



Clinical Researcher™

The Authority in Ethical, Responsible Clinical Research

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Ethics in Action

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Clinical Researcher™

Association of Clinical Research Professionals

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EXECUTIVE DIRECTOR'S MESSAGE

Winning Hearts and Souls

Jim Kremidas

Clinical research is a team sport. If the people conducting the trial aren't working as a seamless team, you're looking at a trial with such potential problems as adverse events, missed enrollment targets, and other inefficiencies threatening quality and extending already costly bench-to-bedside timelines.

I was excited to join the ACRP team just over three years ago for several reasons, including the fact that our primary membership encompasses study coordinators, principal investigators, and site monitors, among professionals in many other roles. So, when you get right down to the execution of the clinical trial, ACRP members are the people on the front lines ensuring the safety of the patients, pulling and entering the data, and monitoring the documentation, among so many other critical tasks day in and day out.

Yes, we're a good team. Now it's time to take it to the next level. That means taking a hard look at how we do things and being open to the idea of change. It's not always an easy transition.

Making Change Stick

Throughout my earlier work with Eli Lilly, Quintiles (now IQVIA), and other sponsors and contract research organizations, when we tried to drive change in management, we usually took it from a top-down perspective—getting senior executives engaged, trying to drive the change initiative down through the organization, and making changes for the better “stick.” But what I found early on was that you can't do it just from the top down, especially in the medical field, because it's like herding cats. If you really want to effect change, you've got to win people's

hearts and souls—getting those at the grassroots level engaged and believing in the principles of what you’re trying to change.

Having seen so much of the research and development cycle from “the other side,” the opportunity to come to an organization that represents the people who are conducting the protocols was exciting. The entire ACRP team—our membership and staff—are working together to change how people work at the protocol level, so that we can make the changes that need to occur in the industry. This includes new training opportunities, new certifications, and new standards to help define the roles and expectations for every member of the trial team.

Past, Present, and Future

Looking back on the past few years, I’m excited about all that we’ve achieved together and the “State of the Union” ACRP finds itself in as 2018 comes to a close. But you know what? I’m even more excited about what we’re going to achieve in 2019.

As always, thank you for your hard work and commitment delivering the safest, efficient and most effective clinical trials possible.



Jim Kremidas (jkremidas@acrpnet.org) is Executive Director of ACRP.

PEER REVIEWED

Revisiting Ethics and Human Subject Safety in Clinical Research

Maribelle Guloy, MSHS, CCRP

Academic institutions have, on occasion, been found to be in gross violation of the norms for ethical conduct of clinical research by subjecting human volunteers to experiments involving untoward risks to their safety and lives. Similarly, pharmaceutical companies have sometimes demonstrated a lack of ethical sensitivity when pursuing clinical trials in resource-poor countries. Together, these historical events suggest that clinical research should be conducted based on careful and sensitive practices following the ethical principles and regulations highlighted in the following sections.

Part I: Ethics and Federal Regulations

Basic Principles of the Belmont Report

Since its release in 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, the U.S. government's volume on "Ethical Principles and Guidelines for the Protection of Human Subjects of Research" (otherwise known as the Belmont Report) has outlined the guiding principles for the treatment of volunteers in clinical research.{1} It is the cornerstone statement of ethical principles, such as "respect for persons," "beneficence," and "justice," upon which the federal regulations for the protections of subjects are based.

The principle of respect for persons requires that each person has the right to autonomy and that those with diminished autonomy should be protected. Therefore, the ethical guidelines must be clear about providing extensive protection to individuals who cannot self-determine.

A requirement of the principle of beneficence is that clinical research should be conducted with the safety of the human subjects as the primary interest.

A mandate of the principle of justice is that research involving human subjects needs to demonstrate fairness. Fairness means that individuals participating in clinical research are likely to benefit from the results or the applications of the research.

These ethical principles are fundamental for understanding the cross-cultural applicability in the era of globalization of research.{2} An issue for the global community, particularly in the low-income countries, would be the acceptability of the ethical principles developed in regions of the world with different standards of healthcare.

The Common Rule

Applicable federal regulations concerning clinical research have been derived from the ethical principles described in the Belmont Report. The regulations governing human subject research collected in the “Federal Policy for the Protection of Human Subjects” (otherwise known as the Common Rule) by the U.S. Department of Health and Human Services{3} apply to studies supported by federal agencies. These regulations establish the main protective mechanisms for safeguarding the rights and welfare of human research subjects.{4}

Review by an Institutional Review Board

Clinical research institutions are required to protect the rights, safety, and welfare of the research participants under the authority of the U.S. Food and Drug Administration (FDA).{5} An institutional review board (IRB) operating in compliance with federal regulations for human subject protection must be in place.{6} Subject to the FDA’s IRB regulations, IRBs conduct ethical, administrative, and scientific peer reviews of FDA-regulated products.{7}

Summary

The ethics of clinical research and federal regulations have evolved over the past 60-plus years. As the cornerstone of ethical principles, the Belmont Report should remain relevant today. Compliance with these ethical principles and federal regulations provides assurance that the rights, safety, and welfare of research participants are protected.

Part II: Review of Literature

Nature of the Problem

Society's perception of research involving human subjects is shaped by the way this research is conducted by the pharmaceutical and medical device industry, clinical research organizations, medical and academic institutions, investigators, and other clinical research professionals.

Since very early in the history of medical research, violations of the rights of human subjects have been documented.^{8} For example, a long-term U.S. study of untreated syphilis in the Black male population was conducted by the government without informed consent or a certainty of treatment; disabled elderly patients who were not capable of giving consent to a study at the Brooklyn Jewish Chronic Disease Hospital were injected with live cancer cells; and mentally retarded children at the Willowbrook State School in Staten Island, N.Y. were deliberately infected with hepatitis C virus.

Beyond the pillars of ethical conduct of clinical research lies the responsibility of researchers at academic medical centers and in the pharmaceutical and medical device industry to design and conduct clinical trials with consideration for the protection of human subjects. Additional ethical principles should be applied for clinical trials conducted outside the United States—particularly in resource-poor settings.

Part III: Principles of Ethical Clinical Research Conduct

Social and Clinical Value

The fundamental principle of clinical research resides in the value the study has for

society.{9} However, there is ambiguity in defining social value and who decides the constitution of social value with respect to research involving human subjects. Clinical research cannot ensue without the participation of human volunteers who submit to medical experimentations, which may involve risks to their safety and lives.{1}

Nevertheless, in late-phase trials, the potential for benefit to future patients as well as the generalizable knowledge produced in the experimentation can be anticipated. Clinical research ethicists argue that the anticipated clinical value of the intervention justifies the risks involved in the experimentation. Further, they posit that social value resides in the knowledge accrued as part of the experimentation and the anticipated clinical value to future patients.{9} While clinical research offers no promise of direct therapeutic benefit to the participants, the experimentation should be justified in relation to social and clinical value.{10}

Scientific Validity

Clinical research must be designed in conformity with valid scientific principles to produce relevant results.{11} Fair subject selection is also required to ensure that the efficacy and adverse effects of the intervention are being tested in the general population, rather than a subset of the population.{12} The research question, study design, methodology, and statistical plan must be carefully considered with respect to scientific validity and relevance.{13} A systematic evaluation of the different aspects of clinical research should be ascertained by the scientific, local research, or independent ethics committees before the launching of any clinical research conduct.{5}

Fair Subject Selection

Ethical research involves promoting respect for all human beings and protecting their rights and welfare. Subject selection should be done on the basis of scientific importance, not on convenience, vulnerability, or bias.{14} Vulnerable individuals, whose decisional capacity might be limited or restrained based on impaired cognitive skills, unfavorable social, or economic condition, should not be targeted for research participation.{8} Therefore, only those prospective human subjects who meet the research criteria and voluntarily submit for

participation should have an equal chance for selection to participate in the study.{11}

Informed Consent

Informed consent is one of the most important aspects of clinical research ethics. The requirement of an informed consent is designed to protect the rights of human subjects, and such rights should be treated above and beyond the interests of science.{14} Autonomy is an essential element of the consent process to ensure human subject protection; it refers to the subject having autonomy of thought, intention, and action when making decisions about participating in clinical research.

The study information disclosure should be aimed at enabling the subject to understand the clinical research process, the risks and benefits associated with clinical research procedures and the intervention, and the likelihood of success. Under the federal regulations, approval by a competent ethics committee or IRB of an informed consent is necessary before it can be executed in clinical research.{5}

Part IV: Important Concepts and Issues

Minimal Risk

The term “risk” in the human subject protection regulations refers to minimal risks—defined as being such that the probability of harm or injury, such as physical, psychological, social, or economic, occurring from research participation is not greater than that for a person involved in the context of going about their ordinary life or undergoing routine medical tests.{15} Following established professional and scientific standards, IRBs should adopt procedures to avoid the possibility of applying subjectivity leading to overestimation or underestimation of harm.{14}

Undue Influence, Coercion, and Exploitation

Payment to research subjects may be construed as undue influence if it constitutes an amount sufficient to induce an individual who would otherwise not participate in a clinical research study.{12} It raises ethical concerns when it influences individuals by distorting their

perception of risks and benefits.{ 11 }

Coercion is best exemplified in the exploitation of prisoners in clinical research because the incarcerated may be at greater risk for true coercion.{ 16 } Additionally, the prison can be a convenient place to conduct research because of easy accessibility to research participants and the convenience of doing research in a controlled environment. Nevertheless, others view the exclusion of prisoners from clinical research equally unjust, particularly if the research study can improve the care of prisoners.{ 17 }

Prisoners should not be excluded from research participation in the guise of human subject protection, but this view should not be interpreted without following the ethical rules and regulatory guidelines for medical research.{ 16 } In the absence of coercion or undue influence, and if the risk-benefit ratio is justifiable, it may seem unjust to exclude prisoners from an opportunity for improved care. Nevertheless, given the wide range of prisoner abuses in the past, it is critical that the clinical research community should exercise greater care in any research conducted in settings involving incarceration.{ 17 }

Data Integrity

The data lifecycle covers the period from data acquisition to interpretation, reporting, and archiving. Any violation of data integrity brings harmful effects, as it could pave a way for deadly treatments to reach the market, and manifestations of the problem range from falsification and fraud to poor data management.

