Available online at www.sciencedirect.com
ScienceDirect
Contemporary Clinical Trials 27 (2006) 554–560
Contemporary Clinical Trials
www.elsevier.com/locate/conclintrial

Quality assurance in a large clinical trials consortium: The experience of the Tuberculosis Trials Consortium ☆

Laurie Sandman [a], Ann Mosher [b,*], Awal Khan [c], Jan Tapy [d], Rany Condos [a], Scott Ferrell [e], Andrew Vernon [c], the Tuberculosis Trials Consortium

[a] *Bellevue Hospital, New York University School of Medicine, New York, NY, USA*
[b] *Duke University Medical Center, Durham, NC, USA*
[c] *Centers for Disease Control and Prevention, Atlanta, GA, USA*
[d] *Department of Public Health, Denver Health and Hospitals, Denver, CO, USA*
[e] *SAIC-Frederick, Inc., Frederick, MD, USA*

Received 29 December 2005; accepted 15 June 2006

Abstract

Quality assurance (QA) is essential for data accuracy and proper evaluation of study objectives in clinical trials. The Tuberculosis Trials Consortium (TBTC)–a collaboration of 28 clinical sites and the Centers for Disease Control and Prevention–has developed a comprehensive QA program that provides quantitative assessments of performance based on clearly defined standards that are communicated to data collectors through a feedback process.

The Implementation and Quality Committee of the TBTC developed a Site Evaluation Report (SER) that assesses performance measures (PMs) critical to the accomplishment of study objectives. PMs are defined, quantified, and evaluated, and goals and minimum acceptable scores are specified. Sites not meeting a PM minimum must provide an explanation and develop a plan to meet the goal. Site-specific and system-wide problems can be readily identified through this process.

Abbreviations: CDC, Centers for Disease Control and Prevention; CRF, Case report form; DCC, Data Coordinating Center at the Centers for Disease Control and Prevention; IQC, Implementation and Quality Committee—one of four Executive Committees of the TBTC. The committee consists of eight study coordinators and one representative each from the clinical monitoring organization (currently, Westat, Inc.) and the DCC. IQC's mission is to ensure that research performance and data are of the highest possible quality. IRB, Institutional Review Board; PM, Performance measure; QA, Quality assurance; SER, Site evaluation report—an instrument for evaluating the quality of data submitted in each study. The SER consists of PMs that address major elements of protocol implementation. IQC sets goals and minimum standards for each PM based on protocol requirements, coordinator consensus, and realistic expectations of what can be accomplished in the day-to-day implementation of a clinical study. SERF, Site evaluation response form; TBTC, Tuberculosis Trials Consortium—a collaboration of the CDC and investigators at 28 international and U.S. clinical sites. It was formally organized in 1998 to conduct research on the diagnosis, treatment, and prevention of tuberculosis. TBTC studies continually recruit patients, and their enrollments are growing, with more than 7000 patients studied from 1995 to date. The TBTC is currently the only tuberculosis clinical trials research network of its kind in the world. USPHS, United State Public Health Service.

☆ Grant support: Centers for Disease Control and Prevention, United States Public Health Service.

* Corresponding author. Box 3306, Duke University Medical Center, Durham, NC 27710, USA. Tel.: +1 919 681 6670; fax: +1 919 681 7494.
E-mail address: moshe001@mc.duke.edu (A. Mosher).

1551-7144/$ - see front matter
doi:10.1016/j.cct.2006.06.003

The SER is used prospectively for all TBTC treatment trials, and a Web site has been developed to maximize the availability and usefulness of performance data. The TBTC's comprehensive QA program is an example of a successful method for ensuring high quality, evaluable data.

