

Ethical Considerations for Clinical Trials in Inflammatory Bowel Disease

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Abstract: Although advancements in the field of inflammatory bowel disease (IBD) include effective therapies for many patients with Crohn's disease and ulcerative colitis, there remains a large unmet need, and there is a large number of investigational agents in the pipeline. Drug development through clinical trials is critical to understanding the safety and efficacy of new therapies in the affected human population, and the need for ethical trial design is of the utmost importance. This paper explores the ethical issues of clinical trials in IBD, focusing on placebo-controlled trials, vulnerable patients, exposure to monoclonal antibodies, globalization of trials, and surgical advances.

Inflammatory bowel disease (IBD) is a chronic, idiopathic condition. Current treatment options often are unable to achieve disease modification or control. Although there are some effective therapies currently available for Crohn's disease (CD) and ulcerative colitis (UC), there remain substantial gaps in effective treatments for the many patients who do not respond to these therapies. Therefore, better treatments with novel mechanisms of action are needed. The development of these treatments requires clinical trials on human subjects.

The design of clinical trials for patients with IBD must adhere to uniformly accepted ethical standards of human subject research, as established by the Declaration of Helsinki, the Belmont Report, and the code of federal regulations on the protection of human subjects.¹⁻³ These ethical principles include beneficence, non-maleficence, respect for persons, and justice (Table). This review of the ethical implications of human subject research includes several concerns that are specifically pertinent to the IBD patient population. Because surgery is frequently necessary for patients with IBD, we also include a discussion of surgical innovations. We conclude with recommendations for the design of future, ethically sound clinical trials and surgical innovations in IBD.

Table. Ethical Principles in IBD Research

Ethical Standard	Specific Considerations in IBD-Related Human Subject Research
Beneficence	<ul style="list-style-type: none"> – Dissemination of experimental findings – Subjects' access to the study drug following conclusion
Non-maleficence	<ul style="list-style-type: none"> – Nonuse of a placebo-only arm – Patient protection accompanying use of biologic agents
Respect for Persons	<ul style="list-style-type: none"> – Informed consent for any protocol with unknown expectations – Full disclosure of surgical innovation and informed consent prior to new procedures
Justice	<ul style="list-style-type: none"> – Participants in global research have clear, direct benefit – Protection of financially burdened subjects – Protection of subjects with acute or refractory illness

IBD, inflammatory bowel disease.

Placebo-Controlled Trials

A 1984 position paper from the American College of Gastroenterology (ACG) describes several circumstances in which placebos may be used in clinical trials.⁴ In this paper, the ACG asserts that placebo use is ethically appropriate when a standard therapy has yet to be established or when a standard therapy has previously been shown to be ineffective. Another ethical use of placebo is for a population that is intolerant to standard therapy and, therefore, unable to receive it. Furthermore, the position paper notes that placebo has been shown to be an effective treatment in many contexts, including induction and maintenance of remission in patients with active CD and UC.

Since the publication of this position paper, several effective standard-line therapies for CD and UC have been developed and clinically validated. Unless study participants are specifically intolerant of these therapies, the rule of clinical equipoise requires that these therapies not be withdrawn from any participant. Regarding the effectiveness of placebo treatment, this speaks mainly to the highly variable nature of placebo-controlled studies. A 2009 analysis by Sands identified multiple factors associated with the effectiveness or ineffectiveness of placebo treatment.⁵ These included regression to the mean during natural disease progression (depending on the severity of disease within the inclusion criteria), subjects' purported knowledge of the effectiveness of the experimental treatment, the number of physician visits during the study, and even the attitude and tone of the physician while describing possible treatment outcomes. The most strictly controlled studies might aim to diminish the placebo

effect by closely attending to these factors and increasing the risk to subjects, while not attending to these measures might diminish the value of a placebo-controlled trial in the first place.

