Ethical Issues in Surgical Research

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Key Points

- Historically, ethical guidelines were established "ad hoc" in response to unethical research behavior. Such guidelines did not offer a complete means of evaluating the ethics of study design.
- Emanuel et al. in 2001 proactively proposed seven requirements that are necessary and sufficient to evaluate the ethical conduct of human subject research.
- Intrinsic barriers make scientific validity, and thus ethical research conduct, more complex in the field of surgery compared to nonsurgical fields.
- The "IDEAL" recommendations for surgical innovation simplify and standardize the ethical conduct for the practice of novel surgical techniques.
- Special topics: communication during informed consent, sham surgery, and authorship.

Surgical research has been criticized for producing low-quality evidence in the form of case series rather than randomized controlled trials. Performance of randomized trials for surgical intervention is inherently more difficult than similar investigation in the medical world due to the nature of surgical disease and therapy. However, in the past decade, the stages of development of surgical technique have been formalized in ways that maximize scientific validity and thus ethics. Surgeons should be aware of what constitutes research versus personal variations in technique and the protocols for developing novel techniques.

Quality improvement (QI) and quality improvement research have increased dramatically in recent years. The line between quality improvement and human subject research is often ambiguous, and although risks to patients are frequently limited to privacy concerns, investigators should be aware of what defines pure QI versus human subject research and the ethical guidelines governing each.

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The hierarchical nature of surgical departments often places investigators in difficult position when assigning authorship. Formalized guidelines are in place to aid in this process; however ultimately communication between all participants is paramount to prevent and avoid unethical and painful situations.

Surgical research, like clinical surgery, creates sustainable value in the societies it serves only if practiced ethically. Surgeons are uniquely positioned in the research community due to the history and culture of our profession. Surgical research is governed by the core ethical principles that apply to all biomedical investigation. However, nuances of surgical disease [1] and the surgeon-patient relationship [2], along with the need for research in surgical technique and devices, are the factors that warrant specific consideration of ethical conduct in surgical research.

Recognizing that it would be difficult to review or identify all ethical dilemmas that confront surgeons involved in research, this chapter will focus in the following aspects: (1) outlines common and critical issues, (2) provides the reader with an understanding of the principles guiding the ethical conduct of surgical research, and (3) explains the context in which these principles arose. Box 1 highlights the idea that we believe underlies all ethical analysis of research conduct.

Box 1 Overarching Theme of Ethical Principles Guiding Surgical Research

Human research subjects are contributors to the common good. They place themselves at risk in order to advance societal knowledge of biology and the treatment of disease in others. As such, investigators owe their subjects exhaustive self- and external examination of their methods with an appreciation of established ethical guidelines in mind and the recognition that their subjects are providing an invaluable resource to both society and the investigator.

Historical Perspective

The ethical conduct of research on human subjects in the modern era is grounded in the failures of the past. In our profession's early history, there are countless examples of unethical research practices including nontherapeutic vivisection and forced sterilization carried out on vulnerable populations under the "care" of surgeons [3]. Out of atrocities committed in Germany in the 1930s and 1940s rose the Nuremberg Code, which established the principles of voluntary informed consent and minimalization of risk to subjects [4]. Expanding on the Nuremberg Code, the Helsinki Declaration was developed in 1964 and subsequently revised by the World Medical Association to protect the rights of the individual research subject from violation in the name of any greater societal good [5]. More recently, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research released the Belmont Report, which codified the concepts of respect for persons, beneficence, and justice in response to grossly unethical human experimentation that took place in the Tuskegee Syphilis Study [6]. These concepts were the foundation of the Common Rule established in 1991 by the American Department of Health and Human Services to govern baseline ethical requirements for study design and implementation in government-funded human subject research [7]. The Common Rule established institutional review boards (IRBs) to protect the rights of research subjects and provided additional protections for populations vulnerable to harm from unethical research practices including prisoners, children, and pregnant women. Updates to the Common Rule will go into effect in 2018, the most notable of which is the waiver of informed consent for biobanking of unidentified specimens [8]. These landmarks have been aptly described as the "property of all humanity [9]."