Keywords: Quality assurance; Multicenter clinical trials; Data management; Monitoring; Data quality assurance

1. Introduction and background

Data integrity and consistency are essential to the success of a research study [1]. Quality assurance (QA) systems should ensure that clinical trials are performed and data are generated and reported in accordance with protocols, good clinical practice guidelines, and regulatory requirements [2]. QA measures can also help to guarantee data accuracy and prevent or detect protocol violations such as enrollment of noneligible patients or assignment of incorrect treatment. These types of errors can reduce statistical power, prevent attainment of study objectives, or lead researchers to erroneous conclusions [3–7].

Multiple studies have shown that a comprehensive QA program must focus on study and case report form design, the training of qualified investigators and study personnel, audits, and data management [3–5,8–12]. It must also include a feedback mechanism whereby sites are informed of problems with data or performance [3,5,9]. Much of the published literature addresses methods for ensuring data quality, such as double entry of data, programming for error detection, audits, and site monitoring visits [1,3–5,7,8,13]. QA activities may also include the replication of instrument and equipment readings or procedural quality control [14–16]. Few models exist, however, for the quantitative assessment of performance with predetermined performance guidelines or standards [3–5,8,17,18].

The Tuberculosis Trials Consortium (TBTC) developed a quality assurance system that uses prospective performance measures and standards as a means for assessing site performance and data quality. A summary of the TBTC QA program has been presented previously [19]. The objective of the present paper is to describe the development, utility, and evolution of the Tuberculosis Trials Consortium's data quality assurance program.

2. Overview of TBTC QA program

The TBTC's assessment of data quality is a collaborative effort. In addition to QA procedures implemented internally by the sites, three TBTC groups–the Implementation and Quality Committee (IQC), the Monitoring and Support Center (currently Westat, Inc.), and the Centers for Disease Control and Prevention's Data Coordinating Center (DCC)–also evaluate data quality. Each group has different functions and produces independent reports (Table 1).

The IQC has assumed a major role in the development of this collaborative QA system. Most significantly, the committee developed the Site Evaluation Report (SER) as an instrument for evaluating the quality of data submitted in each study. The SER consists of performance measures (PMs) that address major elements of protocol implementation such as timeliness of local IRB approval, patient eligibility, correct medication administration, study visit rates during treatment and follow-up phases, and treatment completion rates (Table 2). Additional PMs are identified for each treatment trial based on protocol-specific requirements, such as chest X-rays and blood draws for various laboratory tests. Each measure corresponds to operational definitions with clear numerators (indicating data points achieved) and denominators (indicating total data points possible for the measure) so that a percentage may be calculated showing how well a site has met the performance goal.

Site Evaluation Reports are designed for prospective use from the initiation of each study. Protocol training includes explanations of the performance measures so that site personnel are aware of data quality expectations. Data for the SER are extracted from case report forms, and a computer program created by DCC calculates the results. Sites are not required to submit any additional forms for the report.

As outlined in Fig. 1, DCC sends SERs to the sites twice each year. Sites review their reports for accuracy and have the opportunity to request corrections and updates from DCC. When sites fail to meet a PM minimum requirement, they are instructed to complete a Site Evaluation Response Form (SERF) within an established timeframe. On this form, the sites explain their reasons for not meeting the minimum goal and describe their plans for meeting the goal in the future.

Table 1
Overview of TBTC quality assurance program

	Major functions	Report produced
Implementation and Quality Committee (IQC)	– Evaluates protocols in development for implementation issues – Evaluates CRFs in development stage – Assesses training needs – Develops quantitative QA indicators – Detects site-specific or consortium-wide problems – Suggests methods to improve site performance	*Site Evaluation Report* – Reports site scores – Summary reports compiled twice a year – Site has opportunity to respond and/or request modifications
Monitoring and Support Center (Westat, Inc.)	– Develops manual of operating procedures – Provides training in study procedures and CRF completion – Reviews records for key elements and data validation at least twice a year – Evaluates compliance with federal regulations and Good Clinical Practices – Conducts pharmacy audits – Assesses site performance	*Site Monitoring Report* – Provides chart audit, review of regulatory documents, pharmacy audit, recommendations for improving performance – Sites are visited and assessed twice a year – Site has opportunity to respond to report
CDC Data Coordinating Center (DCC)	– Develops CRFs with protocol team – Maintains database – Conducts double entry of data, checking for out-of-range values – Prepares Site Evaluation Reports – Provides schedule of visits – Provides training in CRF completion – Reviews sites' CRFs for completeness and internal consistency – Requests modifications, clarification, missing forms from sites – Assesses site performance	*Missing Forms Report* – Distributed quarterly
Internal QA (Sites)	– Ensure CRFs are accurate and complete – Ensure compliance with protocol – Conduct assessment for adverse events and study endpoints	*Site Internal QA Plan* – Written QA plan when needed