History is rife with disaster stories related to poor data tracking after an investigational treatment has been dispensed.{ 18 } However, these events led to the development of research regulations and changes in the drug evaluation process. As per Good Clinical Practice guidelines, validation should be conducted to ensure data completeness, accuracy, reliability, and consistency.{ 19 } Professionals in the industry responsible for data reporting and evaluation must ensure that the data are sufficient, valid, and of highest quality.

Conflict of Interest

Investigators with financial interests in companies sponsoring their clinical research studies could create a condition in which their professional judgment may be impaired, favoring their financial interests over the welfare of their patients.{20} As per regulatory guidelines and ethical research, professional judgment regarding the welfare of patients or the validity of research should not be influenced by a secondary interest, such as financial gain.

Scientific interests may also create a condition for conflict. Reported cases of conflict of interest continue to exist, and underscore the need for more ethical oversight to promote transparency and accountability in clinical research.{8} The research community must be vigilant to prevent any potential conflict of interest from arising, and research institutions should create effective and ethical conflict of interest policies to safeguard research quality and trust.{21}

Part V: Special Ethical Concerns in Clinical Research

Research in Resource-Poor Settings

When western pharmaceutical and biotechnology companies conduct research in resource-poor countries, questions arise about which research practice standards should govern the studies.{22} Economic conditions and local cultural traits can influence how these standards are applied.

A critical issue, mainly for low- and middle-income countries (LMICs), is the potential for exploitation. The majority of the population in an LMIC will not have the same resources as those from western countries in terms of health access and affordability.

Clinical research may offer human subjects some benefits of short-term access to care. It may also help build the infrastructure for healthcare and increase research and healthcare capacity. Nevertheless, a requirement of research in LMICs is that it must address the aforementioned questions about rights or justice.

Western pharmaceutical and biotechnology companies should think about whether healthcare economic goals alone constitute suitable reasons to conduct research in an LMIC.{22} To avoid exploitation of an LMIC's population, the research should be relevant to the health needs of the country, better care should be provided, and responsibilities owed to human subjects should be considered.

Another critical issue in conducting clinical research in LMICs is the validity of the consent process.{23} While western standards promote autonomy, some foreign countries view consent as a collective decision-making process.{24} In LMICs in which a subset of the population may be illiterate, or when a tribal chief or elder is traditionally involved in making medical or research decisions, voluntary and fully informed consent may be an issue.

Simply put, the issues surrounding the conduct of clinical research in LMICs can be difficult and challenging, in terms of understanding and knowing which monitoring standards and ethical guidelines to enforce.{22}

The Use of Placebo

There are compelling reasons for the use of placebo in clinical trials, and one notable scenario is when there is no effective treatment available for the condition being studied.{25} The use of placebo is permitted by ethical guidelines when no effective treatment exists, when withholding treatment poses risks, or when compelling methodological reasons are allowed for the use of placebo.{26}

Nevertheless, from an ethics and science standpoint, many consider placebo as contrary to the interests of the subjects, and therefore, not ethical. That view is justified by the argument that when effective treatment exists, the use of placebo is unacceptable.{23}

The relevant question for many is not whether the investigational drug is better than placebo, but whether it is better than standard treatment. Viewed in this light, active treatment controls are because no subject goes without treatment. However, the use of placebo is permissible and ethically acceptable, as it allows researchers to determine whether the effects of a test drug are real or a result of the placebo effect.{25}

Conclusion

Revisiting ethics in clinical research serves to remind the research community about the ethical violations that have occurred in the past. It also serves to enforce the ethical principles and regulatory guidelines that have evolved to protect the rights and safety of human subjects.

Knowledge of the ethical and regulatory aspects of clinical research is essential for all clinical research professionals. Biomedical researchers and other research professionals in the academic community and in the pharmaceutical and device industry have the responsibility to design and conduct clinical trials—in any setting—that make consideration for the protection of human subjects a paramount concern.

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PEER REVIEWED

A Survey on Including Risks in the New “Key Information” Section of an Informed Consent Form

Katelyn Le, MS; Stacy Kopka, MS; Doreen Chaitt, RN, MPH; Jerome Pierson, RPh, PhD; Martha Nason, PhD; Tracey Miller, RN, CCRP



[Note: Since the writing of this article, the Secretary's Advisory Committee on Human Research Protections (SACHRP) of the U.S. Department of Health and Human Services has released recommendations on writing Key Information. The recommendations can be found online at <https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-c-november-13-2018/index.html>.]

Informed consent forms (ICFs) are growing longer and more complex.^{1–4} The forces behind this trend may be well-intentioned, such as the desire to disclose more accurate and complete information^{1}; however, it raises questions about whether important information is buried in lengthy documents, as well as whether ICFs can be structured to better emphasize the information that is most relevant to a study participant.

Recent updates to what is generally known as the Common Rule for protection of human subjects in research are in part meant to respond to this trend. Among these updates is the introduction of a new section called “Key Information”—every ICF now must open with the

most important information that potential subjects would want to know when deciding to join a study. But what exactly should this new section contain?

This question is crucial to us, a group of writers and reviewers who work with investigators to develop ICFs (the program was described in a 2013 issue of the *ACRP Monitor*{5}). For groups like ours, it is important to explore how best to implement the new regulations in a way that promotes consistency across different ICFs.

As an initial step, we wanted to understand how to objectively decide which risks to provide as Key Information. A survey was conducted to investigate how institutional review board (IRB) members, medical monitors, and principal investigators (PIs) view which risks should be considered Key Information. The hypothesis was that cohorts would have differing viewpoints on selecting these risks.

While the findings of this exploratory study demonstrate variability in viewpoints, they also suggest a number of points of consensus to consider when writing Key Information.

A Refresher on Key Information

The Revised Common Rule was issued by the U.S. Department of Health and Human Services in January 2017 and is set to go into effect January 2019. It updates the original 1991 Common Rule regulations to address various issues in modern human subjects research, such as the trend toward longer, more complex ICFs. The addition of the new Key Information section is one such change meant to “combat the growth in length and complexity” of ICFs and stop important information from being “buried.”{6}

As described in the Revised Rule, the consent should give the “information that a reasonable person would want to have in order to make an informed decision” (Title 45 CFR Part 46.116(a)(4) in the *Code of Federal Regulations*). To do this, ICFs now “must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject [...] in understanding the reasons why one might or might not want to participate in the research” (part 46.116(a)(5)(i)).

The Rule's preamble (XIV.A.4) suggests that this section may generally include the following information:

1. "the fact that consent is being sought for research and that participation is voluntary;
2. the purposes of the research, the expected duration of the prospective subject's participation, and the procedures to be followed in the research;
3. the reasonably foreseeable risks or discomforts to the prospective subject;
4. the benefits to the prospective subject or to others that may reasonably be expected from the research; and
5. appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the prospective subject."

Identifying the Most Important Risks

It has been suggested that descriptions of study-related risks and discomforts are one particularly significant factor in bulking up ICFs, { 1 } and risks will likely pose similar challenges to writing "concise and focused" Key Information sections. The regulation provides flexibility in exactly what information to include; the preamble suggests including the "most important risks," like what a doctor might tell a patient in the clinical context with an emphasis on how those risks are changed in a research study (XIV.A.4). The language gives only a rough idea of the length of the "concise and focused presentation."

Although such language gives flexibility to individual projects, it challenges efforts to consistently implement the rule across multiple projects. The subjectivity of this language may make it difficult to reach a consensus on which risks to include in Key Information. In the absence of specific guidance on writing Key Information, a survey was designed to explore outstanding questions about including risks in this new section.

A Survey on Risks in Key Information

A digital survey tool was created using a PDF form and disseminated and returned via e-mail. The survey opened with a brief introduction to the Revised Common Rule and the new Key Information section. Next, the survey presented a four-page ICF Potential Risks section, which

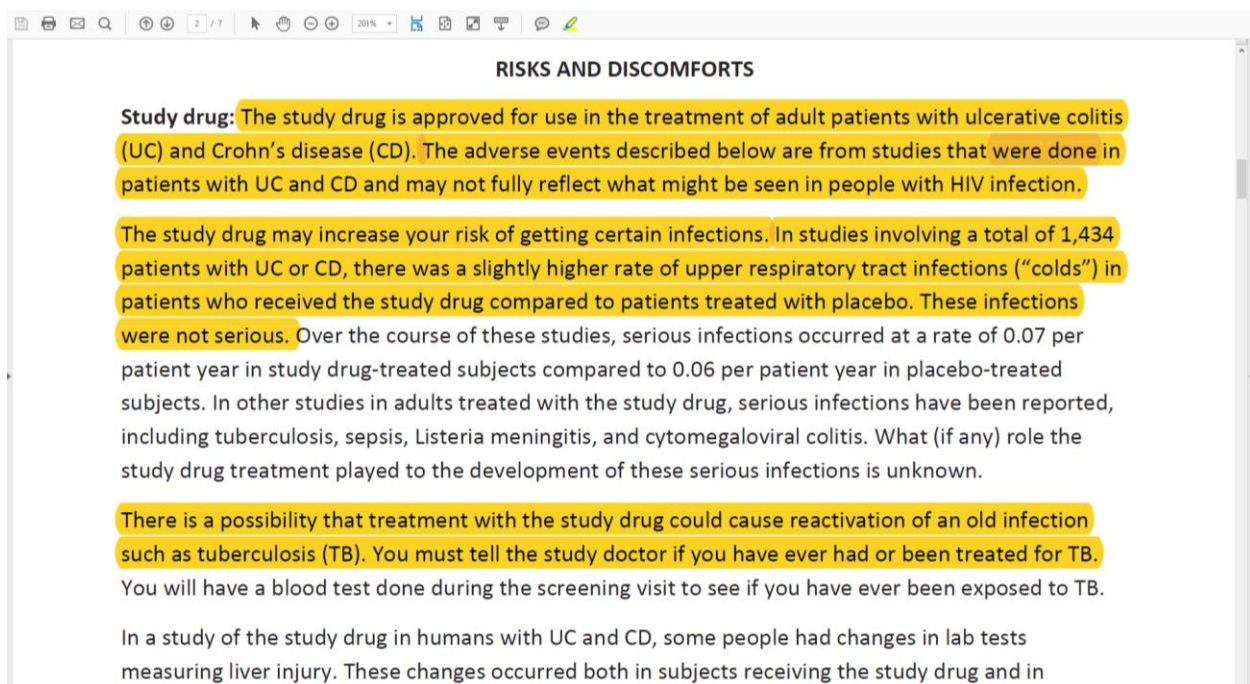
included 39 discrete risk ideas, from an IRB-approved ICF for a Phase I study of a licensed monoclonal antibody in HIV patients.

