Chapter 2
Clinical Trials: Ensuring Quality and Standardization

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2.1 Introduction

Clinical equipoise regarding the best surgical or medical options for a particular illness is widespread in this innovative century and helps drive the hypotheses for clinical trials and in doing so advances in evidence-based medicine. Adherence to regulations and standardized processes within a clinical trial, the focus of this chapter, offers the best means to provide a balance between scientific progress and patient safety. With uncontrolled or nonstandardized clinical trial design and implementation, it is difficult to determine if a new treatment, surgical procedure, device, or drug has made a difference in a human disease or put those who volunteered for the clinical trial at risk for complications and progressive illness. Trials done incorrectly can lead to wasted resources and lost patient confidence in the medical system. It is therefore imperative that the surgeon scientist interested in designing clinical trials understand the historical basis for the current international and national laws and regulations surrounding clinical research as well as the steps to imbed the proper standard quality components into a clinical trial.

The design, conduct, and reporting of *surgical clinical trials* in particular have been the focus of significant criticism over the past 20 years. In 1996 a simple commentary published in Lancet launched an important challenge for surgeons. In that article Richard Horton from London wrote:

"In addition to safety and efficacy studies, more pragmatic trials are needed to determine acceptability, effectiveness and efficiency by comparing new interventions with currently preferred treatments. In 1923, the medical statistician, Major

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Greenwood wrote that 'I should like to shame {surgeons} out of the comic opera performances which they suppose are statistics of operations'. Only when the quality of publications in the surgical literature has improved will surgeons reasonably be able to rebut the charge that as much as half of the research they undertake is misconceived." [1]

How then can surgeons respond to these challenges and recommendations? How can they assure that they are designing and performing high-quality, standardized research? A recent survey of surgical trialists seeks to provide insight into how to build a stronger education platform and resources for clinical trials in surgery. Jarman and colleagues from Methodist Hospital in Texas performed semi-structured interviews of 15 individuals, primarily surgeons, involved in conducting clinical research over the past decade [2]. One of their most important discoveries, which is immensely pertinent to this chapter, was the lack of knowledge surrounding the availability of "regulatory and normative" documents to guide the development and publication of a clinical trial. Between 1949 when the Nuremberg Code was released and 2008, greater than 1,000 documents have been written and/or updated regarding the ethical and methodological standards for clinical trials, the great majority of which are available on the Internet [3]. In addition to seeking out these readings, the four primary recommendations for aspiring surgical trialists from those experts interviewed were:

1. Obtain a formal education in the methods and issues of clinical trials.
2. Identify mentors.
3. Establish a network of collaborators.
4. Search for opportunities to be involved in all aspects of clinical trials [2].

Each of these recommendations is crucial towards becoming a respected surgical trialist in a clinical research arena which is increasingly complex due to the influx of innovative device technology as well as genomic information. There are multiple formal education programs from the Masters of Public Health or Masters of Clinical Research to smaller programs offered by subspecialty societies as well as the week-long clinical trials course offered by the American College of Surgeons. Two recommended textbooks for the surgical clinical trialist which delineate the steps from hypothesis generation to dissemination of results include Lawrence Friedman's *Fundamentals of Clinical Trials* (4th ed, Springer) and Stephen Hulley's *Designing Clinical Research* (3rd ed, Lippincott Williams and Wilkins). For the junior clinical investigator, mentors and collaborators should ideally include, in addition to their senior attendings, biostatisticians with experience in clinical trial design. Finally, opportunities to be involved in clinical trials should be identified during residency or as a junior attending. Even though the resident or young attending surgeon may not play a pivotal role in the design of a clinical trial, attendance at a national clinical trial meeting and in the discussions will help guide the individual's understanding of the standardized steps involved in bringing a quality clinical trial to completion.