Abbreviations: CDC=Centers for Disease Control and Prevention; CRF=case report form; QA=quality assurance; TBTC=Tuberculosis Trials Consortium.

SERs and SERFs are reviewed by a QA Review Group, which includes the chair and co-chair of IQC, representatives from the CDC, DCC, and Westat, and an investigator. The group reviews summary results for each study, as well as SERs of individual sites, and evaluates the adequacy of site responses in the SERFs. When appropriate, the members offer suggestions for improving performance and recommend additional TBTC support or monitoring. Prospective use of the SER and SERF assists in early detection and correction of difficulties related to protocol implementation and data collection.

3. Implementation of the TBTC QA program

The TBTC QA process has been used successfully in five clinical trials that are now closed and two others–USPHS Studies 26 and 28–which are currently enrolling patients (Appendix A). Study 28 recently opened to enrollment, whereas Study 26, which opened in 2001, has enrolled almost 6000 patients toward the target enrollment of 8000.

Because of the large amount of data being generated in Study 26, IQC and DCC collaborated in the planning and creation of a secure, password-protected Web site that features QA information and data. After the case report forms are entered into a database, DCC uses SAS software (version 8.2, SAS Institute, Cary, North Carolina) to generate and publish the QA reports on a nightly basis. The Web site currently includes the Study 26 PMs and scores listed by site, enrollment numbers and percentages, a forum for QA questions, and links to the SERF and other useful Web sites. If performance measure scores are less than 100%, the Web site also lists patient identification numbers by site to facilitate the search for the specific data point(s) cited as deficient in the SER.

The Web site provides QA data by study site so that TBTC member sites can compare their performance to that of their consortium colleagues. Table 3a shows the Study 26 PM for "lost to follow-up," which is defined as patients not

Table 2
Selected performance measures and definitions common to TBTC clinical trials

Performance measure	Operational definition (numerator/denominator)	Goal	Score
Eligibility	# patients meeting all inclusion criteria with absence of any exclusion criteria/# patients enrolled	100%, min 100%	
Adherence to Treatment Phase Therapy Medication Schedule			
a. Dose	a. # patients receiving correct # of doses/# patients completing TP	a. 100%, min 90%	
b. Time	b. # patients completing TP within protocol-defined time frame/# patients completing TP	b. 100%, min 90%	
c. Interval	c. # patients receiving doses at correct intervals/# patients completing TP	c. 100%, min 95%	
Visit Rates			
a. Treatment phase	a. # scheduled patient visits completed during TP/total # scheduled TP visits to date	a. ≥95%, min 85%	
b. Follow-up phase	b. # patient visits during FP/total # scheduled FP visits to date[a]	b. ≥90%, min 85%	
Treatment completion rate	# patients completing TP/total # patients enrolled	≥95%, min 85%	

Abbreviations: FP=follow-up phase; min=minimum; TBTC=Tuberculosis Trials Consortium; TP=treatment phase.
[a] Excluding patients who reached a study endpoint or withdrew consent.

having a study visit for 12 months during the follow-up phase of the study. For this measure, the goal is that fewer than 10% of patients are lost. The maximum loss of 15% is based on sample size calculations that assume that no more than 15% of patients would be lost. Table 3b shows an abbreviated report for this performance measure as it appears on the Web site.