This ICF language was chosen because it is representative of studies at our institute (early-phase trials of investigational agents), and includes a variety of risks to differentiate characteristics such as frequency, seriousness, and certainty. Additionally, the survey included IRB-approved risk language for select standard (non-experimental) study procedures: bone marrow biopsy, apheresis, and venipuncture.

Respondents were asked to review the sample ICF Potential Risks section and use the digital highlighter tool in a PDF viewing program to mark the risk ideas that they would move to Key Information (see Figure 1). Respondents were instructed to focus on risk ideas, not exact wording, with the understanding that language would in practice be revised to fit into a standalone Key Information section.

An open-ended question asked respondents to explain what factors influenced their decisions in selecting key risks. Also, the survey included multiple choice demographic questions.

Figure 1: Excerpt from a Completed Survey



Respondents used the highlighter tool in a PDF-reading program to identify the risks they would move to the new Key Information section. Text that was not highlighted would remain in the main Risks and Discomforts section of the ICF.

To capture the viewpoints of a variety of stakeholders in human subjects research at our institute, the survey was distributed to three cohorts: all primary IRB members (n: 9), all medical monitors (n: 3), and a convenience sample of PIs (n: 17, N: 29). There were nine responses (response rate: 31%). Respondent demographics are presented in Table 1.

Table 1: Survey Respondent Demographics (N=9, response rate=31%)

Role	Medical monitor	3
	PI	1
	IRB member	5
Time in Research	< 5 years	1
	5–10 years	1
	11–20 years	3
	> 20 years	4
Age	40–49 years	3
	50–59 years	2
	60–69 years	4
Sex	Male	4
	Female	5

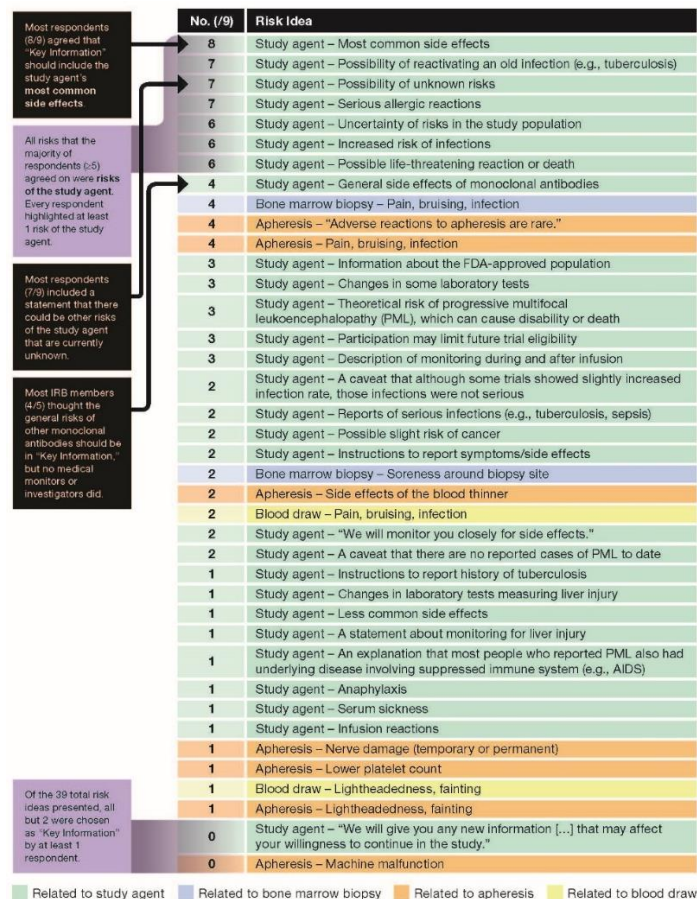
An honest broker deidentified responses before analysis. The surveys were then analyzed by counting and categorizing the risks addressed in the highlighted text.

What Did Respondents Consider Key?

Out of the 39 total risk ideas, there were only seven that most respondents (more than half) agreed to include; all seven were related to the study agent (see Figure 2).

Every respondent highlighted at least one risk of the study agent. The seven risk ideas that most respondents highlighted were the study agent's most common side effects, most serious known risks, risks that are important to the study population, and the possibility of unknown study agent risks. Interestingly, this last risk idea is not a specific "most important risk," but rather a disclosure of theoretical risk. Perhaps respondents felt it important to include as a "reasonably foreseeable risk" an acknowledgement that the study agent is experimental and not all risks can be foreseen.

Figure 2: Respondents Who Thought Each Risk Idea in the Sample ICF Should be Moved to the New Key Information Section



All but one of the IRB members thought the general risks of monoclonal antibodies as a class should be in Key Information, but no medical monitors or PIs did (see Figure 2).

The survey population was not large enough to compare subgroups, so we cannot conclude that there is a significant difference in viewpoints between IRB members and other groups. This finding does, however, support the initial hypothesis that people in different roles in human subjects research will have differing interpretations of Key Information, which is not surprising since one would expect each cohort to review the consent with a different purpose in mind.

Nevertheless, possibly due to the small sample size, this was the only risk idea for which there was a clear difference in response between cohorts. For many of the other 38 risk ideas, individual responses were too variable to identify trends within cohorts. Conceivably, studying a larger population could help identify cohort-specific preferences, but it is also possible that individuals within a single cohort have such differing perspectives that it is impossible to identify trends about what should comprise Key Information.

Of the 39 total risk ideas presented, all but two were chosen as Key Information by at least one respondent (see Figure 2).

This means that almost 95% of the risk ideas in the sample ICF were chosen by at least one respondent. Thus, respondents together thought most of the study risks should be included in Key Information. This may support an argument for considering all study risks as “most important” for a potential subject’s decision.

Of the 39 total risk ideas, each respondent chose an average of 12 risks (range 6 to 19).

Interestingly, the highest and lowest numbers of chosen risk ideas were both from IRB members. These numbers are the result of an artificial task, since respondents were only asked to highlight risks they would move to Key Information, not to write the actual Key Information section. However, differing interpretations of the regulation’s language (for example “concise and focused presentation” of “most important” information) do not define how short this section should be. The Revised Common Rule’s preamble does mention that length may depend on the length of the entire ICF, with longer ICFs having longer Key Information.

What Guided Respondents' Decisions?

When asked what factors influenced their decisions, most respondents mentioned that they considered the severity/seriousness and frequency of the risks. Other factors respondents mentioned were complexity, certainty, and the study population.

Complexity was one topic with divergent implications. For example, one respondent indicated an intention to avoid complexity in Key Information and reserve complex ideas for the main body of the consent (“big concepts [first]...details later”); however, a different respondent preferred to use the Key Information section to address the most complex issues (things anticipated to take the “most time to explain or subjects would most want to know/talk about”).

Also, multiple respondents included discussions of why they did or did not include risks of procedures. Two respondents said that they would include study procedure risks to essentially “kill two birds with one stone”—first to highlight the types of study procedures required on the study and secondly to mention the risks. From these reactions, it appears that when writing Key Information sections, it will most likely be necessary to introduce and briefly explain the study procedures before presenting the risks of those procedures.

Writing Key Information

These findings highlight the variability in viewpoints of research professionals, both between and within cohorts, on selecting risks as Key Information in the absence of more specific guidance. The Revised Common Rule’s language was meant to lend flexibility to the specific contexts of a given study. For example, the content of Key Information will likely differ between Phase I and Phase III studies, since a Phase III study would have more risk information to reference, would be focused primarily on efficacy rather than safety, and in some cases may involve a different study population (e.g., patients versus healthy volunteers).

However, this regulation introduces more subjectivity—and perhaps even bias—into the process of identifying the “most important” risks. Additional official guidance may help minimize variability and facilitate the consistent writing of this new section.

In some situations, a discrete, standalone Key Information section may not be needed. The preamble to the Revised Common Rule acknowledges that institutions may determine that, for simple studies with short ICFs, the requirement for Key Information may be fulfilled by arranging the content so that the “most important” information (such as the required elements of consent) come first, followed by other language and disclosures less relevant to decisions about participation.

This simple solution would avoid repeating content and making broad judgments about which information will be most important to participants. Conversely, in longer ICFs for more complex studies, information would be summarized upfront in Key Information and then provided in greater detail later in the document. For studies with long lists of possible risks, this may mean concisely presenting the most common and severe risks upfront, followed by a comprehensive description of all reasonably foreseeable risks later in the ICF.

In situations where a standalone Key Information section is warranted, the results of this survey suggest considering the following points:

- Focus on the risks of the study agent (or other investigational procedure).
- Mention the possibility of unknown risks in the population being studied.
- Include the risks that are the most frequent and/or serious.
- Anticipate variability in this section based on the protocol specifications (for example, study population, phase, prospect for benefit, treatment alternatives) and the perspectives of reviewers.

Conclusion

This survey was exploratory and limited in nature. It used a small sample at a single institution and, though the overall response rate was within the expected range for electronic surveys, {7–10} the cohort response for PIs was lower than expected (6%).

Respondents could only consider the information provided, which excluded other ICF sections and study documents that may also have affected choices about the content of the Key Information section. In addition to risks, there may be other factors that a “reasonable person”

would find important when deciding to participate, which may affect the length and scope at which risks are discussed upfront.

In the future, the authors of this survey plan to design a larger survey examining risks and the Key Information section in a broader population including research subjects.

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PEER REVIEWED

Ethical Deliberations on Using Placebos in Clinical Trials

Pranali M. Wandile, MS, CCRP

A placebo-controlled, double-blind, randomized clinical trial is the historical gold standard for clinical research, and is fundamental to the development of evidence-based medicine. Research has shown that placebos produce strong, genuine psychobiological effects in both laboratory and clinical settings. Although the approach is scientifically sound, ethical concerns still arise in some cases which outweigh the benefits of this trial design.

