocols are assessed for applicability across multi-centre trial sites, and that the information provided enables standardised actions to be implemented at all participating centres. The TROG Central QA Office consults expert advisors as required for the provision of specialised advice on the techniques to be used in the trial and assist in ensuring that the instructions are unambiguous and can be replicated easily.

CRFs are reviewed to ensure that the data to be collected are adequate to provide results and justifications for trial endpoints. It is essential that statistical input is gained during the design phase of CRF development.

Minimum standards for trial databases are under development

#### **3.2 QA Procedures**

A teleconference will be held during the development phase of a trial to enable discussion about quality assurance procedures between the TROG Central QA Office, Trial Chairperson, Trial Centre Co-ordinator and, if required, any specialist advisors. The objective of this meeting is to agree an adequate program for quality assurance which meets the criteria of minimum standards. This may include devising a list of variables to be reviewed, the sampling rate of patients, nomination of independent reviewers and designating responsibility for reporting of review results.

A standardised quality assurance procedures template has been developed by the TROG Central QA Office for use in all studies, and this document will be amended in accordance after agreement of discussions at the teleconference meeting. A draft copy of the procedures will be circulated for review and approval by the Trial Chairman/person and Trial Centre Co-ordinator before implementation of the quality assurance program.

Information included in the quality assurance procedures will be communicated to the TMC and TSC through regular progress reports.

### 3.2.1 Review Sampling

Prior to the start of each trial the amount of SDV to be performed (variables for review) should be decided by the Trial Chairman/person in collaboration with the TROG Central QA Office.

A sampling rate of patients to be reviewed should be agreed during the development phase of the trial and details included in the protocol. The rate of review may vary for different trial QA activities. An example is provided below.

<i>Type of variable</i>	<i>Source document</i>	<i>Patients to check (%)</i>
Patient existence	MR*	100
Diagnosis	MR	100
Patient visit dates	MR	20
Informed consent (Date)	CF*	100
Inclusion criteria	MR	100
Exclusion criteria	MR	100
Trial treatment	MR	100
Primary trial variable	MR / CRF	100
Adverse events / toxicity	MR / CRF	100
Other assessments	MR / CRF	20

\* MR = Medical Records, CF = Consent Form, CRF = Case Report Form

Discussion about an appropriate QA sampling rate should consider factors such as whether the trial involves a new technique, participation of a new or international trial site and the sample size of the patients to be recruited to the trial.

The following is the TROG minimum standard for review:

- All QA variables are reviewed for each case audit (= 100% SDV) for small sample sized trials or; for larger trials

- A 2-phase review process will be implemented:

Phase 1 - at least the first 5 patients from each trial site. If the initial review results are acceptable the trial site proceeds to Phase 2. Trial sites which do not achieve an acceptable level of compliance or accuracy will continue at the phase 1 sampling rate until the TMC is satisfied that compliance has improved sufficiently to progress to phase 2 review sampling.

Phase 2 - at least 1-in-5 of the subsequent patients registered on the trial are reviewed. Trial sites which do not maintain an acceptable level of compliance or accuracy will return to the phase 1 sampling rate until the TMC is satisfied that compliance has improved to return to phase 2 review sampling.

- Patients from each trial site must be continued to be reviewed throughout the active accrual phase of the trial (patients selected from different parts of the trial, ie early, middle and later registrations).

Also, if there is more than one investigator per trial site, consideration should be given to modifying the trial QA requirement that the sampling procedure is applied to each investigator rather than each trial site.

The estimated rate of review (number of cases reviewed as a percentage of overall accrual) must be more than 30%. The recommended sampling rates based on trial size are:

Trial Accrual Sample Size	Phase 1 Review Sampling Rate	Phase 2 Review Sampling Rate
0 – 100 patients	All patients	N/A
100 – 200 patients	First 5 patients*	1 – in – 3 patients*
200+ patients	First 5 patients*	1 – in – 5 patients*

\* From each trial site

### 3.2.2 Variables/Classifications of Deviations

Tolerance limits are developed for all components of a trial. Each section of audit is assigned a deviation classification and the total number of cases with major deviations and total number of patient cases reviewed should be listed in each audit report. Deviations are defined in section 1.2.2

As per GCP section 4.5.4, the investigator should not deviate from the protocol except in the event of it being necessary to eliminate an immediate hazard to the safety of trial subjects. The investigator must then submit the implemented deviation or change, the reasons for it and (if appropriate) a proposed protocol amendment to the Trial Management Committee (TMC) and their institutional ethics committee (IEC) as soon as possible for review and approval. The TMC must meet urgently to review the event, liaise with the investigator regarding reporting to the regulatory authorities (if appropriate) and notify the TROG Central QA Office and the TROG Scientific Committee of the outcome in terms of trial recommendations, particularly relating to protocol modifications.

