

American Society of Clinical Oncology Statement on Minimum Standards and Exemplary Attributes of Clinical Trial Sites

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A B S T R A C T

Purpose

To describe both minimum requirements for a site conducting quality clinical trials and attributes of an exemplary site.

Methods

Minimum requirements and exemplary attributes were selected based on literature review, prevailing regulatory requirements, and consensus among a group of community and academic clinical researchers.

Results

To provide guidance to oncologists who wish to conduct patient-oriented research, recommendations are made to assist in the development and implementation of high-quality research programs with the priority of protecting the welfare and rights of trial participants. A quality research site complies with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, the accepted international ethical and scientific quality standards for designing, conducting, recording, and reporting trials involving human participants. Recognizing that many research sites conduct clinical trials in compliance with accepted GCP standards, supplemental attributes of an exemplary research site that exceed the GCP criteria are also described. These attributes include diversification of clinical trial mix, high accrual activity, participation in the trial development process, maintenance of high educational standards, quality assurance, multidisciplinary involvement in the clinical trial process, and promotion of clinical trial awareness programs.

Conclusion

Meeting the minimum criteria ensures conduct of quality clinical trials; however, some sites may wish to incorporate value-added attributes to exceed GCP compliance. These attributes are proposed as performance goals rather than requirements, recognizing that all sites conducting research will not necessarily meet each attribute but may still conduct high-quality clinical trials.

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INTRODUCTION

It is estimated that more than 1.4 million cases of cancer will be diagnosed in the United States in 2007 and that nearly 560,000 people will die from these diseases.¹ Despite improvements in early detection and treatment, only modest gains have been achieved in cancer mortality since the first annual decrease was noted in 1993.² Successful development of new cancer therapies requires translation of laboratory observations into the clinic, with clinical trials representing the application of the scientific method to this process. Patient advocacy groups and professional oncology organizations encourage participation in clinical trials as a routine component of patient care^{3,4}; however, only 2% to 7% of cancer patients participate.⁵⁻⁷ Survey data suggest that the public, in general, and

cancer patients, in particular, have a low level of awareness about clinical trials as a treatment option.⁸ In a nationwide survey of approximately 1,000 adults, 40% did not fully understand the concept of a clinical trial. Furthermore, among cancer patients, 80% did not consider the possibility of participating in a treatment clinical trial because they were unaware that this was an option.⁹ Although more recent data indicate that awareness is improving, clinical trial participation rates have not yet increased, suggesting that other key barriers play a role. Practical barriers to participation in clinical trials have been widely investigated and include insurance coverage, logistics, study availability, and strict eligibility criteria. Psychosocial barriers may also exist, including lack of knowledge and negative patient or physician beliefs and attitudes about clinical trials.^{10,11}

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Approximately 85% of cancer patients are treated in the community setting rather than at academic medical centers.¹² Thus, concerns have been raised regarding the dissemination and applicability of results obtained in the highly selected populations that take part in research at academic medical centers. Efforts to improve clinical trial participation rates must address issues relevant to community oncology practice. It is notable that community oncologists play a significant role in accrual to National Cancer Institute (NCI)–sponsored studies through the Cooperative Group Program. Approximately half of accruals to cooperative group trials are made in the community setting (48.4% across all trials and 52.6% for adult trials).¹³ Community oncologists choose to participate in clinical trials to expand treatment options for their patients, offer cutting edge therapies, and gain a competitive market advantage. Well-designed clinical trials offer the opportunity for state-of-the-art medical care to research participants, with costs to the participants that are similar to or only minimally increased above those for standard treatment.¹⁴

Implementing a clinical trial program is challenging in any practice venue. Some oncologists may not know how to establish a clinical trial infrastructure or assess the quality of their current program. To provide guidance to oncologists, this article provides guidelines that clinical sites can use for developing and implementing high-quality clinical trial programs.

First and foremost, a quality clinical trial research site must protect the welfare and rights of all trial participants. In addition, a quality clinical trial site needs to assure that the research data generated are valid and can be used to draw reliable conclusions about study outcomes, thereby ensuring benefits to current and future patients. A quality clinical trial research site is one that is compliant with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, the accepted international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, well-being, and confidentiality of those participating in clinical trials are protected and that the results of the clinical trial are valid. Recognizing that many research sites conduct clinical trials in compliance with accepted GCP standards, this article also proposes supplemental attributes of an exemplary research site, which exceed the minimum and necessary GCP criteria.