According to the critics of placebo-controlled trials (PCTs), if a proven, effective therapy exists, a placebo should not be used. They further stress clause 33 of the Declaration of Helsinki, which states that, “The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s).”{ 1 } It goes on to stress that, “In any medical study, every patient should be assured of the best proven diagnostic and therapeutic methods and no patient should suffer from unnecessary pain.”

However, the proponents of placebo-controlled trials argue that such trials are sometimes essential to prove efficacy and safety of the study intervention. In the absence of PCTs, every adverse event (AE) will be causally linked to the study drug; meanwhile, PCTs are expected to provide a clearer picture of the safety, efficacy, and AEs associated with the investigational drug. In the absence of such trials, ineffective drugs may come in the market, while effective drugs are kept out.

In today’s rapidly developing research and global drug development industry, it’s crucial for regulatory agencies to standardize their recommendations and guidelines for the use of placebos in clinical trials. Implementation of these guidelines will benefit almost all the stakeholders of

clinical research, including human subjects, investigators, members of institutional review boards (IRBs), and sponsors.

Background

Research has shown that placebos produce a strong psychobiological effect in both laboratory and clinical settings.{2} In the 19th century, placebos were prescribed along with remedies which had little therapeutic value, but following World War II, the use of placebos has been seen mainly in clinical research. Psychological factors have been shown to play a major role in the development and progress of such disorders such as psychiatric illness, peptic ulcers, hypertension, cardiac diseases, diabetes, and asthma.{3–6}

In 1962, after the advent of the Kefauver-Harris amendments, there was a paradigm shift in the new drug approval process. For the first time, companies were not only required to prove the efficacy, but also the safety of new drugs for approval by the U.S. Food and Drug Administration (FDA). Thus, the requirement of controlled clinical trials for the approval of investigational products began.{7}

The first rules published by FDA in 1970 identified five types of controls that could be utilized for adherence to the standard of “adequate and well-controlled” trials.{7} While FDA recognized the inconsistencies in assumptions which result in clinical trial interpretations while utilizing different controls such as placebo, dose-comparison, active, historical, and no treatment, it also acknowledged the placebo control as the indispensable tool.{8}

However, some examples of PCTs have triggered serious concerns about their use. For example, in 1996, a patient was enrolled in a clinical trial for Parkinson’s disease which involved injection of embryonic cells into the brain. Prior to study participation, the subject was aware of the possibility of being allotted to the control group. A year after the study’s termination, the subject found that he had not received any beneficial treatment for his disease. During his neurosurgery, there were no embryonic cells injected into his brain since he was randomized to the control group. In this trial, out of 40 study participants only 20 patients received actual treatment.{9}

In the above example, it is clear that those 20 unfortunate Parkinson's disease patients in the control group would have hoped and expected to receive some kind of treatment. This situation raises several questions: In general, under which medical conditions and circumstances are the use of placebos acceptable in clinical trials, and what are the physicians' responsibilities in this regard? Further, in a new interventional treatment trial of critical illnesses or irreversible diseases, should a placebo arm be considered as a part of treatment?{9}

The remainder of this article addresses various situations in which the use of placebos in clinical trials is acceptable versus cases in which it could be unethical. Also discussed are FDA and other regulatory guidelines and views of various research experts.

FDA Guidelines for Ethical Use of Placebo

In 1979, the Belmont Report identified the principles of autonomy, beneficence, and justice as the essential principles of biomedical ethics (for more details about this report, see the article on "Revisiting Ethics and Human Subject Safety in Clinical Research" which can also be found in the December 2018 issue of *Clinical Researcher*).{10}

In 2008, the U.S. Office for Human Research Protections (OHRP) guidelines also stated that, in controlled clinical trials, the subjects must be informed about the risks of participating in a placebo group. The use of placebos must be justified by a positive risk-benefit analysis. Once the evidence of efficacy of the trial therapy is available, it is unethical to continue placebo treatment.{11}

Though the FDA declared in 2008 that foreign clinical trials for New Drug Applications should follow the International Council for Harmonization's tenets of Good Clinical Practice (GCP) rather than the Declaration of Helsinki, the agency hesitated in binding U.S. clinical trials regulations to these guidelines. As what are generally considered GCPs can change without FDA approval, FDA can set its own agenda about placebo controls based on public opinion.{12}

As an example, FDA insisted on placebo controls for antidepressants and proton-pump inhibitors, because it is difficult to read the results of different equivalency trials for such

products due to extensive variations in the responses of study subjects to the active drugs or to placebos.{ 12 }

A Closer Look, Part I: Situations in Which Placebo Use Can be Ethical

According to medical ethics, a physician is legally obligated to act in the best interest of the patient. Hence it's important to know what kind of situation can allow a physician to prescribe a placebo.{ 13 }

The Council of International Organizations of Medical Sciences (CIOMS) created “*International Ethical Guidelines for Biomedical Research Involving Human Subjects*” which mention that the use of placebo in clinical trial is acceptable in the following situations{ 14 }:

When there is no proven, effective intervention available for the condition under study, or when an established treatment is added with placebo and investigational treatment in two different arms. This includes trials of the treatments shown to be efficacious in some populations, but where the data cannot be extrapolated to the population of interest. The use of placebo in this case is typically not ethically controversial.{ 14 }

When withholding an established, effective intervention would expose subjects to, at the most, temporary discomfort or delay in relief of symptoms. Or, we can say, when there are negligible negative consequences of being untreated or receiving no treatment. For example, clinical trials for allergic rhinitis or common headache.{ 15 }

[Placebo usage is not acceptable in a clinical trial where there is a possibility of serious or irreversible harm{ 14 }; for example, in a trial of medications for a serious condition. In trials of new interventions for conditions such as congestive heart failure, if reasonable effective therapy is available, then researchers should compare the new intervention with the available, effective therapy. It could be harmful to use placebo in this situation.

There are some conditions (hypertension, diabetes, etc.) not considered immediately life threatening, but which could eventually be fatal if not treated with effective medications in a

timely manner. It is ethical to use placebo for these conditions for a short duration—a matter of months, rather than years.{ 11 }

When placebo use has compelling methodological reasons which do not expose study participants to risk of excessive harm. For example, compelling methodological reasons may exist for the use of placebo when research participants are not deprived of interventions they would otherwise receive, with the intention to develop interventions that will benefit the host population. In the U.S., Zidovudine reduced HIV transmission rate by two-thirds, however it doesn't produce the same effect in developing countries due to economic factors. PCTs are needed in such cases.{ 16 }

The use of placebo controls is warranted in trials of new treatments for medical conditions when responses to both established treatments and placebo treatments are erratic. For example, depression trials have fluctuating and high placebo response rates. It is common to have inconsistent effects whereby approved antidepressants show superiority to placebos in some trials, but not in others.{ 17,18 } In reference to this phenomenon, please see the sidebar about assay sensitivity.{ 19 }

The Vioxx Gastrointestinal Outcomes Research (VIGOR) trial showed a five times greater incidence of myocardial infarction in the rofecoxib (Vioxx) group as compared to the naproxen group.{ 20 } Naproxen inhibits platelet function, and therefore could have a myocardial protective effect. Due to the lack of a placebo group in this trial, it was unclear if the increased risk of myocardial infarction was due to rofecoxib or due to the naproxen-related, decreased risk of myocardial infarction. Later, based on unpublished results of a PCT of rofecoxib

Assay Sensitivity

Assay sensitivity is a property of a clinical trial which is defined as the ability of a trial to distinguish an effective treatment from a less effective or ineffective intervention. Without assay sensitivity, a trial is not internally valid and is not capable of comparing the efficacy of two interventions.

Research has shown that many classes of drug have problems with assay sensitivity, including analgesics, antiemetics, anxiolytics, antihypertensives, hypnotics, antianginal agents, angiotensin-converting enzyme inhibitors for heart failure, beta-blockers given after myocardial infarction, antihistamines, nonsteroidal asthma prophylaxis, and motility-modifying drugs for gastroesophageal reflux disease.

If equivalence or noninferiority designs are utilized in the clinical trials of drugs which have assay sensitivity problem, it is possible that ineffective drugs will be approved, and it would be unethical to make such drugs available to needy patients based on the flawed science.

(“Adenomatous Polyp Prevention on Vioxx (APPROVe”), Merck decided to withdraw the drug because of an increased cardiovascular risk.{20–23}

If one stuck to the belief that an existing effective therapy is always ethical and preferable, the APPROVe trial might not have been conducted and Vioxx would have caused much more significant damage in later days.

In India, investigators of an acute mania PCT of risperidone were condemned for unreasonably exposing participants to the risks of non-treatment. The investigators defended their work on the basis that the placebo group was required, as patients with mania generally show a high and variable placebo responses, making it difficult to identify their responses to an active medication.{24–26}

Issues

The World Medical Association (WMA) has stated that the non-availability of drugs should not be used as an ethical reason for PCTs, as this may exploit patients and poor countries may become research laboratories for developed countries.{13}

The use of placebos has also involved a risk due to the investigator self-reporting system of continuing review reports to IRBs. A U.S. Department of Health and Human Services’ Office of Inspector General report stated that, in investigator self-reporting system, IRB members are not conducting thorough reviews of previously approved research studies, they generally do not visit or audit research sites, and they rarely oversee the informed consent process.{10}

One of the purposes of continuing review reports is to make sure that a patient’s further participation in a study does not increase his/her health risk. This is very important, especially when the patient is randomized to a placebo-controlled arm lacking investigational or standard therapy. Such insufficient continuing review can mask unnoticed cases of improper, unethical conduct in clinical trials, which can ultimately jeopardize subjects’ health.{10}

In developing countries, access to emergency medical services often is not as prompt as it is in the United States or in other developed countries. Thus, it could be challenging for trial

participants in developing countries to get immediate medical treatment in the event of a serious AE, especially if those patients were randomized to a non-treatment or placebo arm.

Points of View

When the available treatment is moderately and inconstantly effective, and the new treatment is not expected to be more effective than the available treatment, the scientific motivation for performing a PCT should be strongest. {27}

When the available treatment is moderately and inconstantly effective, and the new treatment is expected to be even more effective than the available therapy, a PCT is not required. In other words, we are trying to make sure that the patients will at least receive treatment which could act on their disease rather than something which is completely inert.