2.2 History

Clinical trials involving human subjects have not always been performed ethically and with respect for the subjects involved. Likely the most well-known medical trial which lacked beneficence was that performed by the US Public Health Service in 1932 termed the Tuskegee Syphilis Experiment. Though not a randomized trial, the participants were misled into believing that their syphilis was being treated versus just monitored to obtain a natural history of the disease. It was not until the 1970s when the media exposed the lack of interventions that the research was terminated [4]. It was in 1947 however that the Nuremberg Code was developed because of the atrocious crimes which were committed on individuals of Jewish descent and those with mental disorders during World War II. This Code has not been adopted into law by any nation or medical association but is recognized as the foundation on which all national and international regulations for human subjects research are based [5]. The ten research principles set forth by the Nuremberg judges highlight the importance of voluntary informed consent as well as the novel right of a subject to withdraw from the research project at any time. Interestingly, 50 years prior, Sir William Osler had recommended that informed consent be included in all medical experiments [6]

Over the next half a century, additional clinical research regulations were developed and integrated into trial design to assure the protection and safety of human subjects. These include the Helsinki Declaration, which was last updated by the World Medical Association in Korea in 2008 [7], as well as the Belmont Report set forth in the late 1970s by the US Department of Health and Human Services (DHHS). This latter report defines the three ethical principles for human subjects research which are embedded into most physicians' institutional requirements for performing human clinical trials research:

1. Respect for persons: Informed consent should be obtained voluntarily from all participants.
2. A scientifically researched question is being evaluated and that the risks are acceptable in relation to the benefits.
3. Justice: Requires equitable access to the benefits of the research. Researchers must adequately offer the trials to those who may be underrepresented such as children or minorities or justify why they cannot be included [8].

The ethics of clinical trials and human subjects research is the subject of a myriad of books and publications and is unlikely to be fully covered in a single chapter. The importance of understanding the regulatory requirements for clinical trials research however cannot be overemphasized. One of the most important guides for the conduct of clinical research is the institutional review board (IRB). The mission of an IRB is to assure ethically conducted research with minimal risks, equitable participant selection, and adequate confidentiality. Members of an IRB include researchers as well as community members and lawyers. The IRB system has up until the past few years been decentralized but is undergoing revision and now

includes several "centralized" IRBs for multi-institutional trials [9]. As the central IRBs become commonly used, it is expected that the individual institutional IRBs will be able to more efficiently review and approve research projects. In addition to familiarizing oneself with the requirements for the ethical conduct of clinical research through the aforementioned readings and interaction with an IRB, a surgical clinical trialist also needs to be familiar with several standard methodological practices such as GCP, SOPs, CRFs, and AEs as well as the CONSORT statement for reporting of clinical trials, as described in the next sections of this chapter.

2.3 Good Clinical Practice

> Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. [10]

The International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use (IHC) developed these standards as a quality assurance system to cover all stages of clinical trials. With growth of clinical trials internationally and globalization of medical product sales, GCP provides a means to assure sound research practices and standardized data collection allowing for generalizable measurements of clinical effectiveness of a drug or device. Compliance with GCP can also assure the public that the rights, safety, and well-being of clinical trial subjects are protected, in accordance with the Declaration of Helsinki [7]. In addition to the definitions for GCP by IHC, each of the US government branches within Health and Human Services (HHS) provides their interpretation and description of GCP. For example, the FDA "houses" their description of GCP in the Code of Federal Regulations (CFR) Title 21, while the NIH describes their GCP principles in Title 45 of the CFR [11, 12].

GCP standards require that any proposed clinical trial be reviewed and approved by an institutional review board (IRB) or independent ethics committee (IEC) prior to initiation of the study. Although the IRB and IEC are not necessarily responsible for scientific review, they are charged with the tasks of determining if a study is feasible and assuring that it will not place study subjects at undue risk. For this to be the case, there must be *equipoise* between the study intervention and the control. There must be uncertainty about whether the control or the investigational product is more efficacious. The equipoise between study arms should be described in the trial protocol, the investigator brochure, and informed consent forms. It is critical to specify the primary outcome in the protocol to describe how equipoise will be tested and efficacy will be measured. The IRB or IEC can thus determine from the description of equipoise whether or not the trial design is feasible and safe.