Nevertheless, placebo-controlled studies remain the most statistically powerful method of elucidating the absolute effectiveness of a therapy. The issue, however, lies in the appropriate use of placebo. The primary reason for this obligation lies in the concept of clinical equipoise. The Declaration of Helsinki proposes that the only acceptable use of a placebo is when there is either no other effective therapy in existence or if no serious or irreversible harm to a subject would be risked by participating in a placebo study arm. The former case is not applicable to the majority of patients with CD or UC; the latter case, although not yet quantified across IBD clinical trials, remains of questionable relevance for any chronic illness. A review of clinical trials in asthma concluded that participants in placebo arms were significantly more likely than those in active treatment arms to withdraw from a study due to serious adverse events.⁶ Similarly, a meta-analysis of studies in hypertension found that any active treatment significantly reduced the risk of serious adverse events compared with placebo arms.⁷ Recognizing that IBD is also a chronic and progressive disorder with consequences from ineffective (or non) treatment, one might argue that the ethical range in which placebo-controlled trials would be justifiable is quite narrow. This may especially be true in the development of analog therapies to existing effective standard-of-care strategies, such as the use of aminosalicylates with novel or different delivery systems.

In addition, more recent work has demonstrated that efforts to reduce the placebo response may essentially eradicate equipoise. In other words, as we move toward more objective measures of disease response and remission, placebo responses and remissions are lower. Although there is a benefit to this from a clinical trial design and statistical power point of view, it raises critical questions about whether it remains ethical to perform placebo-controlled trials, especially for drugs within a class that has been previously (and repeatedly) shown to be superior to placebo.⁸

Vulnerable Patients

In establishing the principle of justice in clinical research, the Belmont Report asserts that some populations are more susceptible to harm than others in the context of clinical trials. Specifically, these populations include subjects unable to give informed consent and those especially vulnerable to coercion or undue influence. Within the IBD population, there are several identifiable areas of vulnerability.

Although the magnitude of uninsured or underinsured patients with IBD in the United States is not known, a 2009 study by Nguyen and colleagues analyzed hospitalization and insurance data from the Nationwide Inpatient Sample between 1999 and 2005.⁹ The study found that uninsured patients with IBD are more likely to be hospitalized than both insured patients with IBD and the general patient population. Furthermore, the rate of hospitalization among uninsured patients with IBD underwent a nearly 2-fold increase during the period analyzed, while the hospitalization rate of the general uninsured population remained steady. As the authors indicate, increased hospitalization in this context may be partly attributed to a decrease in outpatient care among the uninsured.¹⁰ Finally, the investigators found that uninsured patients with IBD were significantly more likely to leave the hospital against medical advice. Data regarding hospitalizations of patients with IBD enrolled in Medicaid are only preliminary thus far.¹¹

Although these rates of hospitalization may have changed since 2005, the consideration of health insurance in the context of IBD clinical trials is important. It is clear that patients without insurance are at risk for failing to receive appropriate medical care under normal circumstances. In turn, participation in a clinical trial in which potentially effective therapy is provided without financial cost may seem very attractive to uninsured patients.¹²

These factors point to an overall vulnerability among uninsured patients with IBD, a group that is proportionally larger than the general uninsured population. Uninsured patients may be more likely to volunteer for clinical trials because of easy and payment-free access to any type of therapy or out of desperation to obtain care. Therefore, in enrolling uninsured patients, great care must be taken to ensure that the patient fully understands and consents to the medical risks involved in the trial and is freely acting in his or her own rational interests.

A second area of vulnerability lies in patients with acute or refractory IBD. Unfortunately, this is common among the UC and CD populations. These patients are vulnerable due to their healthcare experiences with ineffective therapies and subsequent poor quality of life, both of which may increase the propensity to make healthcare decisions based solely on desperation.¹³ It is conceivable that some, if not many, of these patients would actively seek out any new therapy via participation in clinical trials, regardless of the risks involved. The Declaration of Helsinki states that in cases in which no effective therapy has been found, the physician “may use an unproven intervention if, in the physician’s judgment, it offers hope of saving life, reestablishing health, or alleviating suffering.” It is therefore apparent that in enrolling a patient with acute UC or CD in a clinical trial, the patient faces 2 risks: the risk

of continued suffering and the risk of adverse events as a result of unproven therapies. The investigator’s guidance is important, both in helping to inform the decision in a rational manner and in explaining to the patient as clearly as possible the rationale of the study.