The Web site provides QA data in real time, which is a significant improvement over the previous distribution of the SERs every 6 months. Sites may now review their performance data at any time and are especially encouraged to consult the Web site when DCC issues the "Missing Case Report Forms" (CRFs) report every month. (There are plans

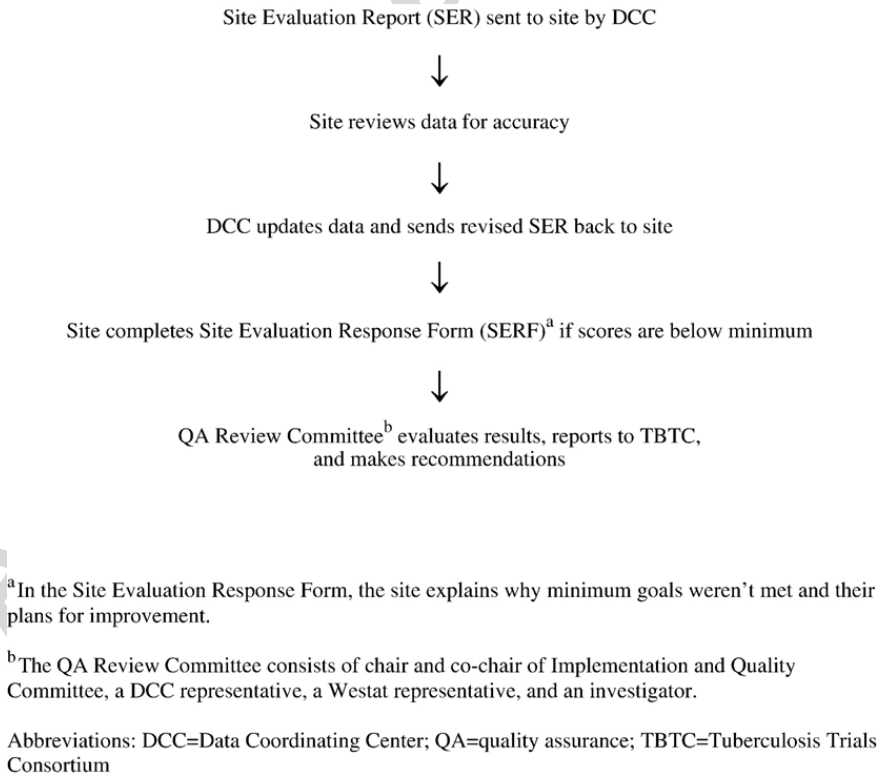

Fig. 1. Implementation and Quality Committee QA process. DCC=Data Coordinating Center; QA=quality assurance; TBTC=Tuberculosis Trials Consortium.

Table 3a
A selected USPHS Study 26 performance measure and definition in the follow-up phase

Performance measure	Operational definition (numerator/denominator)	Goal	Score
Lost to follow-up	# of patients with no study visit for a period of >12 months/total # scheduled FP visits to date, excluding those patients who were ineligible, withdrew, died, or developed TB	≤10%, max 15%	

Abbreviations: FP=follow-up phase; max=maximum; TB=tuberculosis.

to publish the "Missing CRFs" report on the Web site, as well.) In addition, study monitors are now accessing the Web site in order to identify potential problems in between monitoring visits. The formal QA process continues to take place every 6 months.

When study personnel visit the Web site frequently, their familiarity with the QA system increases; conversely, infrequent review results in underuse of the Web site's tools for correcting deficiencies. Individual training has been necessary for some study personnel who were experiencing difficulties in navigating the Web site.

Because of the positive feedback received from sites and the great improvement in the timeliness and availability of QA data, further improvements are planned for the Web site, including the utilization of Web-based CRFs.