The IRB or IEC is not only required to review the trial protocol but also the investigator's current curriculum vitae and qualifications for conducting the trial, available safety information about the investigational product (e.g., drug, medical

device, or surgical technique), investigator brochure if one exists for the drug or device, subject recruitment procedures, informed consent form(s), written information to be provided to subjects, and information about payments and compensation available to subjects [10]. As the principal investigator preparing a clinical trial protocol for IRB review, it will be important to keep in mind the above-listed requirements, utilize institutional templates for required forms, and learn the required or previously utilized *standard operating procedures* (SOPs) for study activities pertinent to a trial. SOPs are detailed, written instructions to achieve uniformity in the performance of specific study functions [10] that should be included in the study protocol. In the conduct of a clinical trial, SOPs provide uniformity in the administration of the investigational product or implementation of the intervention. Detailed SOPs are particularly necessary in surgical clinical trials, where procedural interventions need to be uniform. For example, the Swedish Rectal Cancer Trial was criticized for not having a standardized method of surgical resection in studying the benefits of preoperative radiation therapy [13]. In contrast, the Dutch TME trial [14], which defined a standardized surgical procedure, demonstrated a clear benefit to preoperative radiation therapy after total mesorectal excision of rectal cancer and was widely accepted. This single example demonstrates that if standardized operating procedures, especially in regard to operative technique, are utilized in the conduct of a clinical trial, the results are more likely to be interpretable and generalizable.

2.4 Case Report Forms

The case report form (CRF) is the most basic unit of data collection in a clinical trial. It is a printed or electronic document (remote data capture or data entry (RDC/RDE)) designed to record all of the protocol required information to be reported to the sponsor (national, international, or industry) on each trial subject [10].When designing a clinical trial, the principal investigators need to assure that they include all data that needs to be collected in the protocol, as information that has not been specified as analytic in the protocol cannot be included on a CRF. Trialists should be thoughtful about keeping the data acquisition simple and standardized with minimal free text.

There are currently no universally standard CRF designs; however, there are several ongoing efforts to harmonize the information acquired within and across clinical trials and avoid duplication of efforts in design. For example, a subproject of the Clinical Data Interchange Standards Consortium (CDISC, http://www.cdisc.org), the Clinical Data Acquisition Standards Harmonization (CDASH), is working on standard forms for safety data as well as disease or therapeutic specific forms and data elements [15]. Some of these forms and processes for data acquisition will become outdated quickly due to the burgeoning amount of calculations and information that can be obtained from patients and human tissues. The associated field of clinical research informatics is one that is growing exponentially and is working to

provide leadership and direction on these issues of standardization of common data elements and medical terminology as well as the best methods for compilation and storage of metadata from clinical trials [15]. The National Cancer Institute (NCI) has one such example of a CRF Harmonization and Standardization Initiative to design standardized case report forms incorporating common data elements to "improve information sharing among cancer researchers and optimize data requirements in collaboration with the Federal Drug Administration (FDA)" [16]. By reducing the time spent in developing a data collection strategy for each cancer clinical trial, a core library will allow for rapid initiation of a novel clinical trial and dissemination of information across linked clinical studies (Fig. 2.1).

2.5 Adverse Event Reporting

While the CRF records all events in a trial related to each subject, a subset of the record must include adverse events that occur during and after the course of a clinical trial. *Adverse events (AE)* are defined as any unfavorable or unintended medical occurrence, including any abnormal sign (physical exam or laboratory finding), symptom, or disease temporarily associated with the use of a medical treatment whether or not it is considered related to the medical treatment (causality) [10, 12]. The purpose of AE reporting is to monitor the safety of the study, inform the investigators, regulators, and subjects of risks potentially associated with the intervention and allow for timely intervention if it appears that the risks of the clinical trial have changed. In general the majority of AE reporting has centered around events associated with drugs and devices, and less standardization has occurred with reporting of adverse events in purely surgical clinical trials. In the United States, adverse event reporting has recently been restructured to address causality more specifically [12]. With the globalization and massive growth of clinical trials over the past 10 years [17], the FDA has been flooded with volumes of adverse event reports and other regulatory documentation. Many of these adverse event reports have been uninterpretable or irrelevant as reporting individuals were often blinded and unable to relate events to the investigational drugs or devices [18]. The Clinical Trials Transformation Initiative has since worked to improve the quality and efficiency of reporting by requiring the investigational sponsor to assign attribution or causality to each adverse event and provide both the FDA and the study investigators with an aggregate report of adverse events that are attributable to the investigational drug or device.