Unifying Principles of Ethical Research Conduct

An important distinction exists between clinical research and individualized patient care. The overarching goal of research is hypothesis testing

and advancement of general knowledge. Patient care is the application of a previous hypothesis test with the primary goal of maximizing well-being to the individual [10]. This distinction allows that the ethical treatment of research subjects may differ from ethical treatment of patients in clinical practice. Biomedical research necessarily implies some degree of risk to individual subjects. If an intervention were known to improve outcomes in the absence of risk, it would be the standard of care, and investigation would be unnecessary. Research subjects volunteer for risk exposure and treatment in a fashion that may not maximize individual well-being, whereas treatment of a patient in clinical practice in any fashion other than one intended to maximize individual well-being would be unethical.

The potential for harm to subjects mandates scrutiny of the ethics of proposed research prior to the induction of a study. In 2001, Emanuel et al. published a series of requirements for evaluation of the ethics of clinical research studies. The authors recognized that the various academic and governmental guidelines in existence at the time left investigators with incomplete and often unclear instructions for ethical conduction of research. This was attributed to the reactionary, ad hoc establishment of ethical guidelines for research that persisted through the late twentieth century. Prior to these guidelines, no single set of rules was both necessary and sufficient to determine whether an investigation was ethical. The requirements described below were designed as a unified code of ethics for clinical research. They serve a parallel purpose to the accepted guiding principles of ethical clinical practice: beneficence, nonmaleficence, respect for autonomy, justice, respect for dignity, and veracity [11]. The requirements assume honesty and responsibility from all parties and apply to clinical research in all forms. The seven requirements correspond to the respective phases of investigation: development, implementation, and review. While they are not specific to surgery, it is our belief that these requirements are the most complete and applicable tool for evaluating the ethics of surgical research. The requirements as described in the original manuscript are summarized in Box 2 [12]. Requirements 1, 2, 3, 4, and 7 are considered necessary for the conduct of ethical research. Requirements 5 and 6 are in place to ensure enforcement of the necessary requirements, minimize conflicts of interest, and ensure subject autonomy.

Box 2 Summary of the Seven Requirements for Ethical Conduct of Clinical Research [12]

1. *Social or scientific value*: This requirement applies to hypothesis development and requires familiarity with the current knowledge base and needed future directions of study in a field. Human research subjects are necessarily exposed to risk. To be considered ethical, the proposed research must include potential benefit to the well-being of patients or add to the scientific knowledge base. This prevents the exploitation of subjects and wasting of scarce resources on hypothesis tests without potential social or scientific benefit. A proposal to evaluate the relationship between eye color and severity of cholecystitis would violate this requirement.
2. *Scientific validity*: This requirement applies to methods of data collection and analysis and requires statistical expertise, familiarity with study populations, and pragmatism. Even if performed to test a potentially beneficial hypothesis, invalid data collection methods negate the value of the hypothesis test. This requirement also specifies that intentionally underpowered trials lack validity and thus true scientific value. Adherence to this principle prevents exploitation of subjects and wasting of resources. A proposal to evaluate operative versus nonoperative management of acute appendicitis with five patients per group would violate this requirement.
3. *Fair subject selection*: This requirement applies to decisions on recruitment

along with inclusion and exclusion criteria. It requires knowledge of epidemiology, vulnerable populations, and an understanding of the virtue of justice. Fair subject selection requires that selection of the study population maximizes validity and minimizes risk and that the population being studied stands to benefit from the research being conducted. Under this principle, a valuable and scientifically valid investigation conducted at a safety net hospital that in the end would disproportionately benefit the rich and powerful is considered unethical.