4. Summary and discussion

The TBTC IQC developed the Site Evaluation Report as its primary tool for the assessment of data quality. The SER contains objective performance measures common to all studies in order to provide consistent expectations and to allow for comparison across studies and over time. Its utility has been proven through its use in several studies and has recently been enhanced through the creation of a Web-based version. The Web-based SER newly created for Study 26 has proven to be a more efficient tool for providing QA data in real time. The Web site also provides a useful means by which sites can monitor their performance, as well as the performance of the consortium as a whole. Continued monitoring of the Web site by study staff, even during periods of peak performance, is important for the maintenance of desired site performance to study completion.

Real-time review of QA data via the Web site also provides consortium members and the Monitoring and Support Center with the opportunity to discover problems early enough so that they can be resolved. If data quality and site performance drop at the end of a study, the results will have little value beyond providing a cautionary example for future studies. Through its review of the Web site, the QA Review Group can compare site-to-site performance and assist with corrective action as needed. If all sites show deficiencies in a performance measure, the QA system allows for the re-evaluation of minimum goals or the handling of problems in study design or training.

The TBTC QA processes and tools have conceptual and practical value for other research groups. A commitment to QA and a framework conducive to QA program development are necessary components of any trial. The organizational structure must facilitate collaboration among study coordinators, protocol teams, the monitoring organization, and the data center/sponsor. The principal investigators must support the QA process as well. The QA process should

Table 3b
USPHS Study 26 Site Evaluation Report as presented on Web site: a selected performance measure for sites 22, 54, 63, and the consortium as a whole

No follow-up visit for >12 months in USPHS Study 26[a]			
As of 20MAR06			
Press F5 or click REFRESH to update			
Goal=<10%; Maximum=15%			
Site	Expected to have FP visit (*N*)	Not seen >12 months (*N*)	Not seen >12 Months (%)
22	228	3	1
54	112	7	6
63	302	5	2
TBTC total	4326	180	4

Abbreviations: FP=follow-up phase; TBTC=Tuberculosis Trials Consortium; TP=treatment phase.
[a] Patients who were ineligible, withdrew, or died in the TP or FP or who developed TB are excluded.

be readily accessible to all trial group members, and the TBTC has shown that a Web site can be especially conducive to this.

The Site Evaluation Report can be replicated by other research groups. The major performance measures are common to many clinical trials–not just those in the TBTC–and so they may be used repeatedly rather than developed anew for each individual study. Other research groups can establish their own numerical definitions for the performance measures. Determining the quality of site performance and providing that information to those conducting the study may facilitate quality improvement in clinical trials.

Acknowledgment

We thank Fred Gordin, MD, Network Principal Investigator for Community Programs for Clinical Research on AIDS and Chief of Infectious Diseases at the Veterans Administration Medical Center in Washington, D.C., for his inspiration and his contributions to the TBTC QA program.

Appendix A. TBTC studies using the QA process

1. USPHS Study 22, "Efficacy and Safety of Once Weekly Rifapentine and Isoniazid Compared to Twice Weekly Rifampin and Isoniazid in the Continuation Phase of Therapy for Pulmonary Tuberculosis"
2. USPHS Study 23, "Treatment of HIV-related Tuberculosis Using a Rifabutin-based Regimen"
3. USPHS Study 24, "A Noncomparative Study of the Efficacy of a Largely Intermittent, Six-Month Tuberculosis Treatment Regimen Among Patients Who Will Not Receive Isoniazid Due to the Presence of Initial Isoniazid Resistance or Intolerance"
4. USPHS Study 25, "Research on Higher Doses of Rifapentine in Active Tuberculosis"
5. USPHS Study 26, "A Study of the Effectiveness and Tolerability of Weekly Rifapentine/Isoniazid for Three Months versus Daily Isoniazid for Nine Months for the Treatment of Latent Tuberculosis Infection"
6. USPHS Study 27, "An Evaluation of the Activity and Tolerability of Moxifloxacin during the First Two Months of Treatment for Pulmonary Tuberculosis"
7. USPHS Study 28, "Evaluation of a Moxifloxacin-Based, Isoniazid-Sparing Regimen for Tuberculosis Treatment"