The process surrounding the ascertainment, recording, and reporting of adverse events remains moderately challenging especially to the surgeon scientist who may not be involved in drug- or device-related surgical research. It is however important to understand the basic definitions of AE reporting in order to ensure that the proper information is included in a clinical trial protocol, so AE determination does not become challenging because adequate definitions were not provided a priori. *Expected* adverse events are those that have been identified in nature, severity, or

HEADER: PI NAME, Protocol or IRB Number, Protocol Short Title

Subject Initials ☐☐☐ **Subject ID** ☐☐☐☐☐ **Date:** ☐☐ / ☐☐ / ☐☐
Month Day Year

Demographics

Subject UWHC Medical Record Number*: ☐☐☐☐☐☐☐

First Name*:
Middle Name (or initial):
Last Name*:

Birthdate*: ☐☐ / ☐☐ / ☐☐☐☐ ☐ Approximate ☐ Unavailable
Month Day Year

Gender*: (check one)
☐ Male
☐ Female
☐ Unknown or Not Reported

Ethnicity*: (check one)
☐ Hispanic
☐ Non-Hispanic
☐ Unknown or Not Reported

Race*: (check all that apply)
☐ American Indian or Alaska Native
☐ Asian
☐ Black or African American
☐ Native Hawaiian or Other Pacific Islander
☐ White or Caucasian
☐ Unknown or Not Reported

Other Medical Record Number(s):

Medical Record Number	Hospital/Care Provider (e.g. UW Hospital, VA, etc.)

Contact Information:

Address:		Unit #:
City:	State:	Zip:
Phone Number: ☐ Home ☐ Work ☐ Cell ☐ Other	Alternate Phone Number: ☐ Home ☐ Work ☐ Cell ☐ Other	Email address:
Preferred method of contact:		

Emergency Contact:

Name:		
Address:		Unit #:
City:	State:	Zip:
Phone Number: ☐ Home ☐ Work ☐ Cell ☐ Other	Alternate Phone Number: ☐ Home ☐ Work ☐ Cell ☐ Other	Email address:
Preferred method of contact:		

*indicates required field

Form Completed By: _____ **Date:** _____

Fig. 2.1 Example of case report form template

frequency in the current clinical trial protocol, investigator brochure (if available for a drug or device), and current consent form. For example, a 5 % incidence of surgical site infection is anticipated or expected in a clinical trial that tests the efficacy of laparoscopic versus open distal pancreatectomy for resection of benign pancreatic tumors. The research team is informed of this in the clinical trial protocol, and

subjects are made aware of this risk during the consent process. Therefore an occurrence of surgical site infection in a subject would be an expected event but would still be recorded on the AE forms to determine the extent of this event across the entire patient accrual. Anticipated or expected events can be internally documented, monitored, and analyzed in aggregate.

An *unexpected* adverse event is any event, the severity or specificity of which is not consistent with the risk information described in the clinical protocol or investigator brochure, and is more likely than not related to the research, and it suggests that the research places subjects or others at greater risk than previously known [19]. "Relatedness" of the AE to the clinical study is defined differently for each regulatory body:

1. ICH definition requires evidence suggesting a causal association.
2. FDA definition requires a reasonable possibility that the AE is associated with the research drug or device.
3. NCI has a more complex reporting structure for AEs which is best described below in the description of CTCAE but moves through five categories from not related to definitely related to the intervention.