When the available treatment is highly and consistently effective, a PCT is not required in order to establish effectiveness of the new drug. {27}

PCTs may not be considered as a good option for cancer clinical trials under the standards of some professionals. However, the emergence of novel, molecularly targeted anticancer agents makes some cancer researchers believe that PCTs are feasible now. {28}

Dr. Schilsky and his coauthors stated that a PCT is ethically acceptable in cancer only when there is no effective therapy available for that condition. In this case, patients assigned to a placebo group should receive best supportive care for pain and for other symptoms, but won't receive anticancer treatment. This method led to the approval of molecularly targeted anticancer agents sorafenib for advanced kidney cancer and sunitinib for gastrointestinal stromal tumors.

Dr. Delon Human, Secretary General of the WMA, stated that a good example of the ethical use of placebo is as part of an “add-on” design for a cancer trial. In this design, all patients receive standard cancer therapy, with study drug intervention and placebo added in other arms of the

trial.{ 13} An add-on trial design led to FDA approval of erlotinib for advanced pancreatic cancer and for advanced non-small cell lung cancer.{ 28}

Meanwhile, proponents argue that PCTs are cheaper, easier to enroll for, easier to interpret, and more definitive in their results than active-controlled trials. Some would say that subjects are not harmed by not receiving effective therapy in short-term PCTs. Active-controlled trials, although valuable, informative, and appropriate in many circumstances, often do not provide reliable evidence of the effectiveness of a new therapy.{ 10,29}

A PCT requires fewer study participants than an active-controlled trial. In disease areas where there are limited patient populations (such as in orphan diseases) and subject enrollment becomes a challenging task, PCTs may be a good option.{ 30,31}

A Closer Look, Part II: Situations in Which Placebo Use is Unethical

The randomized, placebo-controlled, double-blind study is widely considered to be the foremost operational revolution in clinical research which produces the best evidence for the new treatment.{ 2} However, situations may arise in which PCTs lack both scientific and clinical merit, and violate the principle of “clinical equipoise.” Their use may be viewed as not only against the principles of beneficence and human autonomy in general, but also as questionable in vulnerable groups such as children, psychiatric patients, and patients suffering from serious conditions.{ 32–34}

Though the FDA requires PCTs for new indications, there is an issue in randomized PCTs when a control group is needed in order to establish evidence of efficacy and safety for the new treatment. Confusion may occur if the response of a placebo arm is not caused by genuine psychosocial effect, but is a reflection of the natural course of the disease; or a fluctuation in symptoms; or a regression of improvement; or indicative of other concurrent treatments; or the result of a patient’s inconsistent responses while reporting his/her subjective symptoms.{ 35,36}

Issues

Proponents of PCTs argue that they are essential to prove efficacy and safety of the study intervention. In the absence of a PCT, every AE will be causally linked to the study drug, but a PCT can give a truer picture of the safety, efficacy, and AEs associated with the investigational drug.

PCTs are still important due to the psychological nature of many diseases (psychiatric conditions, peptic ulcers, etc.), and are required in situations when it is difficult to read the results of different equivalency trials due to extensive variations in the responses of study subjects to the active drug. Further, concerns about a drug's potential to harm, as opposed to its efficacy, may be difficult to validate in the absence of a placebo group.{21}

Conclusion

To summarize, PCTs may be dangerous if used in trials involving serious medical conditions, as they could deprive patients of available, effective therapy due to the principle of beneficence not being followed. Investigators need to be careful on a case-by-case basis, otherwise they could expose patients to unacceptable risks.

PCTs may be ethically acceptable in some situations when a proven therapy is available and there are compelling, scientifically sound methodological reasons which necessitate PCT usage to determine the efficacy or safety of a prophylactic, diagnostic, or therapeutic method. It may be impossible to interpret a drug's potential for harm and to get a true picture of the AEs associated with an investigational drug in the absence of a PCT.

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RECRUITMENT & RETENTION

Best Practices for Patient Engagement in Drug Development: A Brief Background on Patient Engagement

Debra Michaels



The expectation of patients to be engaged in healthcare decision making and medical product development has been on a steady increase since the early 1980s, when AIDS activists demanded the dedication of adequate resources to research treatments for a disease that was then a death sentence. The expansion of that expectation to the population at large has been stimulated by the availability of widespread and multidirectional communication, and by scientific advances making it possible to better understand the mechanisms of disease and the basis for treatment and cure.

Empowered patients increasingly see themselves as equal stakeholders in a collaborative health system with medicines developers, regulatory authorities, healthcare providers, and payers—and rightfully so, for their insights are the best way for us to understand their experiences, their needs, and what constitutes the value of a medical therapy.

In Search of Clarity

Medical product researchers understand the importance of involving patients in the product development process, but progress toward optimal engagement has been slow. Even with good intentions, we're often unsure about *how* to engage patients and how to be “patient-centric.” Nobody today has the full answer, but the good news is that best practices are evolving from the experiences of early adopters, and we can learn from them.

A note about terminology: the terms “patient engagement,” “patient involvement,” and “patient-centric” or “patient centrality” have been used in these opening paragraphs. In this article, “patient centrality” is used as an umbrella term meaning all patient-centered efforts and activities of an organization to engage patients.

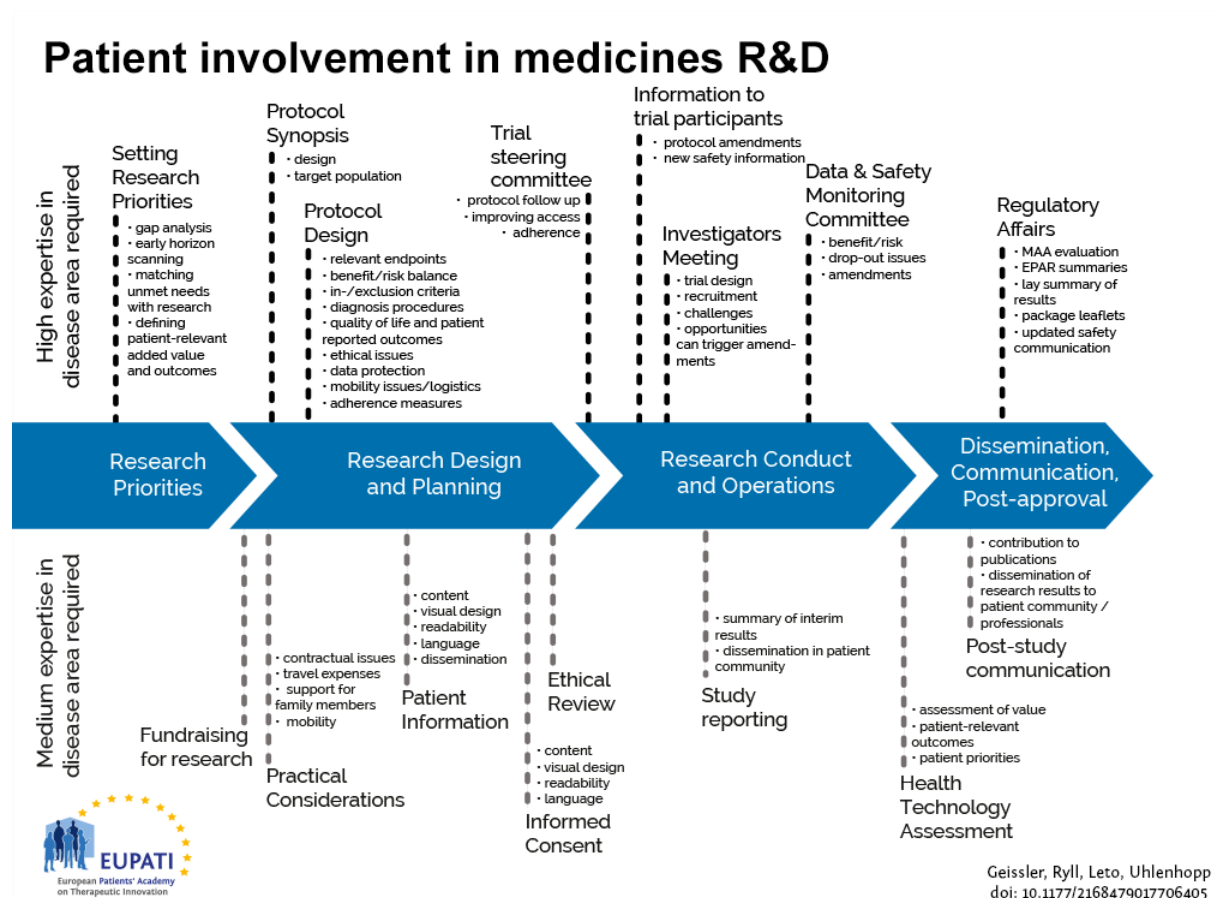
Under this umbrella falls “patient engagement,” meaning direct and constructive interaction with patients in the full medicines life cycle to enable practices that are based on patient perspectives and that result in outcomes that meet patient needs as well as the developer's needs. “Patient advocacy” also falls under this umbrella, and refers to the actions of specific healthcare professionals, known as patient advocates, to advocate for and support the needs of patients, caregivers, and families.

Other terms you'll see in the literature and social media include “patient-centered,” “patient-focused,” and “patient-dedicated,” and new ones are being coined all the time. An insightful industry colleague brought a lengthy terminology discussion to a close by proclaiming, “Let's stop worrying so much about what we call it—the important thing is to just do it.”

How Do We Start to Engage Patients?

Patient involvement in medical product research and development (R&D) can occur at many places throughout the life cycle of the product, as shown in Figure 1 from the [EUPATI Guidance for Patient Involvement in Industry-Led Medicines R&D](#). The ideal would be to engage patients for their input in all of these areas, but to date, that remains an aspiration for most (if not all).

Figure 1



Each organization must start with what is consistent with its own goals and objectives. Often, one functional area within a company decides on its own to seek patient involvement, based on its specific objectives, and this is fine. To paraphrase my industry colleague, the important thing for getting started is to just do it; however, taking the time to follow a few best practices at this stage can lay the foundation for later benefits. For example:

- Bring your team together and discuss where your function fits within the R&D continuum. What outcomes are you charged with? How could patient insights help to improve those outcomes? What would be your team's "win" for successful engagement with the patients you serve?

- Who are the patients you serve, and what does their patient experience look like? What do you know about their patient community? Which patient organizations represent them? What would the “win” be for this community to engage with you? Some companies conduct comprehensive “patient landscapes” to answer these questions and better understand those with whom they should engage.
- Are there start-up or ongoing patient engagement activities elsewhere within your company? What are these, and could collaboration or information sharing be beneficial?