### 3.2.3 Checklists for Source Documentation

Trial-specific QA checklists are developed for the purpose of communicating to local trial sites the remote source data requirements for each patient. The TROG QA Checklist template must be used for all central QA case reviews. Checklists are sent to trial sites at the time of registration of a patient on a trial. Checklists are categorised according to the reviews to be conducted and generally include sections for eligibility, treatment and response. Instructions are included for the type of source documentation required, timeframes for which the data must be submitted and the contact details for submission of the data to the review co-ordinator.

### 3.2.4 Audit Forms

The TROG Central QA Office will design a trial-specific audit variables list sourced from the protocol in conjunction with the Trial Chairman/person and Trial Centre Co-ordinator. The audit variables list will comprise all elements (variables) to be reviewed as part of the trial's quality assurance program and will include variables from the CRF that are required to be validated for accuracy plus any mandatory requirements from the protocol that need to be reviewed to determine compliance.

Audit forms will be developed for each section of the review program using the variables list as a basis. The forms will be designed in the same format as a CRF, in that only a standardised range of data can be entered onto the form, allowing easy comparison and analysis of the data collected. The TROG template for QA audit forms must be used. An independent reviewer, selected by the Trial Chairman/person, will be assigned to each section of the review program and they will assess source documentation for compliance with the protocol. Reviewers may request further information or clarification from the local trial site before deciding on a

classification for deviations. Audit forms and review material will be returned to the TROG Central QA Office after completion of the review for analysis and reporting.

### 3.2.5 Reporting of QA Reviews

Outcomes of QA reviews will be reported to the trial sites as QA case review reports and to the TMC on QA trial progress reports. The TROG templates for these reports are to be used for all central QA case review activities. The TMC must report on any significant issues to the TSC.

Once local trial sites have been notified of the results of QA case reviews Principal Investigators are able to provide additional information and to seek clarification if it is considered that a variation has not been correctly attributed to a case.

Reports will be made available to any regulatory agency as requested and to provide evidence of robust quality assurance mechanisms in the publication of trial results.

## **4. QA Reporting**

### **4.1 QA Progress Reports**

The TROG Central QA Office, in conjunction with the Trial coordinating centre, will facilitate the provision of written quality assurance progress reports every 6 months to the TMC and TSC for all new trials. Information will be provided on the quality assurance procedures for the trial, an overview of any review activities undertaken to date, results of reviews and detailed explanations for any minor or major deviations. Recommended actions to improve the quality of the trial will be detailed in the report.

It is expected that the lead centre for trials in which TROG is a collaborative partner provide bi-annual reports on the performance of Australasian centres in respect to the overall quality assurance results for the trial.

### **4.2 QA Case Reports**

Case reports for central QA case reviews must be sent to local investigators (for example sent by the TROG Central QA Office if they are co-ordinating the reviews) to detail the results of any quality assurance reviews of their patients. The reports are intended to be of educational purpose and will explain the classification of any minor or major deviations. Principal

Investigators are able to provide additional information or seek clarification if it is considered that a variation has not been correctly attributed to a case.

### **4.3 Suspension of Delinquent Trial Sites**

QA progress reports will be submitted to the TSC for review and will provide the basis for any actions in respect to suspension of delinquent trial sites. The following steps must be taken to suspend a trial from participating in TROG trials:

- (1) TSC identifies delinquent institution;
- (2) TSC recommends either a 1:1 or 1:5 sampling rate for QA review;
- (3) TSC appoints facilitators to educate trial site, ie data managers/clinicians;
- (4) If delinquency continues TSC recommends to the Board that the institution is removed from continued participation in TROG trials until the problem is rectified.

## **5. QA Review Categories**

### **5.1 Ethics and Regulatory Approval Quality Assurance**

#### **5.1.1 Introduction**

Before trials involving human participants can commence, there are a number of regulatory and ethics approval processes that need to be performed.

Human Research Ethics Committees (HRECs) have a pivotal role in clinical research in Australia, by virtue of the fact that they undertake the key responsibilities of clinical trial approval and oversight in this country.<sup>6</sup> Each trial site involved in the trial is required to submit an ethics application to an HREC. The HREC is responsible for reviewing as a minimum the trial protocol, investigator's brochure, informed consent forms and patient information documents, procedures for subject recruitment, any planned payment or compensation initiatives, and the investigator(s) qualifications.<sup>6</sup> Once approval is acquired, the trial site is officially able to recruit patients. As well as the original approval, ongoing review of trials is required at intervals determined by the HREC, generally on an annual basis.

The primary purpose of the statement of ethical principles and associated guidelines for research involving humans is the protection of the welfare and the rights of participants in research.<sup>7</sup> Thus, it is important to ensure quality of ethics approval so as the aim of the national statement is achieved and the rights, safety and well-being of all trial subjects are

protected. To achieve this, reviews of the regulatory documents should be conducted for all trial sites including the protocol and any amendments, the original consent and any revised versions, and any other documentation applicable to the trial.<sup>7</sup> It will also be determined whether the HREC responded to all submissions. All dates and approvals will be reviewed to assure no changes to the protocol were implemented before they received HREC approval.