It is worth noting that not all unanticipated problems involve an unexpected adverse event. For example, the absence of laparoscopic equipment for a patient randomized to the laparoscopic approach in the aforementioned distal pancreatectomy trial would be an unanticipated problem but not an unexpected adverse event as would the administration of an incorrect dose of a study medication if drawn up incorrectly by the pharmacy. The distinction between unanticipated and unexpected outcomes in the ascertainment of adverse events is important because they each prompt different documentation and management processes. Unanticipated adverse events such as incorrect study drug dosing are reported to the IRB, the patient, and potentially the sponsor but are recognized to not be causal in adverse events. Unexpected adverse events must be reported to the IRB of the study site and subsequently sent to the Office for Human Research Protection in accordance with US Health and Human Services regulations 45 CFR 46.103(a) and (b)(5) [11, 19].

Prior to management of an unexpected adverse event, some *analysis* is required to understand the process that led to the event and how to address it. First a basic classification of the adverse event is needed. The Medical Dictionary for Regulatory Activities [20] is a standardized system of medical terminology that is used internationally to classify adverse event information associated with the use of biopharmaceuticals and other medical products. MedDRA is maintained by the International Conference on Harmonization and is the required terminology in reports to many regulatory agencies. The National Cancer Institutes' Common Terminology Criteria for Adverse Events (CTCAE) [21] is also an instrument used to classify adverse events. It uses clinical and laboratory evaluation criteria and is required in studies that are funded by the NCI. Grading of adverse event severity is a key component of the classification process. The CTCAE has a grading scale of 0–5. Zero is no adverse event, 1 is mild, 2 is moderate, 3 is severe, 4 is life-threatening, and 5 is

death [21]. Life-threatening adverse events and death must be reported to the IRB and the FDA within 7 calendar days, in accordance with 21 CFR 312.32(a) [12]. Of note, the CTCAE grading scale describes *severity* of an event but not "seriousness." SAEs or serious adverse events are any adverse drug event (experience) occurring at any dose that results in ANY of the following outcomes: "death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization (for >24 h), a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, a congenital anomaly/birth defect. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition" [12]. The process of reporting SAEs is variable for clinical trials and can be anywhere from within 24 h to up to 10 days depending on the sponsor of the trial and associated regulatory agencies. For example, a phase I trial evaluating the safety of a novel drug may require the submission of an SAE within 24 h to assure that additional patients are not placed on the study until the SAE has been fully investigated.

The standard operating procedures of a clinical trial should also delineate the methods for *ascertaining* adverse events. Adverse events can be ascertained by elicited or volunteered report from subjects or by direct observation. Direct observation is the most reliable method to ascertain adverse events, but it is not always feasible. Studies have demonstrated that adverse event reporting increases when subjects are asked open-ended questions to elicit reports of adverse events [22–24]. Subject-elicited adverse events or patient-reported outcomes (PRO) are increasingly studied, particularly with the inception of patient-centered outcomes research [25, 26]. Research focused on the development of standardized and generalizable patient-reported outcome instruments remains ongoing. The majority of clinical trials currently rely on volunteered reporting of adverse events or direct observation of them during study visit examinations.

The ICH has developed the Harmonized Tripartite Guidelines [10] that detail the key components of an adverse event report, summarized here:

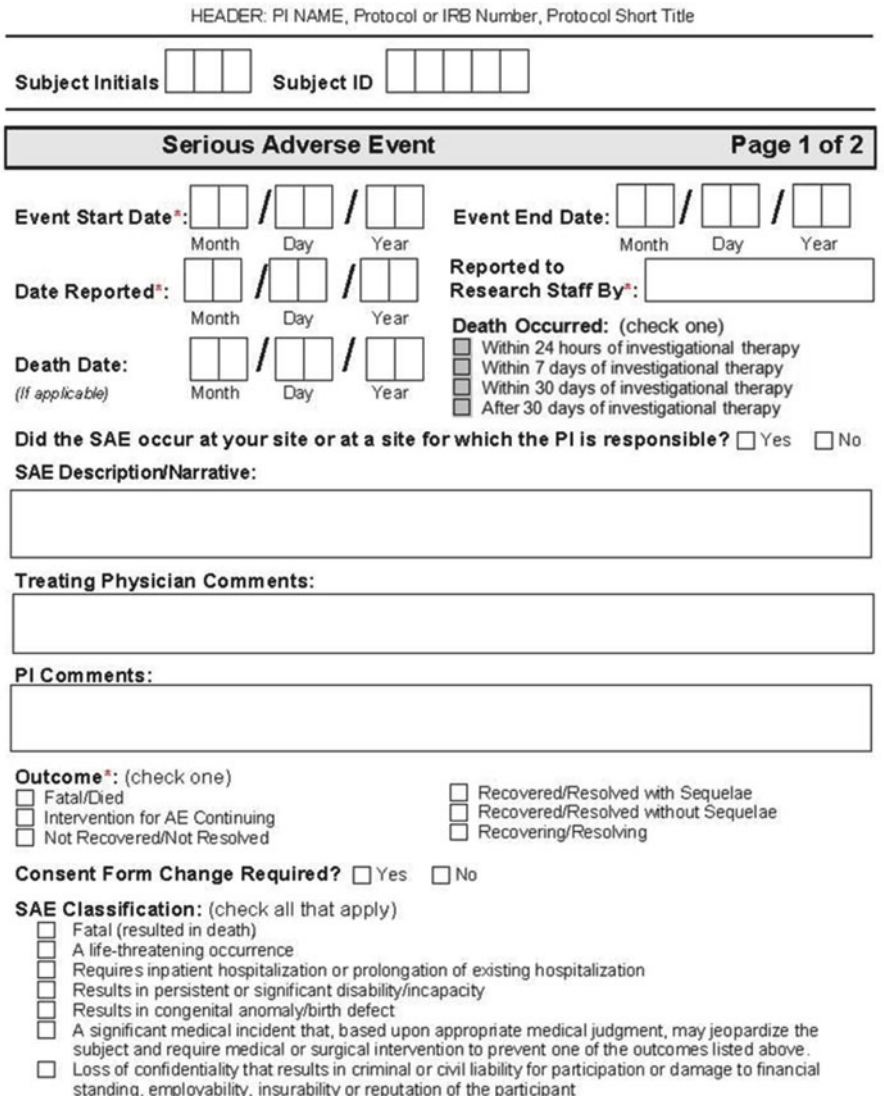
1. Subject identifier
2. Demographic data: age, race, sex, weight, and height
3. Location of case report forms and source documents (for reference)
4. The adverse event
5. Duration of the adverse event
6. Severity (mild, moderate, severe)
7. Seriousness (life-threatening, death)
8. Action taken (none, dose reduced, treatment stopped, specific treatment instituted, etc.)
9. Outcome
10. Causality assessment (unrelated, unlikely, possible, probable, definite causality)

11. Date of onset or date of clinic visit at which the event was discovered
12. Timing and onset of the adverse event in relation to last dose of test drug/investigational product
13. Study treatment at time of event or most recent study treatment taken
14. Test drug/investigational product dose at time of event
15. Drug concentration
16. Duration of test drug/investigational product treatment
17. Concomitant treatment during study

The ICH guidelines state that all adverse events for each patient, including the same event on several occasions, should be documented. Study sponsors and investigators are held responsible for the reporting of adverse events. Separate reporting guidelines exist for trials involving recombinant DNA molecules or gene transfer [27]. In these trials the principal investigator is responsible for ensuring that safety reporting requirements are fulfilled, although such reporting may be delegated to the investigational sponsor.

A recent publication by Virzi et al. from the Pediatric Heart Network (PHN) highlights the complexities of AE reporting in surgical trials [28]. In 2005, the PHN opened a randomized surgical clinical trial evaluating single ventricle reconstruction in children with hypoplastic left heart syndrome. The initial AE reporting system is commonly used for drug trials, but in this critically ill neonatal population, every lab value and event would require a serious AE report. With approval the team was able to switch to a "sentinel" event reporting system for serious AEs thereby reducing the administrative burden and highlighting the critical events of interest in this study [28].