The NCI Clinical Trials Working Group recommended a credentialing system for clinical research sites.¹⁵ Rather than establishing criteria for certification, the American Society of Clinical Oncology (ASCO) determined that its membership could benefit from a statement describing the attributes of an exemplary clinical trial site. At the request of ASCO leadership, ASCO's Cancer Research Committee formed a subcommittee comprised of community and academic clinical researchers to develop this statement. The subcommittee selected exemplary attributes based on literature review and discussion; the Cancer Research Committee and ASCO Board of Directors then reviewed and accepted this statement. These attributes are proposed as performance goals for sites rather than requirements. In particular, we acknowledge that the integration of clinical trials in the community practice setting may be characterized by different challenges and limitations than are faced in academic medical centers. As such, the goals and benchmarks described will likely differ by practice setting, and sites need not necessarily fulfill all of the attributes outlined to conduct clinical trials in an exemplary fashion.

History of Ethical Guidelines for Clinical Research

In the aftermath of World War II, the importance of establishing a comprehensive code of ethical principles to guide physicians and scientists in conducting humane human subject research was recognized. This led to the development of various codes and guidance documents that set forth ethical standards and principles for the conduct of such research. The first document, the Nuremberg Code of 1947,¹⁶ which was developed in the wake of the Nuremberg War Crimes Trial, set forth the standards for conducting ethical and humane research with human participants. Subsequently, the World Medical Association initiated discussions regarding the need to regulate clinical research involving humans. These discussions ultimately led to an international agreement addressing ethical issues in the conduct of clinical trials entitled "Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects." This agreement was adopted in June 1964 by the 18th World Medical Assembly in Helsinki, Finland, and has since been referred to as the Declaration of Helsinki.¹⁷ The Declaration of Helsinki covers the rights of patients and defines clearly the requirement for fully informed consent from the patient. The declaration emphasizes the patient's right to withdraw at any time from participation in the research project and that refusal to participate in the trial should not affect the patient's future treatment or have any negative effect on the patient's relationship with the physician. The principles of this declaration were also incorporated into the 1971 guidelines issued by the US Department of Health, Education and Welfare (now the Department of Health and Human Services) for the conduct of social and behavioral research (codified into federal regulations in 1974 under Title 45 Code of Federal Regulations [CFR] 46).¹⁸ In 1938, the United States developed the CFR, with Title 21 Chapter 1 reserved for rules for the US Food and Drug Administration (FDA).¹⁹ GCP is addressed in 21 CFR Parts 11, 50, 54, 56, 312, 314, 601, 812 and 814 of Chapter 1.²⁰

GCP

Performing a clinical trial at multiple sites facilitates rapid accrual but requires rigorous standards and quality checks to minimize variations in performance and data quality that could impact the accuracy of the study results. These rigorous standards provide assurance that the study results are credible and accurate and, most importantly, that the rights, integrity, and confidentiality of trial participants are protected. To that end, federal regulations, commonly referred to as GCP, have been adopted that define a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials. GCP is not defined within a single document but is the term originally coined by the pharmaceutical industry to encompass all the federal regulations and other accepted practice standards that govern the conduct of clinical research on humans (Appendix Table A1, online only).

The responsibility for compliance with the regulations that comprise GCP standards is shared among the trial sponsor, investigator(s), and institution(s) engaged in the conduct of the study. Each should be fully aware of its respective responsibilities and ensure that systems are in place to meet them.

Depending on factors such as the source of funding, the sponsor, and whether the trial includes an FDA-regulated test article, research

with human participants can fall under various sets of regulations. For example, clinical trials generally have to comply with FDA regulatory requirements codified in 21 CFR. Research involving an investigational drug or device that is partially funded by the National Institutes of Health must also meet NIH regulatory requirements in 45 CFR. In addition, if the study is being performed with a multinational pharmaceutical company, then the sponsor may require that the trial be conducted in compliance with the ICH GCP.

ICH GCP

The ICH was originally convened in 1990 as a joint initiative between industry, academia, and various ministries of health throughout the world. The three regions that participated were the United States, the European Union, and Japan. The key objective, or mission, of the ICH was to discuss and define the minimum standards for the development and registration of investigational products, including both drugs and devices. The current version of the ICH GCP guidance (E6) was finalized and implemented in January 1997 (Appendix Tables A2 and A3, online only). ICH GCP is now the recognized international standard for the conduct of clinical trials. Trials conducted in compliance with ICH GCP facilitate global acceptance of trial data for international marketing applications of pharmaceutical companies.