In some circumstances regulatory approval to conduct clinical trials needs to be obtained from the TGA. There are two routes that can be taken – the Clinical Trial Exemption (CTX) and Clinical Trial Notification (CTN) schemes. These schemes apply to testing of any drug or device not entered on the Australian Register of Therapeutic Goods, including any new formulation of an existing product or any new route of administration, as well as the use of marketed drugs and devices that extends beyond the conditions of the existing marketing approval.<sup>8</sup> Under the CTN scheme, the trial protocol is submitted directly to the HREC which is then responsible for assessing the scientific validity and safety of the protocol. The TGA does not undertake any review of the project. If the HREC approves the trial, the sponsor submits a CTN form to the TGA. Under the CTX scheme, a package of data is submitted to the TGA for evaluation and assessment of the safety of the product.<sup>8</sup>

If regulatory approval is required, it is important that this approval is obtained before participants are entered onto the trial. A major focus of quality assurance is to ensure participants are not entered onto trials involving unapproved protocols.

#### 5.1.2 Examples of Major Deviations<sup>31</sup>

- Protocol and/or consent form never approved by HREC;
- Initial HREC approval documentation missing for protocol and/or informed consent;
- Registration and/or treatment of patient prior to full HREC approval;
- Missing or expired re-approval;
- Reportable adverse events not reported to HREC;
- Lack of documentation of full HREC approval of protocol amendment that affect more than minimal risk.

## 5.2 Eligibility Quality Assurance

### 5.2.1 Introduction

Eligibility is an integral component of patient registration to a clinical trial. A set of eligibility criteria must be met for a patient to enter a trial. This summary criterion includes inclusion and exclusion criteria which both need to be satisfied. Inclusion/exclusion criteria are defined as the medical or social standards determining whether a person may or may not be allowed to enter a clinical trial. These criteria are based on factors such as age, gender, the type and stage of disease, previous treatment history, and other medical conditions. The eligibility criteria should reflect the scientific objectives of the trial and ensure comparison of similar groups or people.<sup>9</sup>

Ineligible cases are those patients that do not meet the inclusion criteria, or that fall under the exclusion criteria.<sup>10</sup> Minimising the incidence of ineligible cases is a key priority for quality assurance in clinical trials. The quality of a trial may be affected if there is a high incidence of ineligible patients as this could introduce bias and affect the results.<sup>11</sup>

In the case of eligibility, centralised data management systems are important to assure quality. One method to decrease the entry of ineligible patients is to design eligibility checklists for patients in clinical trials and have systems that check the data in the central registration office.<sup>11</sup> In addition to this method, TROG also employs remote source data verification to audit eligibility. This approach is employed for 100% of patients participating on a clinical trial and involves central review of source documentation, submitted by trial sites, against the inclusion and exclusion criteria. Classifications for non-adherence to the eligibility criteria are listed below.

### 5.2.2 Examples of Major Deviations

A violation is defined as failure to treat according to protocol. For example<sup>31</sup>:

- Patient did not meet eligibility criteria as specified in the protocol;
- Pre-registration assessment required by the protocol not performed but reported as complete;
- Unable to confirm eligibility due to missing documentation.

### 5.2.3 Example of Minor Deviations

Defined as deviations that do not affect the outcome or interpretation of the trial. For example<sup>31</sup>:

- Few transcription errors in dates or results which do not affect eligibility.

## 5.3 **Informed Consent Quality Assurance**

### 5.3.1 Introduction

Informed consent consists of two essential parts, a document and a process, and is defined as the voluntary confirmation of a subject's willingness to participate in a particular trial.<sup>12</sup> The informed consent document provides a summary of the clinical trial (including its purpose, the treatment procedures and schedule, potential risks and benefits, alternative to participation) and explains the rights of participants.<sup>11</sup> The informed consent process involves a series of conversations between the subject and the research team. It provides for ongoing explanations, so that educated decisions about whether to begin or continue participating in the trial can be made.<sup>10</sup> If the patient decides to enter the trial, the document is signed, indicating official consent to be entered into the trial.

Quality assurance of the informed consent process is usually achieved through audit of the original, or a certified copy, of the informed consent document. In conducting an informed consent form audit, the reviewer will ensure that the patient has signed and dated the form, the investigator has signed and dated the form, the consent date was prior to the patient's trial registration date and that the trial title is noted on the consent form. In the event that the investigator delegates responsibility for the informed consent process to an appropriately qualified person, this should be approved by ethics and a delegation log be kept in the trial site files.

### 5.3.2 Examples of Major Deviations

A violation is defined as failure to treat according to protocol. For example<sup>31</sup>:

- Unable to confirm consent process due to missing documentation;
- Consent form used was not for correct protocol;
- Consent form not signed and/or dated by the patient;
- Consent form not signed and/or dated by the physician;
- Consent form signed by patient after trial registration;

- Consent form used was not the current, HREC approved version at the time of registration;
- Translated informed consent form available but not used to consent patient who is not proficient in reading and speaking English.