With this basic information, you can approach patient engagement more strategically.

Brainstorm with your team to identify a simple starting initiative that will meet patient objectives as well as yours. Win/win efforts are more likely to be successful.

However, sometimes it’s not apparent what a meaningful engagement might be. It’s always appropriate and helpful to begin building relationships with patient groups representing the patient communities of interest (see the section on best practices for more discussion on this point).

Which Patients or Patient Groups Should We Work With?

Meaningful patient engagement starts from the premise that the patient is an equal stakeholder and brings a specific expertise to the medical product development process. “Patient” is a general term, and it’s important to engage patient representation with the skills and expertise required by the objectives of the project.

A patient may be an individual patient, caregiver, patient group or representative, or a patient advocate. These different types of “patients” have different types of knowledge and abilities to represent the broader patient community that you need to engage. Patient groups vary widely as well—in their purposes, functions, services provided, organizational maturity, staffing, and other characteristics.

Product sponsors often find they must work with more than one type of patient to meet the needs of their research, and more than one group within each type to ensure broad representation of the patient community for whom the therapy is intended. A comprehensive list of questions and

considerations for assessing patient group fit with your engagement effort can be found in the [“DIA Considerations Guide to Implementing Patient-Centric Initiatives in Healthcare Product Development.”](#)

What Are Some Best Practices for Engaging with Patient Groups?

One practice in particular sets the foundation for successful engagement with the patient group(s) you believe can be valuable partners, and that is to establish an ongoing relationship as early in the product development process as possible. If you have responsibilities for recruiting patients to trials and want to engage patient groups to provide outreach advice or assistance, you should be relying on relationships that were formed before the protocol was written and even before the trial was designed.

Experienced patient groups share that they have been asked at the last moment to help rescue under-enrolled trials, and may not be successful in helping if the protocol design is too burdensome for patients or the product does not meet patient needs. Had they been involved at the time key decisions were being made, they may have been able to guide the sponsor to a better product or protocol design.

Engaging with patient groups in long-term relationships with the deeper purpose of open communication and sharing of experience from both perspectives can have intangible, but significant, benefits. According to the [Clinical Trials Transformation Initiative](#) (CTTI), the most valuable insights will come from ongoing, bi-directional communication within this type of trusted relationship.

Partnerships for initiatives with patient groups should be approached similarly to any other stakeholder collaboration, beginning with clear definitions for the following:

- Mutually beneficial goals and objectives
- Expectations of each party in terms of roles and responsibilities
- Information/data that will be shared
- Specifics about resources that will be provided

This is also the time for both parties to define how they will measure the success of the project, including achievement of objectives, impact of the effort, and quality of the engagement.

As with unique and expert input provided by other stakeholders (e.g., key opinion leaders), some initiatives amount to the provision of services by the patient group; for example, participation on patient advisory boards, provision of information on diseases or treatments, or informing product development processes. Patient representatives providing services have the right to expect appropriate compensation for time and expenses, and there is ongoing discussion among stakeholders about how to determine the fair market value of such compensation.

Further, ethical principles, including maintaining independence of the collaborating parties, must be strictly observed (a good discussion of this can be found in [EFPIA's](#) (European Federation of Pharmaceutical and Industry Associations) “Ethical Rules for Collaboration between Patient Groups, (etc.) and the Pharmaceutical Industry.”

It Takes a Village

Best practices for communication during and after the project may seem like common sense, but multi-directional communication is sometimes overlooked or only assumed to be taking place. Clear communication between the collaborating partners should be frequent and ongoing throughout the project for addressing progress, points of difficulty, or changes of direction.

At the conclusion of the project, outcomes should be shared, as should appreciation for the commitment and efforts of the partnering group in the collaboration. Share the project outcomes within your company as well—successes encourage further adoption of patient engagement, and lessons learned help you and others to improve the next engagement project.

Which brings us to one last best practice in engaging with patients: Don't expect perfect outcomes, and don't be discouraged by mistakes. The most important outcome of patient engagement is establishing lasting relationships with the patient communities you serve.

Every sponsor-patient relationship is unique, but sincerity, openness, and mutual respect between partners is generally rewarded, regardless of specific project outcomes. Further, the art and

science of patient engagement are in the early stages of development, and though most of us are still learning, we're at a tipping point. Patient engagement will advance as a practice if we all keep working at it.



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DATA-TECH CONNECT

Achieving a “Win-Win” by Using Technology for Recruitment

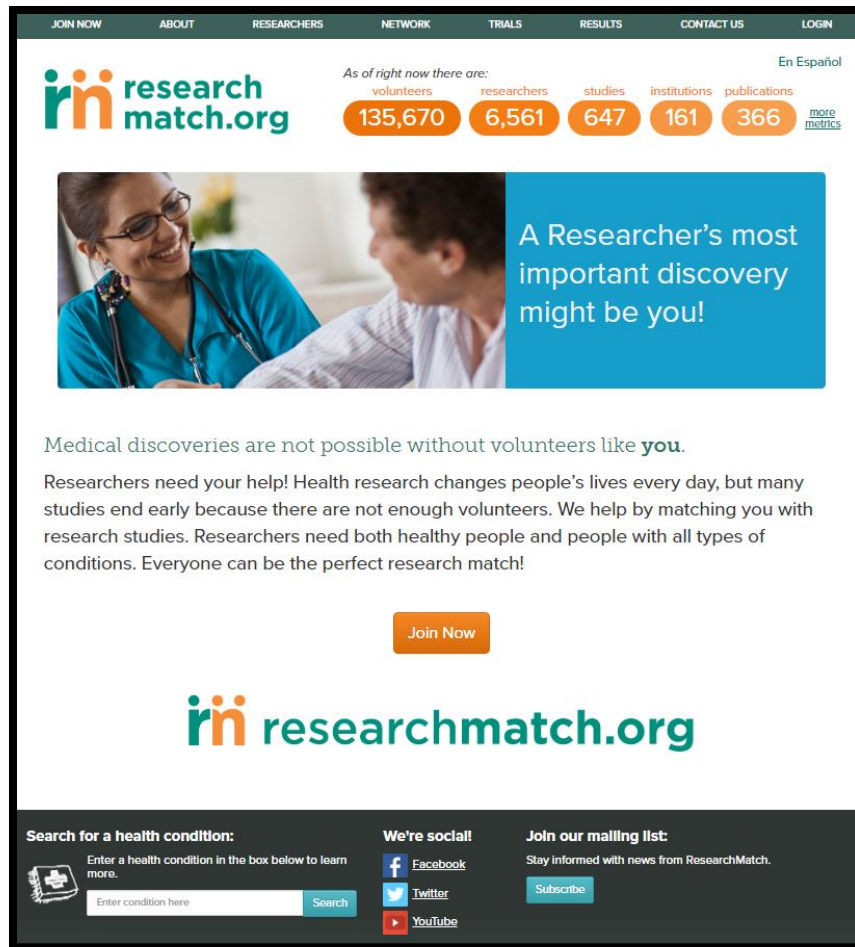
Loretta M. Byrne, RN, MS, CCRP

If you are reading this article, we are part of the same industry, and you know all too well the challenges involved when conducting a clinical trial. Recruitment of research study participants is one of the most challenging aspects of trial completion.

A 2015 analysis of registered trials on ClinicalTrials.gov revealed that 19% were closed or terminated early because they could not accrue enough participants. As many as 86% of clinical trials do not reach recruitment goals within their specified enrollment periods.^{1} Add to this, the challenge of limited budgets for recruitment and the reliance on traditional methods such as word of mouth, physician referral, e-mail and fliers, and institutional or disease-specific registries.^{2}

To create new “win-win” opportunities both for investigators and for U.S. volunteers looking to participate in trials, Dr. Paul Harris and his Vanderbilt team, with input from the Clinical and Translational Scientific Award (CTSA) consortium of academic medical centers, created [ResearchMatch](#) in 2009.^{3} ResearchMatch is a pathway for the public to be connected with researchers, learn about their studies, and get involved, thereby accelerating the completion of trials and promoting the translation of discoveries into treatment.

ResearchMatch receives funding from the National Center for Advancing Translational Sciences within the National Institutes of Health (NIH), but is not specific to the study of any one disease or the work of any one institution. Rather, investigators nationwide share recruitment messages



about a multitude of research topics, such as endocrine and cardiac disorders, rare diseases, and behavioral issues. More than 135,000 people have registered as prospective volunteers on ResearchMatch to be contacted and, if appropriate, be matched to studies. Currently 98% of the volunteers have been contacted with a study opportunity at least once, and of those volunteers, 59% say “Yes, I am interested.”

Support Across the Nation

Asking, listening, and responding to the needs of our audience, changes in the U.S. census, and NIH mandates are paramount to ensuring that the ResearchMatch website is used and is useful.{4,5} Likewise, the development and evolution of new technical features is essential to the sustainability of a scalable and adaptive platform. With institutional review board (IRB) oversight, these additions have included:

- Dissemination of REDCap surveys on behalf of the researchers
- Development of the Trials Today clinical trial search engine
- Integration of Trials Today and ResearchMatch on the volunteer dashboard
- Spanish translation of the ResearchMatch website

Sustainability of this resource is contingent upon enabling a diverse community of volunteers, researchers, and institutional liaisons to use ResearchMatch to its fullest potential, and raising awareness of ResearchMatch as the place to learn about research opportunities and enroll in approved studies. Vanderbilt University Medical Center (VUMC) hosts ResearchMatch, and its IRB provides human subjects protection oversight for the overall project, but specific studies recruiting through ResearchMatch receive approval from their own site-based IRBs or the IRB of record.

