Quality is a multidimensional concept, which could relate to the design, conduct, and analysis of a trial, its clinical relevance, or quality of reporting. The basic essence of quality systems is quite simple: say what you do, do what you say, prove it and improve it.

According to ISO 9000, quality is a set of characteristics that a product or service must have in order to satisfy the needs and expectations of the customer. In clinical trials, the product obtained as the end result of the process is information. Quality in clinical trials may then be defined as obtaining reliable and credible information that provides an answer to a scientific question through a clinical trial process that complies with requirements.

In clinical research, customers include research subjects, hospitals/institutions and ethics committees, regulatory authorities, society/consumers, and sponsors. These customers require clinical trials to be conducted in compliance with ethical standards (Declaration of Helsinki, Belmont Report), laws and regulations (EU directives, US CFR, local legislation), and good practice standards (GXP — GCP, GMP, GLP).

Quality in clinical trials is of utmost importance in ensuring that the rights and wellbeing of human participants are protected and in achieving scientific objectives. The validity of the findings generated by a study is an important dimension of quality. Internal validity implies that the difference observed between groups of patients allocated to different interventions may, apart from random error, be attributed to the treatment under investigation. In contrast, external validity, or generalizability, is the extent to which the results of a study provide a correct basis for generalizations to other circumstances. Internal validity is a prerequisite for external validity. Internal validity is...
threatened by bias, which in clinical trials can fall into four categories: selection bias, biased allocation to comparison groups; performance bias, unequal provision of care apart from treatment under evaluation; detection bias, biased assessment of outcome; and attrition bias, biased occurrence and handling of deviations from protocol and loss to follow-up\(^2\). These biases can cause distortion in the results of clinical trials.

As referred to previously, the main purpose of a clinical trial is to collect data that enables testing of the study hypothesis and achievement of the study objectives. The study protocol provides a statement of the problem, study objectives, research questions, and hypotheses. Key components of a protocol are the same for single- and multi-center clinical studies. It is essential that study investigators and clinical centers follow and adhere to an approved, common protocol to assure that data collected can be aggregated for analysis and interpretation. The data collection and data management processes are as important in achieving the study objectives as having a scientifically sound study design and protocol. To assist in preventing problems with data quality, standard research methodology must be incorporated into the clinical trials.

Generic documents that help to ensure quality in a clinical research environment include SOPs. These, together with policies and guidelines, describe standards/customer requirements that will be complied with and how they will be implemented in core activities within the clinical research process — the “everyday work.” Trial-related instructions, protocols, CRFs, etc. are usually provided by the sponsor or developed by a central study team. The research site needs to have its own procedures for management of the various processes. There should be clear instructions on what should be done, when, and by whom, as well as specifications of required inputs and outputs. Change management should also be facilitated for easy update and review when the requirements change. Quality control (QC) procedures — the operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled — need to be applied to every step of the clinical trial process and each stage of data handling so as to ensure compliance with the trial process and reliability and credibility of the data.

Training tools are essential to maintain consistency of work and achieve quality objectives. This should be conducted for sponsor and site personnel, and such training should be documented to provide evidence of training and qualification. Certification programs to educate staff on the conduct of high-quality research are essential. Formal training sessions for investigators, site coordinators, and other staff (as necessary) are held to review the study goals and procedures and the study forms, and often include a certification process. This is to ensure that the protocol is applied in a standardized manner across sites.

Data used to make decisions in clinical trials must be accurate, as decisions about dosages, risks of adverse events, and risk–benefit profiles of the treatments are made using these data. Major resources are expended to check and correct the data prior to any analysis. This includes source data verification, logical and consistency checks, and looking for outliers. This checking is very expensive and time consuming. Similarly, resources are allocated to assure the quality of computer systems so that the data will not be compromised by the systems processing the data. This detailed checking includes a detailed software development life cycle for software developed in-house, vendor evaluation, and installation and operational qualification for purchased software. The combined effort for the data checking and computer systems validation is indeed huge.
High quality standards for data are needed for global decision making in regulated industries, especially with the realization of dynamic data. Increasing emphasis is placed on the procedure to eliminate errors primarily from the point of database entry to the extraction of data from the database. Data quality has been defined as "data that support conclusions and interpretations equivalent to those derived from error free data." This can be separated into two types: inherent quality, "correctness or accuracy of data"; and pragmatic quality, "the value that accurate data has in supporting the work of the enterprise." ICH E2B established some electronic storage standards, while CDISC established standards for data transfer. GCDMP began the definition of standard processes, providing the link between regulatory guidance and data quality management practice.

While computer systems can collect, edit, store, and report data, the study team comprising investigators, data management specialists, and statisticians must identify and routinely prepare reports that describe study progress and issues. These reports, presented to data-monitoring or steering committees, can provide alerts to potential problems before they compromise the study. Thus, the preparation of reports and procedures for ongoing data review and site monitoring form a quality control plan. Documentation and plans for review of study systems and analysis are also part of a study's quality control plan.

Appropriate standards also positively impact quality. The ISO provides a set of standards that can be applied to various areas in clinical research. In addition, the CDISC has developed data exchange standards for use in clinical research.

The use of standardized terminology is essential for consistency and interpretation of reported events. The MedDRA, developed under the auspices of ICH, is a new international medical terminology that is particularly important in the electronic transmission of adverse event reporting, both in the premarketing and postmarketing areas as well as for the coding of clinical trial data.

Quality assurance (QA) has been defined as all those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented, and reported in compliance with GCP and the applicable regulatory requirements. The objectives of QA procedures are to assure the accuracy and consistency of study data from the original observations through the reporting of results, and to ensure that study results are considered valid and credible within the scientific and clinical communities. Procedures must be in place to prevent, detect, and correct data quality and integrity problems. This is part of the continuous quality improvement loop.

In clinical research, independent audits of all trial-related processes and functions should be performed by QA functions not involved in the research process. This is to assess the efficiency of the QC processes. QA audits can be trial- or project-specific, or system audits where a selected process plus all related activities, resources, organization, documents, facilities, and equipment are reviewed (e.g. data management, pharmacovigilance).

Besides incorporating quality in the design, conduct, and analysis of clinical trials, quality in the reporting of clinical trials is also essential for correct interpretation and use of the results. The CONSORT statement, comprising a checklist and flowchart, is intended to improve the reporting of a randomized clinical trial, enabling readers to understand a trial’s conduct and to assess the validity of its results.
In conclusion, quality is not an option, but a basic requirement in clinical research. In fact, one may say that research conducted without quality is unethical, as it jeopardizes the wellbeing of the clinical trial participants and, ultimately, consumers. Adequate resources must be invested to ensure that the quality requirements are met, especially where the risk is more than minimal. Data obtained from research that has not implemented quality standards are both unreliable and dangerous.

**Abbreviations**


**References**


**Contact Details:**

Contact Person: Dr Shirley Suresh,
Operations Manager

Address: SGS Life Science Services, Clinical Research,
c/o SGS Testing & Control Services
Singapore Pte Ltd,
26 Ayer Rajah Crescent #03-07,
Singapore 139944

Tel: +65 6778 1550
Fax: +65 7669 0527
Email: Shirley.Suresh@sgs.com