### 5.3.3 Examples of Minor Deviations

Defined as deviations that do not affect the outcome or interpretation of the trial. For example<sup>31</sup>:

- Consent form signed by physician more than 1 week after patient;
- Signature is dated by someone other than the patient.

## 5.4 **Pathology Quality Assurance**

### 5.4.1 Introduction

The primary purpose of pathology review is to verify patient eligibility for a protocol. A designated reviewer will examine materials from tissues obtained prior to patient registration to determine if the pathologic features correspond with the trial eligibility criteria. This review process occurs after a patient has consented to the trial and has been registered. In some trials, additional pathology materials from a biopsy or surgical procedure performed after registration are required. These materials are used to document presence or absence of microscopic disease after treatment or to document disease characteristics after response. The purpose of this review is to provide a detailed pathologic assessment of tumour response rather than to establish eligibility.<sup>13</sup>

Many studies have shown that standardised reporting forms, including synoptic reports or checklists, are highly effective in improving report adequacy, particularly for cancer reporting.<sup>14</sup>

### 5.4.2 Examples of Deviations

Major errors with potential clinical significance – errors regarding the extent of disease (e.g. TNM classification and lymph node description) and the completeness of local excision (e.g. circumferential margin involvement).

Clerical errors – errors that can be detected and corrected by careful re-examination of the CRFs: for example, transposition of the measurements that represented the distance of the tumour from the proximal and distal margins, respectively.

Minor errors – errors that must be avoided if a high-quality database is to be maintained but that were unrelated to pathologic end points of the trial.<sup>15</sup>

#### 5.4.3 Central Review Discrepancy Procedure

In the instance of central pathology review discrepancy to the original findings, both the treating clinician and institutional pathologist will be notified in writing of the inconsistency. It is possible that the central review findings may represent a difference in opinions rather than correct diagnosis in which case the treating clinician and institutional pathologist may wish to seek independent review. Communication of the findings to the patient is the responsibility of the treating clinician.

### 5.5 **Radiotherapy Quality Assurance**

#### 5.5.1 Introduction

Radiotherapy is used as a localised cancer treatment modality for a wide range of cancers. The radiation only affects the cells within the treatment area. Although normal cells may be affected, they have a higher resistance and are able to recover back to normal function<sup>16</sup>. Radiotherapy may be used in an attempt to cure, control, to relieve symptoms or as an adjuvant therapy.

The goal of radiotherapy is to damage as many cells as possible, while limiting harm to healthy tissue<sup>17</sup>. This goal is integral to the quality assurance programs ensuring safe and effective treatment. Furthermore, high quality radiotherapy results and safety of treatment requires radiation to be optimally applied to a specified target area and in the correct dose. Due to the need for high precision, quality assurance must cover the entire radiotherapy process. There are three main ways to ensure quality of radiotherapy; these include dummy runs, treatment verification and dosimetry confirmation.

#### 5.5.2 Credentialing

TROG does not currently implement standardised credentialing procedures for all new trials.

##### 5.5.2.1 Dummy Runs/Benchmarks

Dummy runs/benchmark activities are included in the trial QA program if it is thought the risk of protocol compliance justifies the resource implications of the conduct of this pre-trial activity at trial sites and for QA management. Dummy runs are generally employed in TROG trials when there is a complex radiotherapy technique to ensure applicability of the protocol prescription and measure trial site compliance in administering the treatment before accrual commences so that any quality issues can be prospectively addressed.

Dummy runs are a proactive quality assurance measure that aim to discover protocol deviations and institutional differences before the trial begins. The main objectives of a dummy run are to deal with systematic errors and evaluate compliance of a given centre to protocol guidelines. A dummy run, designed to incorporate one or more critical items, is circulated to trial sites wishing to participate, asking them to provide the choices of technique that would be used in that case, following protocol recommendations<sup>18</sup>. Various aspects of a dummy run can be evaluated, such as treatment planning facilities in the participating centre and the dose specification procedure, the clarity of protocol prescriptions and the potential differences in treatment techniques and resulting dose heterogeneity<sup>19</sup>. The dummy run is then used to evaluate details on radiation technique and potential protocol compliance before actual patient accrual<sup>20</sup>. In exceptional cases, patient accrual may begin prior to approval of the dummy run case.

### 5.5.3 Treatment Verification

Treatment verification is a crucial quality assurance measure at all stages of radiotherapy. Verifying treatment is delivered as planned is essential to avoid risks of geographical miss or increased normal tissue toxicity<sup>21</sup>. Verification involves ensuring that what is specified in the treatment plan is the same as the actual treatment the patient receives. During treatment, the prescription and all treatment details are recorded in each patient's treatment sheet.