The FDA formally adopted as one of its guidance documents the ICH E6 GCP guideline. When it released the document in 1997, the FDA indicated that the ICH GCP guideline represented the agency's current thinking on GCPs and was consistent with the agency's existing GCP regulations/guidances. However, the ICH GCP guideline is more specific than FDA and Department of Health and Human Services regulations/guidances in several areas and provides additional standards to ensure data quality and patient protection related to institutional review boards (IRBs). As an example, only ICH GCP guideline explicitly lists the essential documents required to be on file before, during, and after a clinical trial. ICH GCP guideline also details a list of documents the investigator should provide to the IRB.

Although there remain selective differences among the various sets of regulations/guidances, for the most part, these documents are quite similar, with small differences that should not affect the conduct of research at an institution. Over time, the differences in emphasis and specificity between the FDA GCP standards and the ICH GCP guideline should become less evident as the FDA continues to incorporate ICH guidelines when developing new regulations or revising its existing regulations and guidance. Because FDA officials have stated that clinical studies conducted in compliance with ICH GCP standards ensure compliance with FDA regulations, it would be prudent for research sites to adopt the ICH GCP standards for their clinical research programs. For industry-sponsored trials conducted in the United States using ICH GCP standards, the FDA may conduct inspections of investigative sites to ensure adherence to the FDA GCP regulations and guidances, to determine the validity of data from studies used to support marketing applications, and to determine that the rights and welfare of study participants have been protected.

Standard Operating Procedures

Because the GCP guidelines are comprehensive and complex, standard operating procedures (SOPs) are often required by study sponsors. The SOPs function as detailed written instructions to

achieve uniformity in the performance of a specific function. Although SOPs are strongly recommended by the FDA, they are currently not mandatory. From the industry perspective, SOPs not only demonstrate a site's understanding of the regulations and its compliance intentions, but they also provide a mechanism for consistency in continued quality performance and protection of participants' rights in the event of changes in personnel or leadership. SOPs generally address process flow for daily activities, define staff responsibilities, serve as a training tool for new staff, and guide the audit process. Suggested topics for SOPs are included in Table 1. Templates have been developed for purchase that can be easily adapted to a site's particular needs and requirements. These templates concentrate on the activities necessary to conduct the study in compliance with the protocol and reference the applicable regulations and guidelines for both the ICH and federal GCP.

In conclusion, although the ICH GCP is complex, dynamic, and subject to interpretation, compliance with GCP assures compliance with regulations as set forth by the FDA and ICH. As such, all clinical trial research involving human participants should minimally fulfill these standards. In addition, the Department of Health and Human Services Office for Human Research Protections and ASCO strongly recommend that all investigators obtain human subjects training as part of the minimum criteria. Such training is mandatory for investigators who conduct federally funded studies.

PART II: REACHING BEYOND THE MINIMUM—THE EXEMPLARY CLINICAL TRIAL SITE

Meeting the minimum criteria is necessary to conduct quality clinical trials; however, some sites may wish to incorporate additional performance goals to exceed GCP compliance. Among the important

Table 1. Suggested SOP Topics

Preparation and maintenance of SOPs; training on SOPs
Adverse event reporting
Clinical study operations
Managing clinical study supplies
Communication documents
Coordinator selection, qualification, responsibilities, and training
Data management
Informed consent
Investigator agreements
Investigator and subinvestigator selection, qualifications, responsibilities, and training
IRB approval and operations for clinical studies
Prestudy requirements
Protocol handling, review of feasibility, and approval
Quality control
Recruitment methods
Regulatory documentation
Sponsor interactions
Close-out study activities
Study confidentiality
Drug accountability and storage
Chart storage
Scientific misconduct policies and procedures
Abbreviations: SOP, standard operating procedure; IRB, institutional review board.

attributes of an exemplary clinical trial site are the following: diversification of the clinical trial mix; high accrual activity; participation in the clinical trial development process; maintenance of high educational standards; quality assurance; multidisciplinary involvement in the clinical trial process; and promotion of clinical trial awareness programs. This list of attributes is not meant to be exhaustive; additionally, fulfillment of each criterion is not necessary for a particular site to achieve excellence in the clinical trials enterprise. Rather, our goal is to provide a palate of characteristics for consideration by those clinical trials sites wishing to exceed minimum and necessary requirements. Sites should review and implement these characteristics in the context of their particular demographics (eg, size, patient mix, practice setting), resources, and goals. Practice- or institution-based infrastructure devoted to integrating all aspects of the research enterprise can help facilitate achievement of exemplary attributes.

Diversification of Clinical Trial Mix

Established clinical trial sites may wish to diversify the types of clinical trials offered to provide the broadest array of options for patients treated and to maximally use their clinical research infrastructure and resources. A site's trial mix could include treatment, prevention, quality of life, symptom control, and biologic correlative trials.