4. *Favorable risk-benefit ratio*: This requirement applies to study design and implementation. It requires extensive scientific knowledge in the field of study and social values. Favorable risk-benefit ratio requires a study protocol that minimizes risk and maximizes benefit to individual subjects and ensures that the benefits of participation outweigh the risks. Maximization of benefit to the individual is constrained to improvements in well-being. Extraneous benefits such as compensation do not weigh into this calculus. This requirement importantly assumes that the extent and probability of potential benefit and harm to the individual is clearly understood by the patient. The calculus allows that societal benefits may in some cases outweigh risk to the individual, as in the case of phase 1 safety trials and studies where risk to subjects is minimal. A study evaluating management of asymptomatic lipoma with chemoradiation versus radical excision violates this requirement.
5. *Independent review*: This requirement applies to study design and serves to prevent conflict of interest in investigators. Moral hazard exists for investigators in the development, implementation, and review of human subject research. IRBs and data and safety monitoring boards exist to minimize the impact of external pressures such as monetary gain and the desire to advance one's career on the completion of high-quality research. The review process also helps to ensure that principles of ethical research are followed.
6. *Informed consent*: This requirement applies to enrollment and requires scientific knowledge, communication skills, and respect for autonomy. The principle of informed consent requires that patients have full knowledge of the risks, benefits and alternatives to study participation, and full autonomy free from coercion in the decision to participate in research. There are two notable exceptions to these criteria: emergency situations where genuine clinical equipoise between two treatments exists and in the case of surrogate decision-makers practicing substitute judgment for patients unable to make decisions regarding participation in the trial. The responsibility of the surgeon-scientist involved is first to the research subject and second to the community intended to benefit from their research. Surgeons have a fiduciary responsibility to individual patients that supersedes their role as scientists. To minimize conflict of interest, persons other than the principle investigator of a study should perform the informed consent with potential subjects.
7. *Respect for potential and enrolled subjects*: This requirement applies to enrollment and accrual. It ensures the protection of privacy and subject well-being and requires scientific knowledge and communication between subjects and investigators. To fulfill this requirement, investigators must (1) respect rules regarding protected health infor-

mation, (2) keep subjects apprised of developments in their individual health and the study intervention, (3) allow subjections to freely withdraw from studies, (4) vigilantly monitor well-being of subjects throughout the study and care for them accordingly, and (5) disclose to subjects the results of the study and what knowledge or benefit their participation yielded.

Intrinsic Barriers to Ethical Surgical Research

The ideal investigation of an intervention would be a multicenter, double blind randomized controlled trial that includes relevant patient groups without undue risk to each individual subject. Aspects of surgical practice and culture frequently prohibit such investigations. Many current surgical procedures were passed along through generations of hierarchical training programs and "grandfathered" in to practice without rigorous scientific comparison to alternative approaches [13]. These intrinsic factors distinguish surgical from nonsurgical research and warrant consideration in modern study design.

First, variations in methods and surgical expertise add a layer of complexity to the design of surgical research. While nonsurgical investigations do involve a level of diagnostic skill and critical thinking, this requirement is compounded with the technical abilities of individual surgeon in surgical investigations. Standardization of delivery of a medical therapy is more straightforward than standardization of surgical management for research purposes. Varying availability of instruments and care pathways among institutions raises concerns about the internal validity of multicenter trials. In the past, the single-surgeon or single-center case series was the solution of choice to standardization of methods [14]. However, this method leads to poor generalizability of results thus decreasing external validity of the results. One surgeon's outcomes under study conditions may differ vastly from typical outcomes of the same procedure in the community at large.

Learning curves and individual expertise have a role in the implementation of surgical therapy that is absent in nonsurgical interventions. Outcomes early in the life cycle of an operation generally do not match those that can be expected when the procedure is established. For instance, outcome improvements along the learning curve for laparoscopic colectomy are well described in studies including surgeons at various levels of experience [15]. This too impacts internal validity, as the results of a trial comparing various interventional therapies necessarily depend upon the point in each therapy's life cycle at which the trial takes place.

Surgical intervention often represents a physiologic challenge to the patient that is not encountered in trials of medical therapy. This can be prohibitive to the development of randomized trials comparing operative to nonoperative treatment, in the form of channeling bias [16]. Channeling bias occurs when investigators rightly assign patients to one intervention or another if the alternative branch of the study is considered too risky. In practice, this leads to disparate risk profiles of the patient groups in a study and necessarily decreased internal validity.

