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Ethical Issues at Sites and Beyond

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In a 2015 survey of nearly 2,000 global investigative sites, Novo Nordisk was rated **the best biopharmaceutical company to work with.** — *CenterWatch*

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CONTENTS

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ABOUT OUR COVER: Ethical issues arise in innumerable aspects of the clinical research enterprise—ensuring participants' autonomy through the informed consent process (as portrayed taking place here at the University of Virginia Health System), considering additional protections for vulnerable participants, maintaining distributive justice by ensuring that neither the risks nor the benefits of research unfairly accrue to one group, and more.

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Columns

Home Study

Special Conference Section

Features

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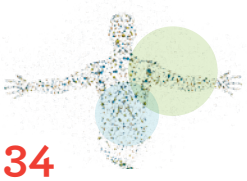

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GUEST EDITOR'S MESSAGE
Lindsay McNair, MD, MPH, MSBioethics

[DOI: 10.14524/CR-16-4004]

Past, Present, and Future: Ethical Issues at Sites and Beyond

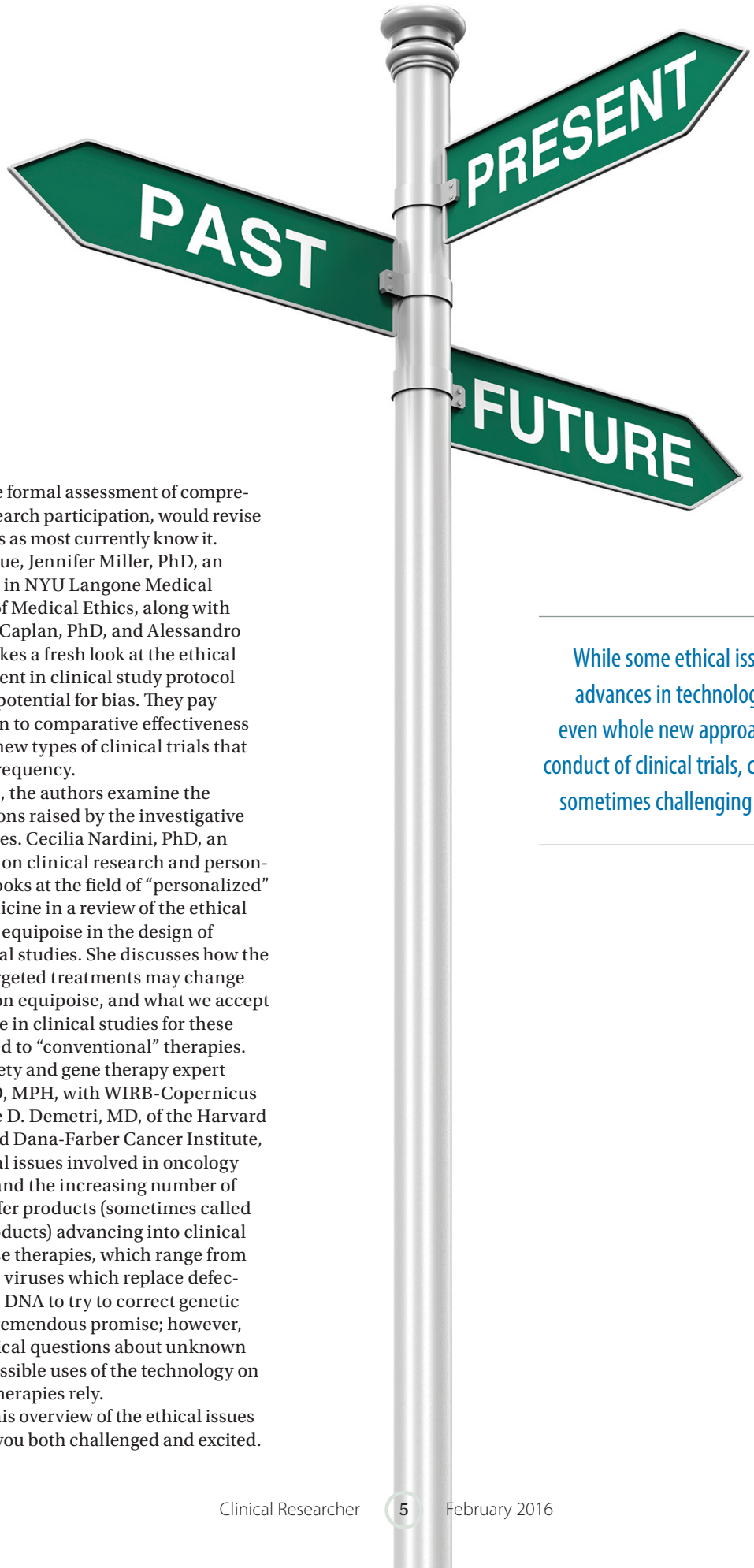
As everyone who works in clinical research knows, ethical issues arise in innumerable aspects of our work. The ethical constructs and codes that direct and support clinical research, and form the basis for most of the regulations, were laid out in the Nuremberg Code, Declaration of Helsinki, and the Belmont Report. The mandates that direct our work now—ensuring participants' autonomy through the informed consent process, considering additional protections for vulnerable participants, maintaining distributive justice by ensuring that neither the risks nor the benefits of research unfairly accrue to one group, and minimizing research risks while ensuring that the risks are reasonable in relation to the potential benefits of the research—will continue to do so in the future.