References

[1] Neaton JD, Duchene AG, Svendsen KH, Wentworth D. An examination of the efficiency of some quality assurance methods commonly employed in clinical trials. Stat Med 1990;9:115–24.
[2] International Conference on Harmonisation; Guideline for Good Clinical Practice. 62 Federal Register 25699 (1997).
[3] Knatterud GL, Rockhold FW, George SL, et al. Guidelines for quality assurance in multicenter trials: a position paper. Control Clin Trials 1998;19:477–93.
[4] Pogash RM, Boehmer SJ, Forand PE, Dyer AM, Kunselman SJ. Asthma Clinical Trials Network. Data management procedures in the Asthma Clinical Research Network. Control Clin Trials 2001;22(Suppl 6):168S–80S.
[5] Pollock BH. Quality assurance for interventions in clinical trials: multicenter data monitoring, data management, and analysis. Cancer 1994;74 (Suppl 9):2647–52.
[6] DeMets DL, Meinert CL. Data integrity. Control Clin Trials 1991;12:727–30.
[7] Weiss RB, Vogelzang NJ, Peterson BA, et al. A successful system of scientific data audits for clinical trials. A report from the Cancer and Leukemia Group B. JAMA 1993;270:459–64.
[8] Meinert CL. Clinical trials: design, conduct, and analysis. New York, NY: Oxford University Press; 1986. pp. 166–176.
[9] Campbell H, Sweatman J. Quality assurance and clinical data management. In: Rondel RK, Varley SA, Webb CF, editors. Clinical data management. Chichester, England: John Wiley and Sons; 2000. p. 123–41.
[10] Gluud C, Sorensen TI. New developments in the conduct and management of multi-center trials: an international review of clinical trial units. Fundam Clin Pharmacol 1995;9:284–9.
[11] Switula D. Principles of good clinical practice (GCP) in clinical research. Sci Eng Ethics 2000;6:71–7.
[12] Gassman JJ, Owen WW, Kuntz TE, Martin JP, Amoroso WP. Data quality assurance, monitoring, and reporting. Control Clin Trials 1995;16 (Suppl 2):104S–36S.
[13] Richardson D, Chen S. Data quality assurance and quality control measures in large multicenter stroke trials: the African-American Antiplatelet Stroke Prevention Study (AAASPS) experience. Curr Control Trials Cardiovasc Med 2001;2:115–7.
[14] Malmstrom K, Peszek I, Botto A, Lu S, Enright PL, Reiss TF. Quality assurance of asthma clinical trials. Control Clin Trials 2002;23: 143–156.
[15] Aird EG, Williams C, Mott GT, Dische S, Saunders MI. Quality assurance in the CHART clinical trial. Radiother Oncol 1995;36:235–44.

[16] Martin RJ, Kephart DK, Dyer AM, Fahy J, Kraft M. Asthma Clinical Trials Network. Quality control within the Asthma Clinical Research Network. Control Clin Trials 2001;22(Suppl 6):207S–21S.
[17] Warden D, Rush AJ, Trivedi M, Ritz L, Stegman D, Wisniewski SR. Quality improvement methods as applied to a multicenter effectiveness trial-STAR*D. Contemp Clin Trials 2005;26:95–112.
[18] Rouff J, Child C. Application of quality improvement theory and process in a national multicenter HIV/AIDS clinical trials network. Qual Manag Health Care, vol. 12. 351 West Camden Street, Baltimore Maryland 21201 United States of America: Lippincott Williams & Wilkins; 2003. pp. 89–96.
[19] Sandman L, Khan A, Mosher A, et al. Data quality assurance in the TB Trials Consortium: a partnership approach. Poster presented at: Society for Clinical Trials International Conference; May 2002. Arlington, Va.