In a qualitative review of good clinical practice (GCP) inspection citations [29], investigators and sponsors were frequently reprimanded for inconsistent adverse event documentation between case report forms, adverse event logs, and other source documents. An important lesson to take from this review is that it is best to either document adverse events consistently and concordantly in designated forms or document adverse events in one central source record. In studies that require adverse events to be reported in more than one document, it is best to reference all source documentation in each report. The review of GCP inspection citations also highlighted a frequent problem with undocumented telephone correspondence between investigators and study sponsors related to the reporting and management of adverse events. Management of adverse events must be documented as accurately and consistently as the events themselves. The best advice for young investigators interested in designing clinical trials is to link with a "seasoned" clinical research specialist who is knowledgeable on AE reporting and has had extensive experience in this process so that the clinical trial protocol can be written and the required forms included to ensure that the AE process goes smoothly and ensures that subject safety is always the first priority (Figs. 2.2 and 2.3).



HEADER: PI NAME, Protocol or IRB Number, Protocol Short Title

Subject Initials ☐☐☐ **Subject ID** ☐☐☐☐☐

Serious Adverse Event **Page 1 of 2**

Event Start Date*: ☐☐ / ☐☐ / ☐☐ (Month / Day / Year)

Event End Date: ☐☐ / ☐☐ / ☐☐ (Month / Day / Year)

Date Reported*: ☐☐ / ☐☐ / ☐☐ (Month / Day / Year)

Reported to Research Staff By*: ☐☐☐☐☐☐☐☐☐☐

Death Date: *(If applicable)* ☐☐ / ☐☐ / ☐☐ (Month / Day / Year)

Death Occurred: (check one)
- ☐ Within 24 hours of investigational therapy
- ☐ Within 7 days of investigational therapy
- ☐ Within 30 days of investigational therapy
- ☐ After 30 days of investigational therapy

Did the SAE occur at your site or at a site for which the PI is responsible? ☐ Yes ☐ No

SAE Description/Narrative:

Treating Physician Comments:

PI Comments:

Outcome*: (check one)
- ☐ Fatal/Died
- ☐ Intervention for AE Continuing
- ☐ Not Recovered/Not Resolved
- ☐ Recovered/Resolved with Sequelae
- ☐ Recovered/Resolved without Sequelae
- ☐ Recovering/Resolving

Consent Form Change Required? ☐ Yes ☐ No

SAE Classification: (check all that apply)
- ☐ Fatal (resulted in death)
- ☐ A life-threatening occurrence
- ☐ Requires inpatient hospitalization or prolongation of existing hospitalization
- ☐ Results in persistent or significant disability/incapacity
- ☐ Results in congenital anomaly/birth defect
- ☐ A significant medical incident that, based upon appropriate medical judgment, may jeopardize the subject and require medical or surgical intervention to prevent one of the outcomes listed above.
- ☐ Loss of confidentiality that results in criminal or civil liability for participation or damage to financial standing, employability, insurability or reputation of the participant

Fig. 2.2 Example of severe adverse event form

HEADER: PI NAME, Protocol or IRB Number, Protocol Short Title

Subject Initials ☐☐☐ **Subject ID** ☐☐☐☐☐

Serious Adverse Event **Page 2 of 2**

SAE Reported Symptom:

Category*: [refer to the Safety Profiler website to search the Category and Toxicity of the SAE symptom reported: http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx]

Toxicity*:

Grade/Severity*: (check one)
- ☐ 1 - Mild
- ☐ 2 - Moderate
- ☐ 3 - Severe
- ☐ 4 - Life Threatening
- ☐ 5 – Death (Fatal)

Unexpected*? ☐ Yes ☐ No

Dose Limiting Toxicity (DLT)? ☐ Yes ☐ No ☐ Not Applicable

Action Taken:
- ☐ Dose Reduced
- ☐ Dose Interrupted, then Reduced
- ☐ None
- ☐ Regimen Interrupted
- ☐ Therapy discontinued