On a final note, discussions are currently taking place to revise the “Common Rule,” a set of regulations from the US Department of Health and Human Services (HHS) that specifically addresses human subject research.¹⁴ Of note within the proposed changes is a program to develop a national consent form template. Citing several studies, the HHS finds a trend toward longer, more complicated consent forms that may include legal jargon and a lack of structure between sections. Together, these factors may result in the inability of a patient to make a decision based on a clear understanding of risk. The proposed template would be used by all federally regulated institutional review boards (IRBs), thus giving clearer guidelines for informed consent, helping to remove disparities between multiple sites, and increasing the overall protection of the vulnerable patients in question.

Exposure to Monoclonal Antibodies

One of the most significant advancements in the treatment of CD and UC was the development of biologic therapies, the first of which have been the anti-tumor necrosis factor (anti-TNF) agents. These antibodies act by binding to the cytokine TNF- α and have been shown to be effective in patients with moderate to severe CD and UC. Additional monoclonal antibodies that target other cytokines and molecules are in development. Like any new drugs, these agents must undergo preliminary evaluations in small phase 2 studies before additional phase 3 studies are completed for subsequent review and potential approval by the US Food and Drug Administration (FDA). These phase 2 trials serve to establish the overall efficacy of the drug, but a great deal of time may pass before a subsequent phase 3 trial is completed and the drug becomes commercially available.

The use of biologic agents in clinical trials is associated with unique issues. After a transient exposure to a biologic agent through a single or short set of treatments, there is a risk of development of immune antibodies against the agent in the absence of continuing therapy. In an analysis of data from the ACCENT I trial, Hanauer and colleagues examined patients with CD who had received an initial infusion of infliximab (Remicade, Janssen) followed by a 46-week period of placebo infusions.¹⁵ At the end of the study period, antibodies to infliximab had developed in 30% of these patients. Furthermore, these antibodies were accompanied by an increased risk of severe hypersensitivity reactions and loss of response with future drug exposure.¹⁶

As more new biologic agents undergo clinical testing, investigators should be wary of this significant risk to subjects. Initial studies of infliximab, which led to FDA approval of the drug, did not extend this effective treatment for subjects beyond their conclusion; consequently, these patients had to wait months to a year until infliximab was marketed commercially.¹⁷ Although concomitant immunosuppressive agents or corticosteroids have been shown to reduce formation of anti-infliximab antibodies,¹⁸ this strategy is time-specific and may not be relevant to patients waiting for FDA approval for market distribution.

If enrollment and experimental treatment decrease or greatly decrease the possibility of a potent therapy when it becomes commercially available, such “sacrifice” by human subjects in clinical trials is unethical. In the case of biologic agents, the risk of disregarding this principle is especially great. Patients who are enrolled in an experimental treatment arm involving biologic agents and who demonstrate clear benefit from their treatment should be allowed access to this therapy as part of their continuing medical regimen. This should be explicitly defined in the protocol of any study involving an experimental agent with the potential to elicit a long-term antibody immune response.

Globalization

Due to difficulties in domestic recruiting of patients as well as efforts to capture more diverse patient populations, pharmaceutical companies and contract researchers have sought international locations for study recruitment. Indeed, globally outsourced clinical trials represent a significant portion of current research in IBD. A search at ClinicalTrials.gov for clinical trials in CD and UC found that approximately 21% of current trials are being conducted in developing nations (as defined by the Human Development Index).¹⁹ Each of these trials is sponsored by foreign research institutions, contract research organizations, and/or pharmaceutical companies. Factors involved in the trend of outsourcing clinical trial sites to developing nations include a general willingness to extend the global research community, global or local prevalence of particular conditions, lower cost of labor among healthcare professionals, and larger and more willing pools of potential subjects.