QA review will require copies of treatment documentation including (but not restricted to) prescription, treatment administration (daily dose record) sheet, treatment plan, portal films and simulator/DRR films. The Institutional Data Manager and Institutional Investigator must rigorously review the completeness and quality of the copies of all the documents and films that are submitted for review. In particular legibility and clarity of isodose plans (specified doses to vital structures, recorded hot and cold spot doses and any off-axis plans required) should be checked.

#### 5.5.3.1 3-D Review of Electronic Treatment Planning Files

TROG is implementing facilities for the 3-D review of electronic treatment planning files in DICOM-RT or RTOG format using SWAN software. Details for the export of these files from TROG trial sites are provided in a document forwarded to each trial site at the commencement of accrual onto a new trial, and specific information pertaining to treatment planning to enable 3-D review are also included in the protocol template.

### 5.5.3.2 Real-Time Review

Real-time or rapid review (review of treatment plans prior to the patient commencing treatment) is implemented if it is thought the risk of protocol compliance justifies the resource implications of the conduct of this trial activity at trial sites and for QA management.

A program for 'timely review' may also be employed where the risks are assessed as requiring review of treatment plans during the initial phase of patient treatment. This activity will be implemented for those trials where real-time review may require too great a resource commitment but valuable feedback to sites is able to be provided from a timely review of protocol compliance.

### 5.5.3.3 RT QA for New Technologies

TROG develops specialised QA resources to ensure that trials involving new radiotherapy technologies have the resources to undertake appropriate QA activities. IMRT QA resources are currently under development and will be added to TROG policy once finalised. Trials may not be activated unless appropriate QA resources can be implemented to ensure patient safety as well as to conduct the activities required to validate data accuracy and verify protocol compliance.

### 5.5.4 Trial site Dosimetry Confirmation

To ensure the dose specified is actually what the patient receives, dosimetric confirmation is employed. This involves the use of a range of different phantoms. Phantoms are used to check many of the factors that could affect treatment by mimicking the radiotherapy pathway of a patient as closely as possible without actually involving patients<sup>22</sup>. Phantom types range from a physical phantom, usually a container of water, to verify dose to the use of an anthropomorphic phantom that is planned and treated as similar to a patient as possible. This form of dosimetry can verify the entire treatment chain from the acquisition of diagnostic images to the treatment set up and delivery<sup>22</sup>.

### 5.5.5 Examples of Major Deviations

A violation is defined as failure to treat according to protocol. For example<sup>31,23</sup>:

- Dose deviations incorrect (error >10%)
- Dose modifications not per protocol
- Inadequate treatment field used resulting in no margin around the tumour
- Fractionation schedule not according to protocol (>10% variation)

- Excessive dose to critical structures
- Unjustified delays in treatment

#### 5.5.6 Examples of Minor Deviations

Defined as deviations that do not affect the outcome or interpretation of the trial. For example<sup>31,23</sup>:

- Dose deviation of between 5-10%
- Inadequate treatment field used resulting in minimal margin around the tumour
- Fractionation schedule not according to protocol (5-10% variation)

### 5.6 **Chemotherapy Quality Assurance**

#### 5.6.1 Introduction

Chemotherapy is used as a systematic treatment for a wide range of cancer and in some cases it is the first choice of treatment.<sup>24</sup> Chemotherapy may be used in an attempt to cure, control or palliate cancer.

Quality assurance of chemotherapy is very important for a wide range reasons. Chemotherapy is a toxic treatment with relatively small therapeutic effects and is a treatment that is repeated several times over a weekly or monthly period.<sup>25</sup> For these reasons, quality assurance is an essential part of chemotherapy and it is important that patients are treated in carefully designed protocols.<sup>26</sup> Quality assurance reviews of chemotherapy treatment should ensure that it was delivered in the correct dose, at the right time and with the appropriate medication.<sup>25</sup>

From a TROG perspective, chemotherapy will generally be used in combination with radiotherapy treatment. Quality assurance procedures will be focused towards adequate documentation (prescription and flowsheet) of the chemotherapy to enable treatment reviews with classifications of deviations for failure to treat according to protocol as listed below.

#### 5.6.2 Examples of Major Deviations

A violation is defined as failure to treat according to protocol. For example<sup>31</sup>:

- Incorrect agent/treatment used;
- Dose deviations incorrect (error  $\geq$  10%);
- Drug treatment incorrectly administered, calculated or documented;
- Dose modifications not per protocol;

- Doses not adjusted for toxicity;
- Unable to verify drug treatment or important components of the treatment due to missing documentation;
- Unjustified delays in treatment;
- Additional agent/treatment used which is not permitted by the protocol.

### 5.6.3 Examples of Minor Deviations

Defined as deviations that do not affect the outcome or interpretation of the trial. For example<sup>31</sup>:

- Dose deviations of drug(s) < 10%;
- Dose amount and/or treatment dates reported incorrectly and actual values do not result in 'major' deficiency;
- BAS not recalculated and resulting dose is not > 10% different.