However, while some ethical issues remain constant, advances in technology and medicine, and even whole new approaches to the design and conduct of clinical trials, can raise unexpected and sometimes challenging ethical considerations. In this issue of *Clinical Researcher*, we will explore the future of research ethics. Our authors examine the recent changes in the science, design, and ethical and regulatory oversight of research, and consider their potential impact on those who conduct clinical studies. In the collection of articles written for this issue, authors who are experts in specific areas of clinical research ethics have contributed their thoughts on where we are today, and the changes we can look for—and look forward to—in this field.

What's Ahead

In the first article, we start at a high level with the regulatory infrastructure for clinical research. WIRB-Copernicus Group Chief Compliance Officer David Forster, JD, MA, CIP, and Copernicus Group IRB Vice President of Quality Management David Borasky, MPH, CIP, look at anticipated changes in research oversight and ethical review of clinical trial protocols. The U.S. Department of Health and Human Services' Notice of Proposed Rulemaking was released on September 8, 2015, and details proposed revisions to the Common Rule which guides institutional review boards (IRBs) in the protection of human research participants. Potential changes include a continuing movement toward the centralization of IRB review, and revision of informed consent for future research on biospecimens collected during clinical trials. While the Common Rule applies only to federally funded research, the U.S. Food and Drug Administration (FDA) has stated that it intends to make regulatory changes to align with the revised Common Rule once the final policy is in place. As a result, researchers and sponsors working on FDA-regulated products have been watching this discussion carefully.

We next move toward the clinical study level, as Elizabeth Bankert, MA, director of the IRB at Dartmouth College, and Judith L. Forman, MPH, research associate in the Clinical Trials Unit of the Dartmouth Institute for Health Policy & Clinical Practice, reassess the informed consent process. In addition to reviewing the important ethical concepts that underlie the basis of informed consent for research, the authors report on a technique that looks at assessment of participant comprehension of information as an essential component of the consent process. Wider adoption of this process, or



similar tools for the formal assessment of comprehension before research participation, would revise the consent process as most currently know it.

Later in this issue, Jennifer Miller, PhD, an assistant professor in NYU Langone Medical Center's Division of Medical Ethics, along with colleagues Arthur Caplan, PhD, and Alessandro Blasimme, PhD, takes a fresh look at the ethical implications inherent in clinical study protocol design, and at the potential for bias. They pay particular attention to comparative effectiveness studies and other new types of clinical trials that are increasing in frequency.

In other papers, the authors examine the ethical complications raised by the investigative products themselves. Cecilia Nardini, PhD, an ethicist and writer on clinical research and personalized medicine, looks at the field of "personalized" or "precision" medicine in a review of the ethical concept of clinical equipoise in the design of randomized clinical studies. She discusses how the development of targeted treatments may change both our reliance on equipoise, and what we accept as clinical evidence in clinical studies for these therapies compared to "conventional" therapies.

Further, biosafety and gene therapy expert Chris Jenkins, PhD, MPH, with WIRB-Copernicus Group, and George D. Demetri, MD, of the Harvard Medical School and Dana-Farber Cancer Institute, describe the ethical issues involved in oncology clinical research, and the increasing number of human gene transfer products (sometimes called "gene therapy" products) advancing into clinical development. These therapies, which range from modified T-cells to viruses which replace defective DNA with new DNA to try to correct genetic mutations, show tremendous promise; however, they also raise ethical questions about unknown risks, and other possible uses of the technology on which these new therapies rely.

We hope that this overview of the ethical issues ahead of us leaves you both challenged and excited.

While some ethical issues remain constant, advances in technology and medicine, and even whole new approaches to the design and conduct of clinical trials, can raise unexpected and sometimes challenging ethical considerations.