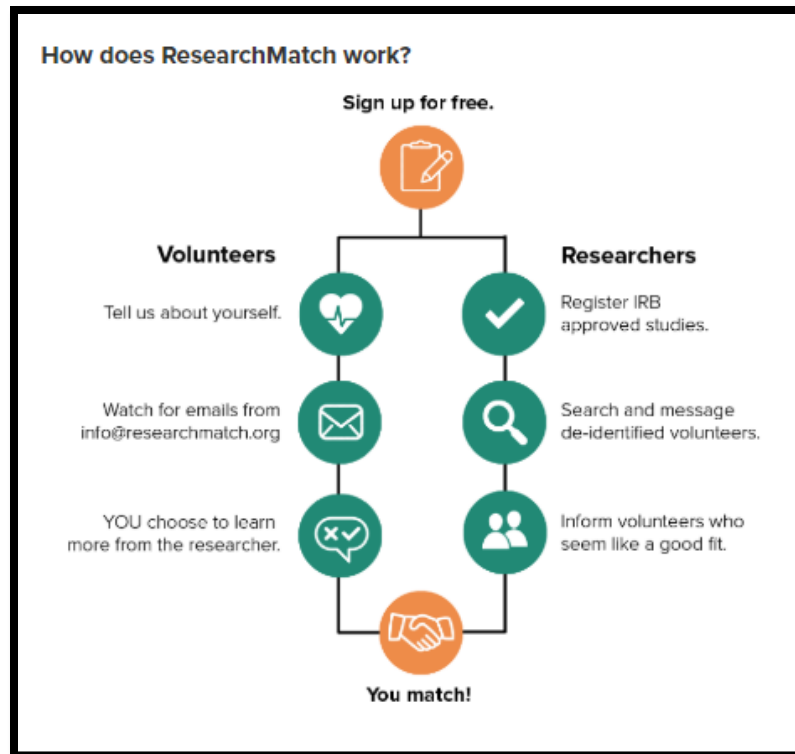
The coordinating team at VUMC engages with researchers and liaisons via monthly webinars and team calls, and provides support via the info@researchmatch.org mailbox. Community events, e-mail, newsletters, social media, and webinars are among the primary methods for engaging volunteers.

The national liaison team is the backbone of ResearchMatch, and is comprised of research administrators, IRB professionals, and recruitment experts from the foremost research facilities in the United States. Not only do the liaisons teach researchers how to use ResearchMatch, they engage with the community and promote use of the platform. Through the promotional efforts of these liaisons, such as handing out brochures at church health fairs and listing the service on their institutions' websites, volunteers find their way to ResearchMatch.

The Network and Volunteers

Each day, new volunteers join ResearchMatch and share information about themselves, including on their demographics, health conditions, medications, and how far they are willing to travel to join a study. By registering, a volunteer essentially raises his or her hand to say "I want to be informed about studies that need my help."

Volunteers' data are securely stored on web servers maintained within the Vanderbilt firewall. All data sent between web server and browsers are encrypted using Secure Sockets Layer protection. Furthermore, all identifiable health and contact information is stored within the database in encrypted format, and never released unless the volunteer specifically gives approval to be contacted by the researcher for a particular study.



The platform is freely available for use by researchers from nonprofit institutions in the ResearchMatch network. Joining the network requires that the institution sign a legal document and assign at least one institutional liaison to coordinate the local IRB's involvement, and to support researchers' and participants' awareness of the platform. Researchers register as users through their institution's

approved portal to ResearchMatch, abide by the oversight of that institution, and agree to treat all volunteers' identifying information as confidential.

ResearchMatch Creates Connection

Researchers with IRB approval to use ResearchMatch and IRB-approved recruitment language register their studies with the system. Before messaging potential participants, the researcher creates a cohort of de-identified individuals who meet inclusion and exclusion criteria specific to the registered study with geographic, demographic, health condition, and medication filters supported by Boolean logic.

The researcher then submits the IRB-approved contact message and may submit an IRB-approved survey, which ResearchMatch sends to the still de-identified volunteers. Volunteers who wish to be contacted by the researcher release their information via a secure dashboard, and the researcher responds to them in a timely manner.

As of the time this column was being written in late 2018, tens of thousands of people had been enrolled in studies with the help of this resource, resulting in 363 publications associated with registered studies. ResearchMatch will continue to develop and grow to support and raise awareness of ways to be involved in research advancements in medicine and improve well-being for everyone.

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GOOD MANAGEMENT PRACTICE

Real-World Evidence: Bridging the Gap Between Clinical and Commercial Development

Heather Fitzpatrick Medlin, MSW



In the highly competitive drug discovery landscape, real-world evidence (RWE) plays an increasingly vital role in commercialization strategies. In fact, the best clinical trial designs deploy RWE to work in tandem with every stage of the product life cycle to ensure ongoing documentation of product value. This way, sponsors are prepared to provide timely answers to key real-world questions.

The reality is that novelty and efficacy, as demonstrated through interventional studies, are no longer adequate indicators of a product's market success. Today's sponsors must address varied information gaps related to RWE that can keep patients, physicians, payers, and policymakers from embracing and using a new therapy in the market.

Fortunately, rapid advancement of health information technology infrastructures and digital solutions in recent years have opened unprecedented access to real-world data. Advanced analytics capabilities enable aggregation and analysis of patient information from electronic health records, claims and billing platforms, product and disease registries, patient-generated data, and other digital sources to power the observational studies that produce RWE. Notably,

recent regulatory initiatives, such as the 21st Century Cures Act, promote use of these data as a driver for better clinical trial design.

The Benefits of RWE

RWE can provide a diverse group of healthcare stakeholders with a deeper understanding of how new therapies work when applied to clinical practice environments. Studies that generate these data can answer questions such as:

- Does the drug or medical device work under actual practice conditions?
- Is it worth the price?
- How does it affect patients' quality of life?
- Is it safe in real-world medical practice?

Traditionally, the scientific community has not done a very good job of integrating interventional discovery with commercial effort. Use of RWE as part of an overarching strategy that documents and communicates the clinical, economic, and human value of a product helps bridge this gap, bringing together the best of interventional research with the best of observational research.

Evidence Strategy and Planning

Like any worthwhile undertaking, research initiatives aimed at building a solid portfolio of evidence require thoughtful planning. Otherwise, the potential positive impact of new therapies can fall flat.

As a first step, sponsors should identify clinical and commercial development priorities and then use formal assessment processes for engaging patient registries and other nontraditional research initiatives to accelerate product acceptance and adoption. Ultimately, the aim is to collect RWE that establishes key value messages for a product that support the clinical trial outcomes data.

Many sponsors engage an experienced contract research organization (CRO) with a dedicated RWE team to develop this plan. Tactics can then be implemented to complement a traditional clinical trial, whether before, during, or after product approval and launch.

Health Economics and Outcomes Research

Understanding the type of RWE that specific stakeholders require before they will accept a new product is critical to successful commercialization. This is accomplished through a health economics and outcomes research (HEOR) strategy that engages various industry groups early in the product development cycle. The goal is to identify key information gaps related to value expectations.

For instance, physicians, patients, payers, and regulators are all interested in how a product improves a patient's quality of life—as well as whether the product is safe in a real-world setting. Additionally, physicians may be interested in how a product works in the care delivery setting. Payers also will likely be interested in health economic data from burden-of-illness and cost-effectiveness studies.

Although these examples provide a glimpse of needed information, stakeholder demands will vary by region and condition, requiring guidance from local experts. An effective HEOR strategy informs what data are needed for an optimal product evidence portfolio and engages approaches such as:

- Economic and patient-reported outcome (PRO) endpoint design
- PRO instrument design and validation
- Economic/PRO literature reviews
- Economic modeling
- Cost-of-illness studies
- Cost-effectiveness analyses
- Retrospective studies
- Product dossier development/updates

Observational Research and Patient Registries

Observational studies also have become an important means of measuring health outcomes, economic viability, the humanistic value of a product, and its safety post market. Supported by

patient registries, these studies collect data such as physician practice patterns and behavior, quality-of-life indicators, health status, resource utilization, and treatment satisfaction.

Like interventional studies, observational research requires a comprehensive approach to design and implementation that must consider such factors as study design and scope, protocol development, regulatory planning, patient enrollment and retention, and data/technology management.

Post-Approval Safety Studies

Time to market is critical once a product receives approval from the U.S. Food and Drug Administration (FDA). Today, the FDA uses RWE to monitor post-market product safety and make key regulatory decisions.

Whether responding to a formal mandate or combining it with a discretionary research initiative, the business case for documenting product safety throughout the product life cycle is an easy one to make. Sponsors can work with a CRO to consider the scope of safety data needs, which can range from focused safety surveillance to broader measures that include clinical effectiveness, cost-effectiveness, and quality of life.

Bridging the Gap

Interventional studies and observational studies complement each other and ensure RWE is available for product commercialization. Strategic clinical trial design guarantees credible RWE supports not only market approval, but also acceptance by key stakeholders.

Because sponsors often have limited resources for conducting clinical research, many turn to an experienced CRO that can deploy a multi-tiered effort. They understand the importance of defining a product's value, as well as supporting its messaging with RWE.

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IRBs IN FOCUS

Dr. Angela Bowen: Pioneer of Research Ethics, and Founder of the Western Institutional Review Board

Lindsay McNair, MD, MPH, MSB; David Forster, JD, MA, CIP

This year marks the 50th anniversary of the founding of Western Institutional Review Board (WIRB), the first established independent ethical review board in the United States. WIRB's parent company, WIRB-Copernicus Group, has spent this year looking back at the last five decades, in recognition of what a remarkable achievement 50 years of human subjects protection really is. An important aspect of this commemoration—and an especially rewarding one for us—was to explore the origins of WIRB, and the woman who made it all happen.



Angela Bowen was born on a farm near Taylorsville, Miss. in 1932, and decided to become a physician early in life, at a time when only about 7% of physicians were female. After graduating from high school at 16, she worked as a nurses' aide to save money to put herself through medical school. In 1951, when she first began attending Mississippi State University (125 miles from Taylorsville), it was the farthest she had ever been from home.

She graduated from the University of Washington School of Medicine in Seattle, Wash. in 1963, one of only four women in a graduating class of 81 students. After graduation, Dr. Bowen completed her medical training and a fellowship in endocrinology in Seattle. She was awarded funding from the National Institutes of Health (NIH) to support her research on diabetes at the Virginia Mason Medical Center in Seattle.

Nurturing the Seeds of an IRB

Dr. Bowen and her husband owned farmland in Olympia, Wash., a town about 40 miles southwest of Seattle. One of Dr. Bowen's patients was Robert Schmidt, owner of the Olympia Brewing Company. In 1967, Mr. Schmidt asked Dr. Bowen to consider moving her medical practice from Seattle to Olympia, to increase the number of local medical providers for the Olympia community. However, moving into private practice would have meant giving up the research grants from the NIH, since the grants had to be awarded to an institution rather than to an individual.