Treatment trials offered may include phase I to III trials, as appropriate, and efforts should be made to develop a clinical trial portfolio that meets the diverse needs of the population served by the practice. Because patients who are willing to participate in a treatment trial often have a heightened awareness of the importance of clinical trials, they may be candidates for simultaneous enrollment onto symptom control, quality of life, and biologic correlative trials. In cases where individuals elect not to enroll onto a treatment trial, these same individuals may still choose to enroll onto a symptom control or laboratory science trial. There is increasing recognition of the importance of correlative studies involving blood and other tissues. The NCI has developed a useful resource document for sites that outlines the best practices for biospecimen collection.²¹ Whereas the infrastructure requirements for phase I clinical trials and biospecimen collection may not be feasible in many community practices, this setting may be more conducive to other types of investigation (eg, phase III treatment or prevention studies).

A unique opportunity can be made available for family members of individuals diagnosed with a malignancy to also participate in the clinical trial process; for example, risk assessment and prevention trials can be offered. Scenarios such as these demonstrate how diversification can assist a research site in maximally using the existing resources and infrastructure while successfully improving accrual and addressing the needs of the community.

High Accrual Activity

One goal of an exemplary clinical research site should be to demonstrate the highest accrual activity possible for the area demographics within which the site practices. Ideally, an exemplary clinical trial site would accrue at least 10% of its patients on clinical trials. However, each site should establish its own benchmark based on a critical analysis of its patient volume, patient mix, and available clinical trials. Furthermore, ongoing assessment of progress and goals is encouraged. Recognizing that there are sites where demographics allow for potential accrual of under-represented populations, it would be appropriate for such sites to assess and improve current methods for

engaging these populations. Timely activation of a trial can help maximize accrual, optimize access for patients, and reduce time to study completion and analysis. Working closely with the scientific review committee and IRB locally and using central IRBs when appropriate can facilitate efficient study initiation.

Participation in the Clinical Trial Process

Active collaboration between the community practice, an affiliated academic center, and the trial sponsor can be instrumental in the development and implementation of clinical trials. Such involvement offers a venue for investigators and research support staff to provide scientific input, communicate concerns, assess resources, and address the practical aspects of conducting the trial at the community and academic sites, thus contributing to the successful implementation of the clinical trial. Examples of these activities include attendance at research meetings of the trial sponsors, developing and authoring a protocol, assuming leadership roles such as serving as the local principal investigator or coinvestigator for a trial, and volunteering as an active member on trial sponsor boards and committees.

Formal Maintenance of High Educational Standards

ASCO recommends that all US investigators be specialty board certified. Recognizing that international investigators may not have board certification as an option, it is suggested that certification should be obtained when available. GCP requires that research support staff be adequately qualified by education and training for the research-related functions they have been authorized to perform by the investigator. Certification of clinical research associates and coordinators provides evidence of their qualifications to serve in this capacity and is preferred but currently not mandated by the GCP regulations. Continuing education for investigators and research staff should be performed by exemplary sites. Many physician investigators may not have received formal training regarding the regulatory issues governing the conduct of clinical research. Although GCP standards recognize that investigators may, and should, delegate a number of their responsibilities to qualified support staff, the investigators remain ultimately responsible for the conduct of the study and must demonstrate adequate supervision of their staff. Organizations such as the Society of Clinical Research Associates and the Association of Clinical Research Professionals offer classes that prepare the clinical research staff and investigator to conduct the highest level of research from a regulatory standpoint. In addition to ensuring high educational standards, providing staff with protected time dedicated to research activities can help ensure exemplary performance.

Quality Assurance

Research sites that internally implement quality assurance programs ensure adherence to GCP guidelines and the consistent generation of high-quality data. Quality assurance programs include routine self-audits, modification of existing SOPs or implementation of new SOPs for issues identified during the internal quality assurance process, recording of minor and major violations, and implementation of programs of corrective action. Exemplary clinical trial sites should also undergo periodic external audits to document and enhance the quality of their research enterprise.

As clinical sites implement information technology such as electronic health records (EHR), there will be an opportunity to select systems that facilitate the high-quality conduct of clinical trials by

assuring accurate and timely data collection and audit activities. An electronic repository of current consent forms and updated protocols will help ensure that investigators at multiple sites within a research entity are accessing the most accurate information. Searching EHRs for potentially eligible patients can be performed by entering specific search terms, and digitized radiology studies can be archived for confirmation of response at the time of audit. The NCI has initiated a process to standardize case report forms that can be electronically submitted to research sponsors.²² Ideally, required data elements such as laboratory values and dates and chemotherapy doses can be transferred from the EHR directly into the case report form fields.