Lindsay McNair, MD, MPH, MSBioethics, (LMcNair@wcgclinical.com) is chief medical officer and president of consulting services at WIRB-Copernicus Group in Princeton, N.J.

BY THE NUMBERS

Presenting some of the latest big-dollar and big-controversy trends affecting the health and welfare of the clinical research enterprise.

A recent study found that implementing an authorized generics strategy produces a **5,100%** return-on-investment for drug companies, or higher than any other lifecycle management strategy examined in the research as companies seek to maintain profits and avoid patent litigation.

Source: Cutting Edge Information, www.marketwired.com/press-release/-2079407.htm

If not for the veto of the California Right to Try Act from the state's governor last October, the Golden State would have been the **25th** to adopt the legislation (after Illinois and Oregon in August), which lets doctors prescribe treatments for terminally ill patients that are being used in clinical trials, but are still awaiting final approval by the U.S. Food and Drug Administration.

Source: The Goldwater Institute, http://goldwaterinstitute.org/en/work/topics/healthcare/right-to-try/calif-gov-brown-vetoes-right-to-try-bill-denies-te/

Top 10 pharmaceutical companies' global health economics and outcomes research (HEOR) budgets range from **$18** million to **$30** million, according to a recent benchmarking study, and roughly half of this spending is dedicated to brand-specific HEOR activities.

Source: Cutting Edge Information, www.marketwired.com/press-release/-2082080.htm

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[DOI: 10.14524/CR-16-4002]

It's Time to Tackle Ethics

Ethics can be subjective. Your viewpoint could be different from mine. What we define as good ethics can also change over time.

Google makes it so easy to find a simple definition of ethics. Take your pick:

- "A branch of philosophy considering the rightness and wrongness of actions and the goodness or badness of the motives and ends of such action."
- "Systematic rules or principles governing right conduct."
- "Rules or standards governing the conduct of a person or the conduct of the members of a profession."

However, the essence of ethics as a concept, as a concrete way of living and working each day, is not always so easy to articulate.

Ethics can be subjective. Your viewpoint could be different from mine. What we define as good ethics can also change over time. For example, 50 or 60 years ago, few parents thought twice about smoking in the car with their child in the backseat. Today, of course, it is a clear ethical dilemma: You might really enjoy smoking that cigarette while riding down the highway, but it's proven to be harmful to your child's health. It's an ethical choice that was not even recognized as one by most people until relatively recently.

Going further back in time, consider that some of the so-called ethical practices of even a recognized genius like ancient Greece's physician Hippocrates would land him in jail today.

WHERE WE STAND

For so many reasons, people and organizations benefit from rigorously vetted and updated ethical guidelines. These can serve as the foundation for the protection of shared values.

At ACRP, we've been actively working with members to help promote the highest possible standards for everyone in our industry. It's a group effort that must incorporate new information and new understandings.

While ethics matter everywhere, ACRP professionals literally work in life-and-death environments. I can think of no other situation where strong, clearly defined, ethical best practices are so important. Put simply, the stakes could not be higher.

LET'S TALK

I hope some of the topics raised in this issue of *Clinical Researcher* will spark discussions. I'd like to thank Guest Editor Lindsay McNair for laying out the reasoning behind the articles selected to appear in these pages.

As always, I encourage you to reach out to me to share your thoughts and experiences. Each of us needs to work hard, and to help each other, as we seek to articulate a strong code ethics for life in a complex world.

Brent Ibata, PhD, JD, MPH, FACHE, RAC, CCRC, CPI, CHRC

[DOI: 10.14524/CR-16-4001]

Hospital Approval—

Non-Delegable Obligations of a Covered Entity

Non-academic hospitals knowingly and unknowingly engage in clinical research every day, and these hospitals have non-transferable obligations, particularly when the research has been reviewed and approved by an external institutional review board (IRB).

These studies utilize a wide gamut of hospital services, from outpatient diagnostics to surgical services for implantable investigational devices, and the non-delegable obligations (see Table 1) depend on the variety and complexity of research-related items and services.