Although these factors may be tremendously advantageous in increasing the effectiveness of research investments and expediting the process of developing new therapies, there are several ethical concerns associated with outsourced clinical trials. The type of ethical oversight for clinical trials in developed countries, such as IRBs or even enforced laws regarding ethical research, may not be as comprehensive in developing nations. The burden then falls mainly to off-site investigators, in which case thorough ethical oversight may prove to be difficult.^{20,21} For example, a recent placebo-con-

trolled trial of granulocyte macrophage colony-stimulating factor for treatment of CD drew enrollment from several Eastern Bloc nations, and the off-site investigators were found to have violated the inclusion criteria and study protocol, clearly skewing the results of the study (C. A. Siegel, oral communication, August 2013).

Specifically, what are the most salient ethical concerns in outsourced research? First, the differences between monetary compensation for both labor and subject participation may prompt a coercive or exploitative research environment. Compensation that is considered standard or modestly adjusted in the Western world may be much greater in a developing economy. Therefore, an excessive payment to overseas research professionals may inspire the pursuit of potentially unethical means to achieve a certain level of patient participation. In addition, excessive subject reward for participation is a definitively coercive method of enrollment; scrutiny of payment for outsourced research is required for proper ethical oversight.

Another concern is the lack of general healthcare access in developing nations. It is often the case in poorer nations that participants in clinical trials do not have access to any basic healthcare outside of the research setting. This is an acknowledged motivation for participation in clinical trials among foreign investigators and subjects.²²

Currently, the best possible way to ensure that clinical trials conducted within this environment are ethically sound is to firmly maintain the system of informed consent and to have appropriate IRB review for patient protection. Although there is a clear benefit for poor participants from developing countries to have access to experimental therapies, the reality is that trial participation is often risky.²³ This should be made absolutely clear to all participating subjects.

Finally, according to the principle of beneficence outlined in the Belmont Report, any research involving human subjects must benefit the patient population on which the research is being conducted. Accordingly, study participants should be guaranteed access to an effective therapy if one should be discovered. As Glickman and colleagues indicate, however, the primary markets for therapies for the most commonly known diseases are developed nations.²⁰ This is a much broader concern to be addressed, and currently it is unclear to what extent outsourced research in IBD benefits the populations of subjects being tested, or if the increasing presence of clinical trials in developing nations is leading to better healthcare and easier access to new therapies in this area.

Surgical Advances

In surgical treatments for IBD, there has been a movement toward new, less invasive procedures, as well as more effective protocols, such as staging and differential timing of restorative ileoanal pouch surgery. Such advances have,

in general, been performed in the hopes of reducing complications of IBD-related surgery, but as with most surgical innovations, they have been implemented without the use of existing standard practices.

Innovations in surgery differ from new drugs in several respects, most notable of which is the fact that patients undergoing surgery present unique profiles that, in many cases, require variation and improvisation on the part of the surgeon. In turn, the use of a novel procedure often arises outside of an explicit research context. The question for surgical innovators then is whether their novel methods should be conducted with the same type of ethical oversight mandated by drug investigators in the ways previously described.

In a 2008 position statement of the Society of University Surgeons, Biffi and colleagues state that any planned procedure that has unknown or less-understood outcomes or contains an apparent risk must not only be accompanied by informed consent, but also must be formally proposed to a local “surgical innovations committee” analogous to an IRB.²⁴ Furthermore, after the procedure is performed, the positive or negative outcome must be made known to the field. This point is important in maintaining the standard of beneficence, as the work performed by the surgeon will then provide a benefit to the patient population at large.

Conclusions

In this review, we have explored the ethical issues of clinical trials in IBD, with a focus on several unique situations for patients with IBD and the healthcare community that cares for them. Although there is a clear need for additional therapies that offer more successful disease control and modification of outcomes, such therapies must be developed through ethically sound clinical trials with appropriate involvement of the global patient population. Patients who volunteer for early-phase clinical trials of biologic therapies should be given access to such therapies so that they do not risk loss of response due to immunogenicity. Surgical innovation in IBD does not always occur in standard IRB-approved clinical trial settings and, therefore, should be accompanied by careful informed consent and appropriate communication of such advances to the rest of the surgical and medical communities.

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