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# Quality assurance in EORTC clinical trials

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**Abstract**

Quality assurance (QA) has become a major factor over recent years in the management and analysis of clinical trials. The EORTC recognised very early the importance of QA in clinical data handling and started in 1992 with the development of the first SOP in the format of a 'Procedures manual' which, from the beginning, had incorporated the EU GCP guidelines. In 1995, a Quality Assurance Unit (QAU) was created to coordinate the various QA activities and to guarantee that all clinical trials do comply at all levels with a minimum of QA requirements. The QAU coordinates internal and external audits and is a mandatory partner in the audits performed by national/international authorities and pharmaceutical industries. This process has been prolonged at the Data Center with the development of a full set of standard operating procedures (SOPs), the implementation of training programmes for each category of staff and an ongoing interval monitoring process. 

## 1. Background

The Data Center of the EORTC was set up in 1974, when two statisticians and one data manager became part of the EORTC staff. Until 1974, clinical trials were coordinated from different sites, mainly the hospital/university of an investigator coordinating a particular trial.

The first computer management tools that were used for data management were very limited in use and exploitation.

From the beginning, clinical data have been double keypunched, first by an external organisation, later at the data centre by the data entry clerk. Data verification, consistency check and query handling were all performed prior to data entry, and only forms which were fully reviewed and validated for data entry were entered into the database.

The data manager's task was limited to manual review, the statistician was working, in collaboration with the IT unit, on the data analysis and final report preparation.

In the 1980s, the computer software 'System for Management and Analysis of Randomized Trials' (SMART) was developed by the Data Center IT unit. At that time, all data managers received their first VAX terminal and the first software for data management was developed.

It took until 1989 before all data managers had switched to the SMART system, just prior to the move in 1990 from the Bordet Institute to the current location. In 1990, 10 data managers were covering the activities of 14 clinical research groups. There were four statisticians, two IT programmers, one secretary, one data entry clerk, two administrative assistants and one director.

## 2. The Quality Assurance Committee

In the autumn of 1987, the Board appointed officially a Quality Control Committee (QCC).

The merits of the QCC were:

1. to assess all problems related to quality control in clinical trials within the EORTC;
2. to make practical proposals for specific steps to be taken in order to strengthen this aspect within the EORTC;
3. to evaluate projects, submitted by the groups, to be included in the a project submitted to the European Communion.

Already, in previous years, several projects related to quality control had been activated in different groups [1,2]. Mainly, these had been aimed at an external

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review of tumour response and centralised assessment of diagnostic procedures such as pathology, radiology, biochemistry and nuclear medicine. First attempts to harmonise radiotherapy procedures were also carried out.

In 1998, the QCC was renamed the Quality Assurance Committee (QAC). One of the primary tasks of the QAC has been to coordinate these efforts in order to develop comprehensive guideline for the different steps of quality control. These guidelines could then be used by the 'Clinical groups' in order to enable them to implement an adequate quality assurance system within their activities. This is reported in the other section of this paper.

## 3. Data Center quality assurance

In 1991, the Data Center issued the *1st Procedures Manual* [3]. This manual provided the 1st guidelines attempting to set standard criteria for the data managers and statisticians in the Data Center for management and analysis of clinical data received.

These guidelines also helped the study coordinators in defining full or partial availability of patients.

This procedures manual, which also addressed some of the recently published EU GCP guidelines, can be seen nowadays as the first set of standard operating procedures (SOPs) entering their way into the EORTC Data Center functioning. An updated version was printed in 1992 [4].

In parallel to the development of the procedure manual, a committee was set up to look at the format of the Case Report Forms (CRFs) to be used in newly activated studies.

In 1991, a grant from the EORTC QAC was provided to the EORTC Data Center to:

- develop software for the establishment of an inventory of investigators and institutions participating in EORTC studies;
- implement a computerised definition of CRF request schedules to allow data managers to automatically generate retrospective and prospective forms requests;
- define a report module which allows a series of QC cross checks to be carried out on a patients' CRF in order to assure consistency of data within the patient CRF.