When an institution does not have its own IRB, it may delegate some, but not all institutional obligations to an external IRB. For example, while a central/external IRB may review and approve a protocol and informed consent, a central/external IRB cannot determine whether there are adequate resources available at a local site, nor can it verify that local staff has been adequately informed about the protocol.[1]

With the trend for centralization of IRBs, there remains a need for local institutional administrative review of research, since certain obligations may not be delegated to centralized review. Federal regulations anticipate and allow for separate and distinct institutional review of IRB-approved research:

> [Research] that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.[2]

While an institution may rely on the review and approval by another institution's IRB, the responsibility for "safeguarding the rights and welfare of human subjects" and compliance with the policy of the U.S. Department of Health and Human Services (HHS) for the protection of human research subjects remains with the institution, and may not be delegated for federally funded cooperative group research. Additionally, institutions with federalwide assurances (FWAs) on file with HHS's Office for Human Research Protections (OHRP) have obligations under those FWAs that are non-transferable.[3]

TABLE 1: Non-Delegable Institutional Obligations

Obligation	Reference
Adequate facilities with qualified staff	ICH E6 4.2.3
Adequately informed hospital staff	ICH E6 4.2.4
Federalwide assurance (FWA)	45 CFR 46.103
HIPAA waiver—verification of documentation	45 CFR 164.512(i)(2)
HIPAA accounting of research disclosures of PHI	45 CFR 164.528(b)(4)
Mandatory billing codes and modifiers National Clinical Trial number Z00.6 Diagnostic Code (formerly V70.7) IDE number (device studies) Q0/Q1 HCPCS modifier	Medicare Claims Processing Manual, Chapter 32, Sections 68-69
Medicare coverage of Category A and B IDEs	42 CFR 405.201-215
Non-commercialization of investigational devices	21 CFR 812.7
Qualified clinical trial verification	NCD 310.1

Adequate Facilities with Adequately Informed Staff

For clinical research utilizing institutional resources at a hospital, the International Conference on Harmonization (ICH) E6 Good Clinical Practice Consolidated Guidance (ICH E6) requires that the investigator confirm that the institution has qualified staff and adequate facilities, and that the institution's staff has been adequately informed (emphasis added):

> 4.2.3 The investigator should have available an adequate number of **qualified staff** and **adequate facilities** for the foreseen duration of the trial to conduct the trial properly and safely.
>
> 4.2.4 The investigator should ensure that **all persons** assisting with the trial are **adequately informed** about the protocol, the investigational product(s), and their trial-related duties and functions.

HIPAA, HITECH, and Protected Health Information

The Health Insurance Portability and Accountability Act (HIPAA)[4] of 1996 permits IRBs or privacy boards to approve research uses of protected health information (PHI). However, multiple obligations remain with the covered entity related to research uses of PHI. The Health Information Technology for Economic and Clinical Health (HITECH) Act of 2009 substantially increased the monetary penalties for violations of HIPAA, and covered entities have continuing obligations to ensure that research uses and disclosures of PHI are compliant with HIPAA regulations.[5]

If an IRB or privacy board has approved an alteration to or waiver of a patient's right to individually authorize research uses of PHI, the covered entity must obtain documentation signed by the chair (or designee) of the IRB/privacy board before granting access to PHI. For the documentation to be valid, it must include the elements listed at 45 CFR 164.512(i)(2) in the *Code of Federal Regulations*.[6]

An individual has a right to receive an accounting of disclosures of his or her PHI, including research uses, going back six years. This includes research uses approved by an IRB or privacy board that altered or waived the individual authorization.[7] This accounting of disclosure must be provided within 60 days of the request. Therefore, each hospital must keep and maintain an accurate inventory of all research, and must maintain this list for six years after the last use or disclosure of PHI.

Research Billing Compliance

Institutions that participate in Medicare and collaborate with providers engaged in clinical research have the non-delegable obligation to appropriately code and bill for research-related items and services provided as part of a qualified clinical trial. The institution's first obligation is to confirm that the clinical trial is a qualified clinical trial within the meaning of the National Coverage Determinations Manual Section 310.1 (NCD 310.1).[8]

If a clinical trial is a qualifying clinical trial within the meaning of NCD 310.1, the covered entity has an obligation to appropriately code and bill the research-related encounters as provided in Pub. 100-04, Medicare Claims Processing Manual, Chapter 32, Sections 68 and 69.[9] Specifically, it is now mandatory to report a National Clinical Trial number with the appropriate diagnosis code (ICD-9 V70.7 now ICD-10 Z00.6) and appropriate modifier (Q0 with Investigational Device Exemption [IDE] number for device trials and Q1 modifier, if applicable).

While an institution may rely on the review and approval by another institution's IRB, the responsibility for "safeguarding the rights and welfare of human subjects" and compliance with the policy of the U.S. Department of Health and Human Services for the protection of human research subjects remains with the institution, and may not be delegated for federally funded cooperative group research.

Institutions that participate in Medicare and collaborate with providers engaged in clinical research have the non-delegable obligation to appropriately code and bill for research-related items and services provided as part of a qualified clinical trial.