Primary Attribution*: (check one)
- ☐ Definite
- ☐ Probable
- ☐ Possible
- ☐ Unlikely
- ☐ Unrelated

Detailed Attribution: (check one)
- ☐ Disease/Condition Specify:
- ☐ Investigational Treatment Specify:
- ☐ Non-investigational Treatment Specify:
- ☐ Other Specify:

Principal Investigator Signature: _____ Date: _____

Fig. 2.2 (continued)

2.6 DSMB

The FDA recommends involving a data and safety monitoring committee in the system-level management of serious adverse events [30]. A Data and Safety Monitoring Board (DSMB) is required for multisite clinical trials with interventions that involve potential risk to the participants [31]. The NIH also requires a DSMB for any NIH-supported clinical trial that has direct implications for clinical care and/or public health, involves a highly vulnerable patient population, or a high-risk intervention. The role of the DSMB is to verify that:

1. The rights and well-being of human subjects are protected.
2. The reported trial data are accurate, complete, and verifiable (esp. CRFs and AEs).

HEADER: PI NAME, Protocol or IRB Number, Protocol Short Title

Subject Initials ☐☐☐ **Subject ID#** ☐☐☐☐☐ **Page** ☐☐ **of** ☐☐

Question to ask subject: Have you had any physical, emotional or behavioral problems, symptoms, or side effects since your last visit on [DATE]? Include anything that *started* to become a problem during this time or an old problem that *worsened*.

Adverse Event Tracking Log

#	Date Reported	Adverse Event Description	Adverse Event Category**	Start Date	End Date	Ongoing (Y or N)	Outcome[1]	Severity[2]	Serious (Y or N)	Expected (Y or N)	Treatment[3]	Action Taken[4]	Attribution[5]	PI Initials

**look up corresponding AE Category at: http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx

Outcome[1]
0 – Fatal
1 – Intervention continues
2 – Not recovered/not resolved
3 – Recovered w/sequelae
4 – Recovered w/o sequelae
5 – Recovering/Resolving

Severity[2]
1 – Mild
2 – Moderate
3 – Severe
4 – Life-threatening
5 – Fatal

Treatment[3]
0 – None
1 – Medication(s)
2 – Non-medication TX
3 – Subject discontinued

Action Taken[4] with Study Treatment
0 – Not Applicable
1 – None
2 – Interrupted
3 – Discontinued
4 – Dose reduced
5 – Dose increase

Attribution[5]
1 – Unrelated
2 – Unlikely
3 – Possible
4 – Probable
5 – Definite

Fig. 2.3 Example of adverse event log

The conduct of the trial is in compliance with good clinical practice, the IRB-approved protocol, and with any applicable regulatory requirement(s) [10].

2.7 CONSORT

The Consolidated Standards of Reporting Trials (CONSORT) statement, which was first written in 1996 and updated in 2010, provides guidance for reporting the aims, methods, results, and implications of randomized controlled trials. This statement includes a 25-item checklist and study flow diagram to guide the reporting and publication of an RCT [32]. At the start of the design of a clinical trial, a principal investigator is advised to review the CONSORT checklist and flow diagram and the *examples* of good reporting provided on the CONSORT website (http://www.consort-statement.org/consort-statement/). By reviewing the examples a PI can gain understanding of what methodologies and processes were used during a trial to ensure standardization and quality of the trial outcomes. In 2008, the CONSORT group provided an "extension" document for non-pharmacologic treatment interventions [33]. This document provides a 22-item checklist which is more applicable to surgical or device interventions, and the surgical trialist is advised to review this statement and its notable examples.

2.8 Conclusions

The surgical trialist is tasked with assuring that a clinical trial will be valid and generalizable to their population of interest but also needs to standardize processes and demand quality to ensure the safety of the consented subjects. This chapter provides a small introduction to the large group of acronyms that accompany the design and implementation of a clinical protocol. The academic surgical scientist interested in translational research and human clinical trials is advised to review the "regulatory and normative documents" and identify key mentors both within a Department of Surgery and within their institutions' clinical trials and statistical offices to begin to learn and speak the language associated with clinical research.

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