Mr. Schmidt had a solution; he suggested that the Olympia Tumwater Foundation, the nonprofit that was founded by the Brewing Company, could act as the recipient institution for her NIH grants. In December 1967, the foundation's board agreed. However, the foundation wasn't experienced in overseeing medical research, and wanted to make sure that appropriate protections were in place both for the foundation and the research. Before agreeing to take receipt of the grants, the foundation required that Dr. Bowen establish a committee of local physicians to review her research, and that the committee had to find the research conduct ethical and acceptable.

In 1968, this research oversight committee was established. Meeting monthly in Dr. Bowen's office over lunch, the committee members discussed the ongoing conduct of the clinical research studies being conducted under the NIH grants and provided research oversight for Dr. Bowen and soon, for other local physicians as well. Notably, the committee was formed six years before there were any regulations requiring the independent review of clinical research.

Crises and Response

The 1960s marked a critical period in research ethics. In 1962, the U.S. Food and Drug Administration (FDA) regulations for drug approval were greatly strengthened in response to the discovery that thalidomide was causing birth defects. FDA was given the power to approve a drug for marketing only if it was satisfied with the data demonstrating both the drug's safety and efficacy.

Among the era's cases of unethical research, in 1963, it was revealed that researchers at the Jewish Chronic Disease Hospital were injecting patients with live cancer cells to see if they would develop cancer, without consent of the patients. From 1956 to 1972, doctors at the Willowbrook State School for the Retarded in New York were injecting children with hepatitis so they could research treatments. Although consent was technically obtained from the children's parents, admission to the overcrowded school was likely dependent on agreeing to allow the injections, with parents also told that infection was inevitable in the school setting in any case.

Most significant and impactful on research oversight was the publication on the conduct of the "Tuskegee Study of Untreated Syphilis in the Negro Male." Started in 1932, the year Dr. Bowen was born and only 250 miles from her hometown, this Public Health Service study began as an effort to document the outcomes of untreated syphilis to support requests for funding treatments, although the available therapies were largely toxic and ineffective. The study continued for 41 years, despite the subsequent widespread availability of effective antibiotic therapies, which were withheld from study participants, with the continuing support of both the Public Health Service and medical organizations. In 1973, a reporter became aware of the study and wrote about it in the *New York Times*, bringing it to the attention of the public and Congress.

These incidents, among others, finally led to Congressional action. Congress passed the National Research Act of 1974. These issues also drove the Department of Health, Education, and Welfare (now the Department of Health and Human Services [HHS]) to adopt the first regulations for the protection of human subjects in research in the same year. These regulations required institutions to form a committee—an institutional review board (IRB)—to review and approve all research proposals before they were submitted for federal funding requests. Adopting this new terminology, Dr. Bowen incorporated her research oversight committee as the Western Institutional Review Board (Western IRB, or WIRB) in 1974.

Since these new regulations were part of the federal research funding process, they did not apply to research that was privately funded (such as by pharmaceutical companies) or conducted under the oversight of agencies such as the FDA. The National Research Act also led to the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral

Research. The National Commission wrote a series of carefully deliberated reports on the ethical conduct of research, culminating in the Belmont Report in 1979.

In 1981, as a result of the National Commission recommendations, HHS modified its regulations. For the first time, the FDA adopted regulations requiring IRB review of FDA-regulated clinical research, whether it happened in an institution or in a private doctor's office.

Many hospitals conducting research had already established IRBs for federally funded projects which could absorb the additional review of FDA-regulated research. However, anyone practicing medicine and doing research in private practice, or at an institution that didn't already have an IRB in place, needed to find an IRB to review their work.

By that time, Dr. Bowen and WIRB were well-known to the FDA and to many pharmaceutical companies with which she or the other Olympia physicians had worked. Dr. Bowen had established a reputation as an ethical researcher, with an IRB that already had 13 years of research review experience. During the next several years, WIRB grew rapidly as it became the primary IRB for FDA-regulated research conducted in physicians' practices and clinics. WIRB was the original model of a "central IRB" in the United States.

A Continuing Legacy

In subsequent years, WIRB has been prominent in many landmark events shaping the clinical research oversight and regulatory structure of the United States. For example, when regulatory lapses caused the shutdown of local IRBs at some major academic research centers in the late 1990s, Dr. Bowen and WIRB were asked to step in and provide the necessary research oversight to allow critical research studies to continue until the local IRBs could become compliant and be reopened.

Support of research institutions grew rapidly. WIRB now has formal agreements to act as the reviewing IRB for more than 2,700 institutions and academic medical centers. From those lunchtime meetings in Dr. Bowen's office in Olympia, WIRB has grown into an organization that now reviews almost 3,000 new protocols each year, with oversight of more than 30,000 investigators.

WIRB's central IRB structure also foreshadowed the significant changes in IRB oversight for all clinical research in the United States. In January 2018, the NIH implemented a policy mandating that all multicenter studies under NIH grants be overseen by a central, single IRB rather than multiple local IRBs. The revised Common Rule, which is currently expected to become effective in January 2019, also includes a single IRB requirement for multicenter research. The IRB system in the United States has steadily evolved during the past four decades to look more and more like Dr. Bowen's original model of IRB oversight.

After retiring from WIRB in 2012, Dr. Bowen passed away at her home in Olympia in 2017. The organization she founded continues, celebrating its 50th anniversary this year. It is a privilege for all those at WIRB to be part of an organization which had played such a remarkable role in the facilitation of scientifically rigorous and ethically conducted clinical research during the last half-century.

Several of Dr. Bowen's former colleagues share their memories of her compassion and determination in a video at <https://wgcclinical.wistia.com/medias/evwue1d2uz>.

To learn more about the history of WIRB, visit <https://www.wcgirb.com/50>.



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Rather consistently over the years, several general areas have comprised the most usual areas of clinical investigator noncompliance, although there are emerging signs that CDER is finding more cases of significant noncompliance today.[1] Overall, the following five areas represented the most frequent citations in CDER-issued Form 483-Domestic Inspectional Observations in FY2017:

- Failure to follow investigational plan/protocol (26% of sites cited);
- Inadequate/inaccurate records (14% of sites cited);
- Inadequate drug accountability (3% of sites cited);
- IRB communication (2% of sites cited); and
- Failure to obtain and/or appropriately document subject consent (2% of sites cited).

For trials conducted outside the U.S., the list of most frequent citations is similar, and given year-over-year trends, it is likely that many of the above deficiencies will remain on the top 5 lists in 2018. Why is it that we as an industry cannot meaningfully impact these statistics?

It can be argued that all of the above areas of noncompliance can be easily addressed with focused training programs. When the root cause of the learning need is clearly identified, a well-designed training solution with relevant case scenarios, practice in building new skills, and measurement of learning outcomes can be quite powerful. Training, thoughtfully designed and done well, can present a prime opportunity to address knowledge gaps, and ultimately, circumvent the types of issues that are seen over and over again in common inspection findings.

Despite numerous ROI-focused studies that demonstrate the positive outcomes on well-designed training initiatives on overall job performance, employee engagement and retention, and ultimately costs, all too often we hear that training budgets are minimal (or non-existent), and employers commonly delay training due to their employees' inability to take time away from critical work tasks. However, it is important to remember that the key benefits of well-planned training initiatives include:

- Improved overall employee performance
- Improved job satisfaction and morale
- Increased adherence to quality standards and role requirements
- The opportunity to identify and address knowledge gaps and weaknesses
- Reduced employee turnover and an enhanced company image

Given technology advances in training, many training platforms are available to meet the demands of busy professionals, providing flexibility in costs and time away from daily job

responsibilities. Successful implementation of competency-based training programs includes the design and delivery of training using an appropriate platform that supports employee engagement and optimal performance. Some options include:

Virtual Classrooms: Interactive online learning environments such as virtual classrooms (i.e. Blackboard, Saba, and others) include many of the same attributes as instructor-led classes. Live engagement between the trainer and learners (presentations, information sharing [whiteboard], discussion and Q&A, access to learning resources, and group collaboration) promotes learner collaboration on course activities in groups via a designated online "room." This approach also allows the trainer to work with each group in their "room" to answer questions and to support and facilitate learning. In a virtual classroom environment, assessment mechanisms can include knowledge checks, case study reviews, and more robust exams. Virtual classrooms provide the platform for the trainer and globally located participants to collaborate and interact just as they would in an instructor-led class, or at their own pace.

Live Classrooms: The value of face-to-face training cannot be understated, and live, instructor-led classroom training brings the trainer and learners into the same room, in the same location, allowing for active, intimate engagement and interaction between the trainer and learners. In addition to course delivery, facilitated discussion and Q&A time helps learners to internalize training and often, team collaboration is greatly enhanced through group work. Assessments can be delivered in a variety of ways, including knowledge checks, robust exams, and/or demonstration of learning through interactive exercises.

Web Seminars: Web seminars are interactive, live training presentations in which the trainer and learner connect via platforms such as WebEx, Adobe Connect, and others. Webinars include: live training presentations, discussion and Q&A with the trainer and learners, knowledge checks, as well as communication features via the “chat” tool and breakout groups.

Self-Paced eLearning: eLearning is a self-paced, online learning activity that delivers training to the learner, but does not include live trainer interaction (discussion, Q&A, etc.). eLearning content and technology use varies, particularly as it relates to interactivity with the learner. For example, slides with audio narration do not allow learner engagement with the course materials; however, the use of eLearning software engages the learner with exercises, activities, knowledge checks, and quizzes.

The value of training your teams – including new and experienced personnel – cannot be overstated, particularly in ensuring that your teams have the skills they need to operate in a GCP-compliant fashion. As an industry, it is critical that we recognize the value of employee training and development, and in particular how it raises the competencies of our shared workforce as a whole.

[1] [Barnett’s *Good Clinical Practice: A Question and Answer Reference Guide 2018*](https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM438250.pdf) and (<https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM438250.pdf>)

About Barnett International:

Barnett International's consulting, education and training services provide thought leadership and the expertise required to achieve your training goals while utilizing a variety of training platforms, resulting in the initial and on-going development of a competent and compliant workforce. We invite you to hear several of Barnett's senior trainers address critical training topics at the upcoming ACRP 2019 in Nashville:

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