ABOUT THE AUTHORS

LEAD AUTHOR

Anna J. DeMarinis, M.A. MT (ASCP) SBB, CQA (ASQ) is Director of Regulatory Affairs for the New England Institutional Review Board and the Center for Clinical Research Practice. She has 27 years of experience in education, training and auditing, most notably within the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) and the Health Industry Manufacturers Association (HIMA). She is a Certified Quality Auditor and is a graduate of George Washington University and has a Master's Degree in Health Care Education from Central Michigan University. She has significant regulatory expertise in the areas of investigational drugs and biologics, blood transfusions, and devices. She has over 10 years of experience in medical education and has a current teaching appointment at Northeastern University.

CONTRIBUTING AUTHORS

Carol Saunders, RN, BSN is President and CEO of the Center for Clinical Research Practice (CCRP), a corporation that produces and publishes educational and management resources for institutions, sponsors and clinical research professionals. She is the Executive Director of the New England Institutional Review Board, which provides ethical review services for sponsors and investigators of drug and device studies. Coeditor of Research Practitioner, she has published extensively and lectured on a broad range of research-related topics and has been recognized for excellence in medical communications by the American Medical Writers Association. She has co-authored several textbooks on clinical research and human subject protection, including standard operating procedures for investigative sites, sponsors and sponsor-investigators. She served as an expert advisor on the Institute of Medicine’s Committee on Assessing the System for Protecting Human Research Subjects.
Herbert Swarz, M.D. is an internist who began his career in the pharmaceutical industry in Pfizer where he worked on a number of clinical research programs in the International and domestic divisions for almost 20 years. After retiring from Pfizer eleven years ago, he founded a small and focused consulting company, International Pharmaceutical Consultants, Inc. located in Scarsdale, NY. During his career in the industry, he has lectured on the regulatory and clinical aspects of INDs, NDAs, and protocol writing and has worked on a number of INDs and drug development projects, in a variety of therapeutic areas that have led to successful NDAs. He approaches the writing and editing of Standard Operating Procedures (SOPs) from the practical clinical point of view and has written SOPs for large international and small start-up pharmaceutical companies. Based on his extensive background in clinical research, he has a fundamental knowledge and understanding of the need for SOPs to plan, monitor, implement, and successfully conduct clinical research.
INTRODUCTION

Clinical research has grown over the last fifty years from an Investigator-driven, informal activity to a multi-billion dollar global business, intensely regulated and controlled by the federal government. Biomedical research requires specialized knowledge, which includes regulatory requirements, Good Clinical Practice (GCP), and medical ethics. Failure to understand the intricacies of conducting clinical trials may lead to serious errors in implementation of a study and compromise the ensuing data. The interpretation of the intervention effects may be flawed and therefore, unacceptable to regulatory authorities.

While Food and Drug Administration (FDA) regulations define the fundamentals of GCP, there are numerous other guidelines and codes that also dictate standards in the conduct of clinical research. For example, the Nuremberg Code serves as the basis for the protection of human subjects. When combined, these concepts serve as the gold standard in the practice of clinical research.

In recent years, international GCP standards have emerged in an effort to harmonize research efforts, reduce waste, and expedite approval. The United States, European Union, and Japan have joined forces at the International Conference on Harmonisation (ICH) to develop global standards for the conduct of clinical research. The purpose of ICH is to facilitate mutual acceptance of data submitted in support of drug marketing applications. Their GCP guideline (E6) has been adopted by industry and academia worldwide. With all countries conducting research according to the same standards, duplication of effort and resources should be minimized.

GCP is defined as, “A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.” This definition accurately captures the whole of GCP, both data integrity and subject protection, and specifies areas of trial implementation that directly affect GCP.

Recently, FDA and other federal regulatory authorities have halted research activities at a dozen major academic institutions and a VA Medical Center due to non-compliance with regulations involving data integrity, protection of human subjects and conflicts of interest. The clinical research enterprise will never escape from regulation. It is the responsibility of the Sponsor, the Investigator and their institutions to establish an institutional culture where studies are conducted in an ethical and scientifically rigorous manner and where safeguards to subjects who participate in clinical studies are of paramount importance. The first step in establishing an institutional culture of research excellence is through the establishment of operational policies and standard operating procedures that address the regulatory requirements, ethical conduct and sound implementation of all research conducted on human subjects.
The first step in establishing an institutional culture of research excellence is through the establishment of operational policies and standard operating procedures (SOP) that address the regulatory requirements, ethical conduct and sound implementation of all research conducted by investigators and staff employed or contracted by the institution.

The organization of this SOP Manual is intended to group together related activities and/or concepts. Further, each individual SOP is numbered with the group abbreviation and a sequential number, to facilitate categorizing the particular SOP.

The first section, General Administration (GA) includes sections on the Sponsor’s responsibilities (GA 101), the development of other important clinical research documents (GA 102), training (GA 103), financial disclosure (GA 104) and vendor selection (GA 105). These activities form the infrastructure of a clinical research program.

The second section, Regulatory Affairs (RA), addresses regulatory contacts with FDA and certain submissions to that agency (RA 201) and required regulatory reports to FDA, such as periodic progress, final and safety reports (RA 202). The section also includes an SOP on submissions and reports to the NIH Office of Biotechnology Activities (RA 203), for gene transfer research programs subject to that agency’s oversight.

The third section, Protocol Development (PD), includes SOP on writing clinical protocols and case report forms (PD 301), and creating the documents that FDA requires to inform Investigators about the research they intend to perform on behalf of a Sponsor, such as the Investigator Brochure (PD 302) and comparable investigational medical device documents (PD 303).

The fourth section, Study Start-up (SS), describes how potential Investigators are identified and selected (SS 401), and then trained to begin their clinical investigations (SS 402).

The fifth section, Project Management (PM), addresses the main activities during the conduct of a clinical study. These activities include the conduct and recording of communications (PM 501), the management of the investigational products (PM 502), study document and records maintenance (PM 503), study monitoring (PM 504) and the closing of a study, either because desired enrollment has been achieved, or the site is being suspended or terminated for some reason (PM 505).

The sixth section, Subject Management (SM), addresses issues related to the research subject, including IRB requirements and the informed consent process (SM 601), recruitment practices (SM 602), screening and enrollment of potential research subjects (SM 603), managing collected biological specimens (SM 604),
reporting adverse events (SM 605) and protecting personal health information (SM 606).

The seventh section, Data Management (DM), focuses on the data that are captured during the conduct of a clinical study. An SOP on the routine handling of those clinical data (DM 701) is provided and is accompanied by a companion SOP that addresses compliance with FDA’s regulation on electronic records and electronic signatures (DM 702).

The eighth and final section, Quality Assurance (QA), provides SOP on the conduct of internal and third party audits (QA 801) as well as how to manage an FDA inspection (QA 802).

Finally, this SOP Manual contains an extensive library of attachments, which include narrative guidelines, checklists, logs and other forms. These tools are not required (with just a few exceptions), but are available as a resource. The attachments may be used as is, modified or adapted as needed, or simply replaced with forms that have been developed previously and are already being used. The sole exceptions are certain template forms (e.g., SOP template), which are to be used as written.

In conclusion, this SOP Manual is the starting line in establishing the institutional culture of research excellence, and not the finish line. These SOP must be read, understood and used by all staff for an appropriate period of time. After this “shake-out” period, the SOP Manual should be assessed, adapted and improved as experience dictates. Thereafter, periodic review and updating will ensure this SOP Manual remains a living, useful document, and not a placeholder on a shelf, gathering dust.