Finally, the degree of personal responsibility that surgeons take for their outcomes impacts the degree of willingness to participate in investigations of novel surgical therapies. If surgical therapy fails, the surgeon rather than the therapy itself is more often held accountable. This equates to the unlikelihood of separating their roles as care providers from their roles as scientists for surgeons participating in a clinical investigation. If a pharmaceutical approach fails, blame frequently falls on the drug and the state of the science, not the treating physician.

Pathways to Ethical Innovation

With the above concerns in mind, McCulloch et al. have developed the IDEAL model, a strategy for practical and scientifically valid surgical

innovation. This pathway couples innovation and continuous evaluation using a staged rollout of novel invasive procedures. This model is summarized in Box 3.

Box 3 Summary of the IDEAL Recommendations for Surgical Innovation [17]

Stage 1 – Innovation: This stage entails proof of concept for a novel intervention, performed by select innovators for the first time on humans, whether in a planned or unplanned fashion. The procedure is still in development and best practices are not established. Authors publish complete technical descriptions of the procedure and details of patient selection in case reports. Ethics committee approval is recommended but institution-dependent. Outcomes, particularly adverse events, should be reported to avoid replication of ineffective or dangerous methods.

Stage 2a – Development: This stage involves development of a standardized technique. The procedure remains in its infancy and is performed again on a small number of patients by innovators and early adopters. At this point prospective evaluations of safety and efficacy are performed, and the initial learning curve is established. In the past, innovation at this phase has been published as retrospective case series. However, prospective, planned out study with IRB approval is both scientifically and ethically superior and should be performed whenever possible.

Stage 2b – Exploration: Once technique is standardized, replication outside the original center is appropriate to determine scalability of the technique. Early adopters should perform rigorous tracking of patient-reported and clinical outcomes in the form of uncontrolled prospective case series. Initial response and complication rates are critical to power analyses in the planning of randomized trials to be performed in later stages.

Stage 3 – Assessment: If initial outcomes are comparable to the established standard of care and true clinical equipoise exists, progression to a comparative trial is appropriate. Ideally, the new procedure is compared to the existing standard in a randomized controlled trial; however as discussed above, difficulties exist in designing such trials for surgical therapy. If an RCT is not feasible, alternative comparative methods such as controlled interrupted-time series studies and others are a viable, albeit less valid alternative.

Stage 4 – Long-term study: Established procedures should proceed to long-term monitoring of outcomes and rare events. Monitoring is generally achieved through a registry compiled with administrative data. Longitudinal data collected at a single center is valuable; however between-center comparison can be fraught with complications related to risk adjustment.

Personal developments in the art of surgical technique are considered improvements in individual patient care. Parameters such as suture material and technique, laparoscopic port placement, and patient positioning are at the discretion of the operating surgeon and should reflect what he or she believes is in the best interest of the patient. Often in the usual discourse of patient care, alterations in technique come about that, if disseminated and generalized, would contribute to the existing knowledge base and help large groups of patients in the future. An example of this would include the critical view of safety in laparoscopic cholecystectomy [18]. It is our view that if and when an investigator has intent to publish or otherwise disseminate a technique, he or she is obliged to treat the use of the technique as research, and its investigation should proceed as outlined in the IDEAL recommendations.

Special Considerations

Quality Improvement

In recent years, surgeons and trainees have increasingly participated in systematic, data-guided analysis of healthcare processes to improve the quality of care. Quality improvement (QI) initiatives measure adherence to evidence-based guidelines for processes of care across disciplines. Initiatives to continuously review practice patterns and surgical outcomes represent an attempt to maintain clinical standards of care at the level of the most recent research-based guidelines.

QI projects often resemble both research and normal clinical practice [19]. This lack of distinction often creates an ethical gray area – are QI projects subject to the same ethical requirements as human subject research? The *Belmont Report* states that research is undertaken with the intent to develop generalizable knowledge, whereas practice is intended only to improve the well-being of an individual. Kass et al. argue that in current practice patterns, this distinction is nearly impossible, as the goal of delivering the best possible care to the individual patient is often inseparable from the continuous processes of institutional learning and improvement. Practice-derived data drives production of generalizable knowledge, and that knowledge is rapidly incorporated into clinical practice in an iterative cycle of analysis and implementation [20].