## 5.7 **Pharmaceutical Products Quality Assurance**

### 5.7.1 Introduction

Pharmaceutical product interventions, for example hormone therapy, may form part of the protocol treatment in a clinical trial. On some occasions these products will be utilised as part of the standard treatment regimen and will be reviewed only from a CRF data accuracy viewpoint. In these instances, it is important to ensure processes are in place at the beginning of a trial to obtain documentation verifying the source of the data included in the CRF.

### 5.7.2 Examples of Major Deviations<sup>31</sup>

- Incorrect agent/treatment used;
- Dose deviations incorrect (error  $\geq$  10%);
- Unable to verify drug treatment due to missing documentation.

### 5.7.3 Examples of Minor Deviations<sup>31</sup>

- Dose deviations of drug(s) < 10%;
- Data recorded on CRF inconsistent with source documentation.

## 5.8 Medical Devices Quality Assurance

### 5.8.1 Introduction

The *Therapeutic Goods Act 1989* defines a medical device as “any instrument, apparatus, appliance, material or other article (whether used alone or in combination, and including the software necessary for its proper application) intended by the person under whose name it is to be supplied, to be used for human beings for the purposes of one or more of the following:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

and does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means; or an accessory to such an instrument, apparatus, appliance, material or other article.”<sup>27</sup>

Quality assurance reviews for medical devices will ensure that use of the device was conducted according to protocol and that the intervention can be verified through source documentation. A monitoring program may also need to incorporate techniques such as verification of training of staff and patients in the use of a medical device, patient diaries or logs to verify times of medical device application or digital photos to provide graphic evidence of devices in practice. Methods to verify compliance with medical device protocol requirements will need to be established at the development phase of each trial to ensure appropriate measures are established for each trial.

### 5.8.2 Examples of Major Deviations<sup>31</sup>

- Incorrect medical device used;
- Medical device not used as per protocol specifications;
- Unable to verify use of medical device due to missing documentation.

## 5.9 Surgical Oncology Quality Assurance

### 5.9.1 Introduction

Surgery is involved in the diagnosis, staging, and therapy of solid malignancies and as such active surgical leadership in cancer studies is important<sup>28</sup>. Clear evidence has found that an improvement in quality of the surgical procedure could have major implications for the

prognosis and quality of life of cancer patients. There is a need for strict quality control procedures in surgical oncology and this might imply a considerable change in cancer treatment strategies, because the routine use of adjuvant therapies could be questioned<sup>29</sup>.

To address these concerns, substantive surgical leadership is being developed throughout the cooperative group system with surgical co-principal investigators being appointed. Uniform surgical standards and operative guidelines are being developed which are reviewed through central audits and surgical monitoring committees<sup>28</sup>. In the EORTC, several methods have been used or are currently under investigation to ensure the quality of surgery within clinical trials. These include review of reported data, standardisation of surgery and pathology forms, training sessions and trial site visits. However, there has been no attempt to harmonise these initiatives across the different medical specialties<sup>30</sup>.

A quality control method implemented in the EORTC is the design of specific guidelines for the descriptions of surgery in the protocol and standard items for CRFs. The minimum criteria for protocols to evaluate the surgical intervention include the type of surgical procedure, the extent of local surgery and the extent of lymphadenectomy. The margins of resection and the number of lymph nodes were considered as minimum criteria for the reporting of the pathological examination<sup>30</sup>.

Surgical oncology from a TROG perspective may be utilised as an intervention or form part of the eligibility criteria for an adjuvant trial. Quality assurance procedures will be focused towards adequate documentation of the surgery to enable eligibility or treatment reviews with classifications of deviations for failure to treat according to protocol as listed below.

#### 5.9.2 Examples of Major Deviations

A violation is defined as failure to treat according to the protocol. For example<sup>31</sup>:

- Incorrect operative intervention performed;
- Operative intervention not performed per protocol specifications;
- Unable to verify operative procedure or important components of the procedure due to missing documentation;
- Incorrect intervention or treatment is used;
- Additional treatment which is not permitted by protocol.

## 5.10 Response Assessment Quality Assurance

### 5.10.1 Introduction

Ensuring the validity of response evaluations is identified as a primary aspect of quality assurance<sup>32</sup>. In clinical trials, response is often defined as an endpoint and as such necessitates procedures to ensure transparent verification and independent confirmation of results. Incorrect response assessment may result in needless exposure of patients to an ineffective agent, early trial closure, incorrectly labelling an agent as ineffective, or a biased response rate estimate. Response assessment is only possible when all trial sites are reviewed and disease extent is recorded accurately.<sup>33</sup>

Protocol content for the assessment of outcomes should include the following information<sup>34</sup>:

- Endpoint/outcome definitions;
- Frequency with which endpoint data are to be collected;
- Description of toxicity standards adopted;
- Definitions of treatment failure;
- Detailing response criteria (where appropriate) including measurable, evaluable and dimensional;
- If disease sites are to be routinely followed, how many and which sites should be clearly specified;
- Definitions of objective response including time between measurements, number of measurements;
- Details of the collection of non-clinical information such as quality of life, treatment costs, hospitalisations, etc. All pictorial or schematic (flow chart) representations should be included where appropriate.