In 1994, the first *Practical Guide to EORTC Studies* [5] was published under the sponsorship of the EORTC QAC. It contained chapters on EORTC structure and organisation, ethical issues, trial methodology, submission to the Protocol Review Committee, CRFs and data submission. In addition, it gave some practical information on how to set up a clinical trial on the local site. This practical guide resulted from a QAC project, which was carried out with the collaboration of several EORTC Cooperative groups and the EORTC Data Management group [6,7]. It became an indispensable reference for clinicians and data managers involved in EORTC clinical research activities. This EORTC practical guide has been restructured to the *EORTC Investigators Handbook* [8], which is currently in review for update.

In the mean time, the work of the data managers and statisticians at the EORTC Data Center became more and more complex. The EORTC Data Center had to comply with the EU GCP and all efforts were undertaken to assure that EORTC clinical trials were performed in the GCP spirit. All the different tasks of the data managers were reviewed in the perspective of further standardisation of the data management work. Since 1992, medical fellows have been integrated into the Data Center staff, besides data management and statistical expertise, and the EORTC Data Center could also offer the medical expertise to the Data Center staff and to the groups.

In 1997, the Genito-Urinary Group first tested the monitoring of the data timeliness in their clinical trials. The EORTC Data Center received from the board the authority to take decisions for centres that did not comply in a timely manner with the submission of data to the Data Center. In 1998, this procedure was officially installed in all clinical groups.

In the same year, the EORTC staff started the development of the SOPs following the ISO 9000 format. A full training programme was developed to present to and teach the staff the SOPs covering all trial-related actions from protocol development to publication.

With the introduction of the EU-GCP and the ICH-GCP into the EORTC clinical trials, the data management staff has grown today to 44 people for 21 clinical groups which perform their clinical trials through the EORTC Data Center. Quality assurance is guaranteed at all levels of the clinical trial, from protocol development to publication.

## 4. Quality Assurance Unit

The Quality Assurance Unit (QAU) had been created in early 1995 in order to coordinate the Quality Projects carried out by the QAC. Gradually, the QAU assisted in the development of the monitoring plan for EORTC Studies and in the development of the SOPs.

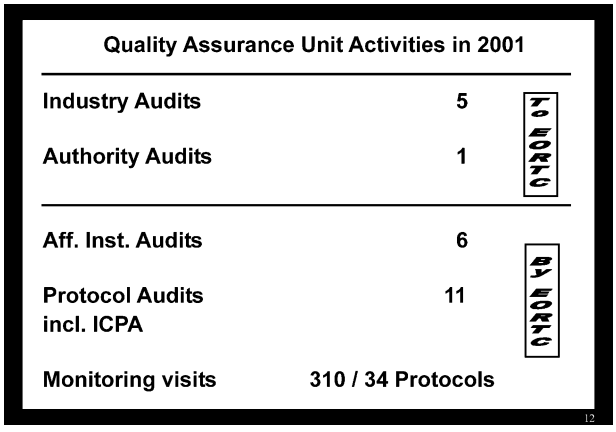
Since the end of 1997, the QAU has organised systematic SOP training sessions for the Data Center staff. Over the last 5 years, 80 SOP trainings have been organised.

The QAU is involved in the audits performed at the EORTC Data Center by our industry research partners

and the national authorities. Systematically, centres that are selected for external audits are assisted in the preparation of these audits.

With the implementation of the Affiliated Institution certificates, the EORTC committed to an audit plan of these institutions on a rotation of 3 years. Since January 2000, the QAU has started to perform these visits on a regular basis.

In addition to these regular audits, the QAU also performs so-called 'for cause' audits. These visits are initiated following problems that are encountered by the Data Center group team in the collection or quality of the data reported to the Data Center.




## 5. Conclusion

The EORTC has put every effort in ensuring high quality standards conform to ICH-GCP and FDA/EMEA requirements in place for the conduct of its clinical research. This is applicable at the level of the data collected and analysed, and also on the required infrastructures of its affiliated institutions/departments.

EORTC groups are bound by their statutes to implement quality assurance and quality control measures to guarantee quality and compliance of their participating members.

Quality Assurance is an ongoing process which required an optimal support and infrastructure in place to comply with high quality standards in the development of new anticancer treatments.

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