Entities identified as QI initiatives range from departmental morbidity and mortality conferences to the creation of vast administrative datasets such as the National Surgery Quality Improvement Program (NSQIP). As QI initiatives range widely in scope, scale, and purpose, the line between QI and human subject research is often blurred, and ethical oversight is difficult. This is further complicated by varying definitions among institutions and federal agencies. QI projects are generally subject to less oversight by institutional review boards (IRBs) than human subject research. Under the premise that continuous quality improvement is in the best interest of patients and designed to promote well-being with minimal risk, informed consent is frequently waived or considered part of a global consent for treatment during prospective QI studies. Studies that involve human subjects, but only through retrospective review of medical records, involve no physical risks to the subjects. These studies again involve minimal risk and undergo expedited IRB review without the requirement of informed consent. Studies that utilize protected health information (PHI) do involve significant risks to patient privacy, however, and this risk should be recognized and mitigated by the investigator with appropriate data security. Any study that involves more than minimal risk to the participant should be fully subject to the seven requirements for the ethical conduct of research as outlined above. It should proceed through IRB review and require informed consent on the part of the subject.

Communication During Informed Consent

Communication is the cornerstone of the informed consent process in clinical research. The burden of communication lies with the investigator and not with the patient [21]. It is necessary to explain the risks and potential benefits of participation in terms that the patient understands. This may include but is not limited to the use of illustrations, certified foreign language interpreters, and nonscientific terminology. If, after the informed consent discussion, the patient is unable to clearly explain the goals of the trial and the risks associated with participation, informed consent has not been obtained even if that patient signs a document attesting that it has. In informed consent proceedings in the clinical practice setting, the guiding principle is that of veracity, which requires complete honesty from the provider to his or her patients when conveying information about their condition and its progression and prognosis.

An informed consent for clinical research must include the attendant risks of participation along with the goals of the study and potential benefits. Participants' preconceived notions of clinical research and the specific innovations at

use in the study must also be accounted for. Cultural and societal factors influence perceptions of clinical research and surgery at large but also specific interventions. Out of therapeutic optimism, patients may assume that because a surgical technology is new, it is superior to previous methods [22]. In the setting of surgical innovation, this is not necessarily true, and again, the burden of truth lies with the investigator. It follows that in discussing an investigative robotic approach to surgery with a patient, the surgeon would be justified in explaining to the patient that use of the robot offers increased range of motion through articulation inside the abdomen. However, if, for example, the surgeon fails to disclose that outcomes in robotic-assisted cholecystectomy are not superior to conventional laparoscopy (at least at the present time), they have committed an unethical lie of omission.

Sham Procedures

The relative paucity of randomized controlled trials in the surgical literature is well documented. This has been attributed to difficulties with study design, particularly in blinding patients and surgeons to the treatment group, and the ethics of sham surgery. Sham-controlled investigations historically have been utilized to dispute the utility of procedures that were "grandfathered" into practice based on basic pathophysiology and animal studies, but never rigorously tested. Most frequently, sham operations are used to remove ineffective procedures from general clinical practice. Such has been the case for arthroscopic procedures in degenerative meniscal tear [23], gastric "freezing" for duodenal ulcer [24], and internal mammary artery ligation for angina [25]. Investigators frequently encounter moral hazard in their approach to such studies, given that surgeons in a fee-for-service system may suffer financially if a procedure is disproven.

Sham surgery is often necessary to maximize scientific validity in investigations of invasive procedures. A sham operation controls for the placebo effect, which may be pronounced in surgical compared to medical therapy due to higher levels of therapeutic optimism [16]. However, unlike placebo controls in randomized trials of medical therapy, which are biologically inert substances that cause no harm to the subject, sham surgery puts the research subject at risk of pain and complications of anesthesia. Opponents criticize the idea that subjects are necessarily harmed without any reasonable expectation of improvement in their condition. However as discussed above, the goals of clinical research differ from individualized patient care, and a small amount of risk is acceptable if it is a necessary component of an ethically designed study. Phase 1 clinical trials regularly expose human subjects to untested pharmaceuticals with the potential to do harm so that the rest of society may benefit from drug safety data. Some authors pose that the risks of sham surgery are not categorically distinct from the risk to subjects in phase 1 trials [26]. It is understandable, however, that surgical investigators have misgivings about causing physical injury to subjects, a reality rarely confronted by researchers in nonsurgical fields.