### 5.10.2 Examples of Major Deviations

A violation is defined as failure to evaluate response according to the protocol. For example<sup>35</sup>:

- Inaccurate documentation of initial sites of involvement
- Tumour measurements/evaluation of status of disease not performed according to protocol
- Protocol-directed response criteria not being followed
- Claimed response (PR, CR) cannot be verified
- Failure to detect cancer (as in prevention trial) or failure to identify cancer progression

## 5.11 Adverse Event Reporting

### 5.11.1 Introduction

The TGA defines an Adverse Event as 'any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.'<sup>36</sup>

A Serious Adverse Event is defined by the TGA as any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

Investigators are required to adhere to expedited reporting guidelines for SAEs as specified in the safety reporting section of the trial protocol. The standardised TROG SAE Report form should be submitted, in accordance with the timelines stipulated in the protocol, to the Trial coordinating centre and TROG Central Operations Office. The Trial coordinating centre, in partnership with the TMC, will review all SAE reports from a clinical perspective and recommend any actions as a consequence of the report. TROG will review the reports from an operational perspective to ensure all reports are submitted as complete, with the required information included, that reports have been signed by the Principal Investigator and that any changes to the report template are implemented across all trials.

Failure to assess and report toxicities and adverse events according to the protocol will be classified as variations.

### 5.11.2 Examples of Major Deviations<sup>31</sup>

- Unable to verify adverse event(s) due to missing documentation
- Grades, types, or dates/duration of serious adverse events inaccurately recorded
- Unreported major adverse event (Grade 4 or 5)
- Failure to obtain follow-up studies required to effectively assess adverse event(s)
- Repetitive failure to properly characterise adverse event or grade
- Failure to file reportable adverse event(s) according to protocol and TROG guidelines

- Recurrent under- or over-reporting of adverse event(s)

#### 5.11.3 Examples of Minor Deviations<sup>31</sup>

- Few Grade 2 or 3 adverse event(s) not reported, if applicable
- Delay in filing reportable adverse events according to protocol and TROG guidelines

### 5.12 Data Quality

#### 5.12.1 Introduction

Data quality monitoring will address accuracy and timeliness of Case Report Form (CRF) submission. ICH GCP guidelines for data handling require transparency and proper documentation of all procedures<sup>37</sup>. These include data cleaning and procedures for making changes to data and ensuring an audit trail is maintained for any alterations to CRF data. In order to be effective, prompt feedback and suggestions for corrective action must be provided whenever a data quality problem is discovered<sup>38</sup>. Data quality reviews will be performed by Trial coordinating centres, with the implementation of an appropriate and documented form of data cleaning and expectations for data submission.

#### 5.12.2 Examples of Major Deviations<sup>31</sup>

- Frequent data inaccuracies;
- Errors in submitted data;
- Delinquent data submission >3 months for intervention data and pathology reports, >6 months for follow-up data
- Use of “liquid erasure product” in a primary record or CRF.

#### 5.12.3 Examples of Minor Deficiencies<sup>31</sup>

- Few data inaccuracies or errors in data submitted;
- Minor delinquency (<3 months) in data submission.