Although not considered an educational standard, it is an essential responsibility of the principal investigator to interact with the IRB. Possessing a basic understanding of the responsibilities and procedures of the local IRB, as well as the IRB's SOPs, is recommended to improve a site's ability to interact and work with the IRB.

Multidisciplinary Involvement

Multidisciplinary involvement of both specialty physicians and nonphysicians is desirable within any research setting. Increasing the breadth of expertise at a research site may permit an increase in the scope and complexity of clinical trials that can be offered, ideally resulting in higher accrual at a particular site. The ability to increase practitioner participation depends on area resources. In addition to medical oncology, physician disciplines to be considered as investigators include radiation oncology, surgery and its subspecialties, pathology, radiology, and primary care physicians. Although multimodality studies clearly require the coordination of several subspecialties, single-modality trials also may benefit from efforts at coordination and involvement with other specialties (eg, adjuvant treatment studies) for patient recruitment or follow-up. Although primary care physicians do not prescribe cancer therapies, they may contribute as champions for cancer prevention trials or survivorship studies. Other health professionals who may contribute to cancer research include clinical pharmacists, psychologists, clinical research coordinators, and nurses, all of whom could potentially contribute in the areas of cancer control research and patient recruitment, as well as cancer treatment.

Clinical Trial Awareness Programs

Clinical trial success depends on accrual; therefore a value-added element that a research site may consider is implementing a program to increase awareness in both the lay and physician communities. If potential participants and physicians do not know trials are available, then accrual will be slow. There are a number of ways to increase awareness; however, community, institutional, and individual practice resources may dictate the extent of marketing efforts to facilitate participation. Plans to increase awareness may include educational programs directed toward the public and physicians, with emphasis on including minorities and underserved populations. Participation in local health fairs and cancer screening events provides additional opportunities for educating the public. Many avenues and resources for raising awareness currently exist that a site could easily integrate into a planned program. Examples of Internet-based resources are listed in Table 2. Ideally, the program would undergo periodic review and adapt to the changing needs of the site and the community. Sites may also wish to involve patient advocacy groups by either creating a community advocacy board or including a patient advocate on the protocol review committee.

Limitations

This document represents a consensus based on literature review and the experiences of clinical trials and regulatory experts from academia, community practice, and industry. The list of exemplary attributes provided is not meant to be exhaustive, and it is recognized that it may appropriately evolve over time. Ideally, a proposal of exemplary attributes would include metrics of success based on relevant outcome data. In the case of clinical trials conduct, these types of data do not currently exist for the characteristics that we outline herein. This description of the features of an exemplary clinical trial site is intended as an initial guide for planning of a clinical trials enterprise and for designing an individualized self-evaluation process. ASCO is exploring development of tools to assist with this self-assessment. It is hoped that further research will help clarify appropriate metrics of success that will ultimately facilitate the achievement of excellence by those wishing to conduct cancer clinical trials. In addition, ASCO is developing resources to assist oncologists in the integration of these attributes into their practices.

Table 2. Examples of Web-Based Resources for Creating Clinical Trial Awareness Programs

Name	Description	Web Address
National Cancer Institute	Provides education materials describing what clinical trials are, how they work, why they are useful, patient care costs, and more	www.cancer.gov/clinicaltrials/learning
People Living with Cancer	Oncologist-approved information for cancer patients developed by ASCO and The ASCO Foundation	www.plwc.org —click on “Diagnosis and Treatment”; clinical trials information is found under “Treating Cancer”
Coalition of Cancer Cooperative Groups	Provides information about clinical trials for patients and the medical community, including an interactive educational program	www.cancertrials-help.org/patientsCaregivers/aboutClinTrials.jsp
American Cancer Society	Patient-centered information on clinical trials, including what they are, why they are important, potential benefits, questions to ask a physician, and how to find a clinical trial.	www.cancer.org/docroot/ETO/ETO_6.asp

Abbreviation: ASCO, American Society of Clinical Oncology.

CONCLUSION

ASCO has historically been committed to providing oncologists with the resources necessary to ensure that all patients receive the highest level of cancer care, and clinical research has, and continues to be, a priority for ASCO. The ASCO Clinical Trials Workshop (www.asco.org/ctw), which is designed to assist community oncologists in successfully implementing clinical trials into community practice, is an example of a program initiative to provide such resources.

Conducting clinical investigation in oncology is an integral part of the professional activities of oncologists and serves the mission of improving the survival and quality of life for cancer patients. All quality clinical trial sites will adhere to the ICH GCP guidelines. ASCO describes herein characteristics of exemplary sites that could contribute to improved accrual and assist in maximizing the opportunities for patients and research staff to participate in the clinical trials process.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).