Industry Relationships

The use of surgical instruments and materials manufactured by corporate entities in the healthcare industry necessitates a relationship between surgeons and the makers of their tools. Often, industry representatives have expertise in the use of instruments or materials that exceeds that of the operating surgeon, particularly early in the life of a device. The American College of Surgeons released guidelines for the presence and role of healthcare industry representatives in the operating room as it relates to individual patient care [27]. To our knowledge no similar set of guidelines exists to govern the role of industry in surgical research investigating the use of devices and materials. A meta-analysis of industry vs nonprofit-funded research showed a clear loss of clinical equipoise with bias toward the implementation of industry-sponsored products [28]. We recognize the importance of industry relationships to foster innovation and advances in clinical care and see a clear role for industry in

hypothesis development and procurement of materials. However, we believe it is self-evident that profit motive has no place in the results and conclusions of a hypothesis test. Disclosure of industry relationships in the presentation and publication of scientific data has been significantly bolstered by recent requirements for public reporting of financial relationships between physicians and industry.

Authorship

Publication is essential in academia for career advancement and promotion. Publication also has social and financial implications. Ethical dilemmas arise when attempting to give appropriate credit to those who deserve it and avoiding listing those members who did not contribute in a meaningful manner.

Efforts to standardize criteria for authorship have been made to avoid ethical issues. The International Committee of Medical Journal Editors (ICMJE) defines the role of authors and contributors based on four criteria: (1) substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work, (2) drafting the work or revising it critically for important intellectual content, (3) final approval of the version to be published, and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. If there are other contributors that do not meet all four criteria, they should not be listed as authors, but should be acknowledged for their contribution to the work. By establishing these standardized criteria, there is less ambiguity in terms of who should be included as an author [29].

Pitfalls exist, however, when following this system. For example, in collaborative projects, no one author may fit all four criteria. These standards can be used as a guideline, but each case should be viewed independently. Because of this, authorship should be determined at the beginning of a research project. This allows for roles to be clearly defined prior to writing a manuscript [30]. It is equally important for journals and editors to have written authorship guidelines.

The concept of authorship applies widely across academics but also specifically to the surgeon-scientist. Often surgical residents are required to have research experience during their training. Resident research programs supported by faculty mentorship are essential during training to teach these principles early in an individual's career. The definition of "first" and "senior" authorship can vary greatly between fields. Authorship is unfortunately not always determined by contribution but instead unethically "gifted" to individuals based on seniority or honor [30]. Mentors should recognize how the power dynamics of mentor-mentees can be problematic in determining authorship [31]. This stresses the importance of having authorship discussions early in the research process. Principal investigators/attending surgeons should make clear what is expected of the junior researcher to achieve first authorship. Furthermore, mentors in this situation should be aware of their power and be certain not take advantage.

The gender gap is also a consideration as a part of the ethical debate of authorship. The number of women in medicine has increased drastically in recent years, but women are still underrepresented in academic surgery. This directly applies to women's involvement in publication and authorship as well. In female-dominated fields such as obstetrics and pediatrics, there has been an overall increase in women as first and senior authors. However, the numbers are still low in surgical journals. This may be related to the number of women in the field but it is clear that a gap still exists. The gap is likely related to the lack of senior women available to merit these roles. There are barriers to academic advancement of women, specifically the constraints of traditional sex roles, manifestations of sexism, and lack of effective mentors [32]. Career choice differences between men and women may also play a role. In order to increase the number of women represented in surgical journals, it is crucial that effective mentorship programs begin early in surgical training.

There are many factors to be weighed in determining authorship. Overall it is essential to provide framework and guidelines for authorship at the onset of each individual research project. Furthermore, effective mentor-mentee programs can assist to lay down fundamentals for determining authorship and establish clear roles for all individuals involved in the project.