## 6. References

- <sup>1</sup> National Health and Medical Research Council (2003) When does quality assurance in health care require independent ethical review?
- <sup>2</sup> Quality Assurance in Radiotherapy, World Health Organisation (1988)
- <sup>3</sup> Guideline for Good Clinical Practice, ICH Harmonised Tripartite Guideline (1996)
- <sup>4</sup> National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP): Guidelines for Monitoring of Clinical Trials for Cooperative Groups, CCOP Research Bases, and the Cancer Trials Support Unit (CTSU) <http://ctep.cancer.gov/monitoring/guidelines.html>
- <sup>5</sup> NCRI Key Competencies for Clinical Trials Units - [www.ncri.org.uk](http://www.ncri.org.uk)
- <sup>6</sup> The Australian Clinical Trial Handbook – March 2006
- <sup>7</sup> National Statement on Ethical Conduct in Research Involving Humans
- <sup>8</sup> NHMRC – Human Research Handbook
- <sup>9</sup> [Clinicaltrials.gov](http://clinicaltrials.gov) (16/06/06)
- <sup>10</sup> Factors that influence the eligibility of cases for inclusion in clinical trials (Kasai, T, Ohe, Y, Nishio, K, et al) Japanese Journal of Clinical Oncology, 1998, Vol. 3, pp 214-21
- <sup>11</sup> <http://www.cancer.gov/clinicaltrials/conducting/informed-consent-guide/page2> (16/06/06)
- <sup>12</sup> Ensuring quality in the informed consent process (Nallen, R) The Quality Assurance Journal, 1997, Vol. 2, pp 179-185
- <sup>13</sup> Southwest Oncology Group Clinical Research Associate Manual, Discipline Review, December 2005
- <sup>14</sup> Postanalytic variables: report adequacy and integrity (Fitzgibbons P.L.) College of American Pathologists, Quality Management in Anatomic Pathology
- <sup>15</sup> Pathology data in central databases of multicentre randomized trials need to be based on pathology reports and controlled by trained quality managers (Nagtegaak I.D., Klein Kranenbarg E., Hermans J., van de Velde C.J.H., van Krieken J.H.J.M, Pathology Review Committee) Journal of Clinical Oncology, Vol 18, Issue 8 (April), 2000: 1771-1779
- <sup>16</sup> Understanding Radiotherapy – A guide for people with cancer, families and friends. The Cancer Council New South Wales.
- <sup>17</sup> National Cancer Institute, Cancer Facts – Radiation Therapy for Cancer
- <sup>18</sup> Quality Assurance Activities in Radiotherapy (Ikeda, H) Jpn J Clin Oncology 2002, Vol 32, pp:493-496
- <sup>19</sup> Quality assurance in clinical trials (Ottevanger, P, Therasse, P, van de Vekilde, C, Bernier, J, van Krieken, H, Grol, R, de Mulder, P) Critical Reviews in Oncology/Hematology 2003, Vol 47, pp:213-235
- <sup>20</sup> Quality assurance of axillary radiotherapy in the EORTC AMAROS trial 10981/22023: the dummy run (Hurkmans, C, Borger, J, Rutgers, E, Tienhoven, G) Radiotherapy and Oncology 2003, Vol 68, pp:233-240
- <sup>21</sup> Radiotherapy treatment verification in the UK: An audit of practice in 2004 (Stratford, J, Ball, K, Henry, A, Cullen, J, Swindell, R, Price, R, Jain, P) Clinical Oncology 2006, Vol 18, pp:15-22

- <sup>22</sup> Dosimetric intercomparison for two Australasian clinical trials using an anthropomorphic phantom (Kron, T, Hamilton, C, Roff, M, Denham, J) *Int, J Radiation Oncology Biol. Physics* 2002, Vol 52, No 2, pp:566-579
- <sup>23</sup> RTOG QA Program: Criteria for the final evaluation of radiation therapy
- <sup>24</sup> American Cancer Society – Chemotherapy Principles
- <sup>25</sup> The quality of chemotherapy and its quality assurance (Ottevanger, P, de Mulder, P) *European Journal of Cancer Surgery*, 2005, Vol 31, pp 656-666
- <sup>26</sup> Chemotherapy administration and data collection in an EORTC Collaborative Group – can we trust the results? (Steward, W, Vantongelen, K, Verweij, J, Thomas, D, van Oosterom, A) *European Journal of Cancer*, 1993, Vol 29A, No. 7, pp 943-947.
- <sup>27</sup> Australian Medical Devices Guidelines – An Overview of the New Medical Devices Regulatory System, Therapeutic Goods Administration (2003)
- <sup>28</sup> The implications of surgical quality assurance in cancer clinical trial (Haase, GM) *Cancer*. 1994 Nov 1; 74(9 Suppl):2630-7
- <sup>29</sup> The importance of quality assurance in surgical oncology (Landheer, ML, Therasse, P, van de Velde, CJ) *Eur J Surg Oncol*. 2002 Sep; 28(6): 571-602.
- <sup>30</sup> Quality assurance in surgical oncology (QASO) within the European Organisation for Research and Treatment of Cancer (EORTC) – current status and future prospects (Landheer, MLEA, Therasse, P, van de Velde, CJH) *European Journal of Cancer*, Vol 37, No 12, August 2001, pp:1450-1462
- <sup>31</sup> American College of Surgeons Oncology Group Audit Manual, Revised 28 December 2004
- <sup>32</sup> EORTC Investigator's Handbook, 17th November 2003
- <sup>33</sup> Southwest Oncology Group Clinical Research Associate Manual – December 2005
- <sup>34</sup> Australasian Gastro-Intestinal Trial Group, Quality Assurance Policy, V1 18 November 1998
- <sup>35</sup> National Cancer Institute – Cancer Therapy Evaluation Program – Section 5 Conducting the Quality Assurance Audit
- <sup>36</sup> Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95) Therapeutic Goods Administration, July 2000
- <sup>37</sup> Section 5.5, ICH Harmonised Tripartite Guideline for Good Clinical Practice (1996)
- <sup>38</sup> Data quality assurance, monitoring and reporting (Gassman, JJ, Owen, WW, Kuntz, TE, Martin, JP, Amoroso, WP) *Control Clin Trials*, 1995 Apr, 16 (2 Suppl), pp:104S-136S