Ethical Concerns for the "Basic Science" Surgeon-Investigator

Certain ethical concerns apply specifically to the basic science surgeon-investigator. It is essential that reproducible, unbiased scientific knowledge is produced. Open publication of methods and data, collaboration between labs, and peer review allow others to confirm or raise questions about results [33]. In recent years, publication of raw data from basic science studies in supplemental figures has become increasingly common [34]. We believe this practice represents a large step forward in the ethical conduct of research.

Replication and repetition must be taken into consideration in all experiments. Replication refers to multiple experimental runs independent of one another, probing variability between separate runs. In contrast, repeat measurements are taken during the same experimental run. It is advantageous to triplicate (or more) experimental runs for statistical reasons. This increases the sample size and thus precision and accuracy of the measurements. It is necessary to recognize that replicates do not necessarily allow interpretations to be made or allow us to draw conclusions about the hypothesis being tested. This is due to the idea that the samples are independent and therefore inferences can only be made about the population from which they are drawn. However, replicating data can act as an internal quality check on how the experiment was performed. Although replicability is important, it can be expensive or impractical in certain situations. In any case, all methods should be detailed, and scientists should be transparent about potential difficulties in replicability [35]. Communication with corresponding authors for clarification of methods is encouraged if questions of replicability arise.

Reproducibility assumes changes to be present in a distinctive setting, while replicability attempts identical conditions [36]. Reproducibility differs from replicability in the amount of variability present and relates to the generalizability of a finding. Casadevall et al. point out that when it is stated that something is reproducible, it is actually meant that it was replicated. Best practice involves repeating experiments on separate occasions, with each experimental run in triplicate. Results and figure legends in publication should be specific on how rigorously reproducibility was tested.

Finally, honest and accurate reporting of data is a fundamental ethical practice. Statistical outliers are frequently removed for analysis of data and are assumed to be nonsignificant. Other practices such as "massaging" data to make it fit, expected, or hoped-for outcomes should be discouraged. Outliers should still be reported even if not included in the final analysis, and the reason for exclusion should be explicatively stated. All authors and contributors to the final paper are accountable for the data that is reported and analyzed [33].

Concluding Remarks

- The ethical conduct of any human subject research requires that investigators be familiar with the best available guidelines as discussed in this chapter. These guidelines, if applied with an appreciation for the humanity of their subjects and their position as contributors to the common good, help to prevent unethical practices.
- Research into surgical therapy is intrinsically different from research into medical therapy; thus research practices necessarily differ. However, the guiding principles of ethical research conduct apply to surgical research.
- Quality improvement initiatives represent an ethical gray area between clinical practice and human subject research. Some forms of qual-

ity improvement are exempt from the rules that govern human subject research; however as a rule, investigation intended to produce generalizable knowledge, whether for broad publication or not, should be considered human subject research.

- Authorship should be discussed openly by all stakeholders at the onset of an investigation, rather than post hoc, and should be determined through objective evaluation of contributions cross-referenced with existing guidelines for authorship.

Glossary

Human subject research A systematic investigation designed to produce generalizable knowledge from observations of human subjects. This term applies broadly, and investigations classified as human subject research are generally subject to IRB review.

Protected health information (PHI) Personally identifiable health information (by which the identity of a study subject could be ascertained) maintained in a medical record that includes data on physical health, mental health, payment information, or genetic information.

Clinical equipoise A state in which two or more therapeutics exist that could treat a given condition; however a lack of strong evidence regarding superiority of either treatment exists. Equipoise is essential to the ethical conduct of clinical research.

Internal validity The relative truth of conclusions drawn through experimentation. Internal validity is directly related to the accuracy with which experimental conditions eliminate confounding and minimize bias. A study with high internal validity can make strong claims regarding causality, rather than simple associations.

External validity The extent to which the results of a study apply to the population being modeled. A study with high external validity is highly generalizable to large patient populations.

Quality improvement Any systematic, data-guided analysis of healthcare processes to improve the quality of care by measuring adherence to evidence-based guidelines of clinical best practice.

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