Failure to appropriately code the bill will result in the claim being returned as unprocessable. Hospitals ought to know that inappropriate billing of research-related costs to Medicare can result in monetary fines in the millions of dollars.[10] NCD 310.1 contains a cautionary note (emphasis added):

> Should [the Centers for Medicare and Medicaid Services] find that a trial's principal investigator misrepresented that the trial met the necessary qualifying criteria in order to gain Medicare coverage of routine costs, Medicare coverage of the routine costs would be denied under §1862(a)(1)(E) of the Act. In the case of such a denial, the Medicare beneficiaries enrolled in the trial would not be held liable (i.e., would be held harmless from collection) for the costs consistent with the provisions of §§1879, 1842(l), or 1834(j)(4) of the Act, as applicable. **Where appropriate, the billing providers would be held liable for the costs and fraud investigations of the billing providers and the trial's principal investigator may be pursued.**[11]

Investigational Devices

There are specific hospital obligations when investigators wish to use non-FDA approved devices. Generally, an IDE number must be issued by the FDA to use a non-approved device. There are very narrow exceptions to this requirement at 21 CFR 812.2(c), including an exemption for custom devices within the meaning of 21 CFR 812.3(b). All other non-approved devices must have either an IDE number or IRB approval as a nonsignificant risk device.

Medicare may approve coverage of Category B and hospital-IRB approved non-significant risk devices in addition to reasonable and necessary items and services.[12] However, the hospital may not pay a "price larger than that necessary to recover costs of manufacturer, research, development, and handling" for investigational devices.[13]

Conclusion

Hospitals that collaborate with researchers must ensure that they have qualified staff and adequate facilities (ICH E6 4.2.3), and that staff have been adequately informed (ICH E6 4.2.4) before giving institutional approval under 21 CFR 56.112 or 45 CFR 46.112.

First, hospitals must verify that the clinical research has IRB approval. As a covered entity, a hospital must be prepared to provide an accounting of research disclosures of PHI and the hospital is liable under HITECH for inappropriate research uses of PHI.

If the hospital is participating in Medicare, it is also responsible for appropriately coding and billing research-related items and services, and must ensure that payment and promotion of investigational devices does not violate the non-commercialization restriction.

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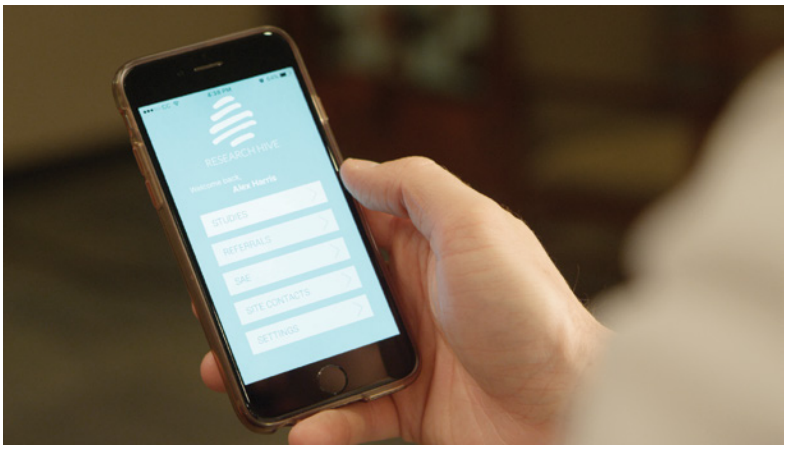

"...our weekly referral rate increased over **70%** above our pre-Research Hive levels."

Let's face it: clinical research coordinators (CRCs) can make or break any trial. Beginning with the site selection visit, the coordinator is carrying a large load. Tasked to learn new trial procedures, vendors, and schedules, they must also explain these details to patients and their team. Tight timelines and pressure from all sides wreak havoc during startup and recruitment, especially when managing multiple protocols. CRCs must play the role of symphony conductor (or circus ringleader), with tools that haven't changed for decades. Intent upon creating a solution, a team of coordinators developed Research Hive.

Research Hive is an innovative recruitment and retention platform.

At the core it is a straight-forward mobile app, developed to help coordinators. Neil Schmitz, head of product development, shared the initial vision: "We developed Research Hive to improve team communication and give sites all study details in one familiar place; their smartphone. We knew recruitment would improve if we could give a team real-time access to critical study information. It had to be fast to review the study criteria and then refer a patient, so that was our focus."

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In this issue of *Clinical Researcher,* the three articles that follow this page have been selected as the basis for a Home Study test that contains 30 questions. For your convenience, the articles and questions are provided in print as well as online (members only) in the form of a PDF. This activity is anticipated to take three hours.

Answers must be submitted using the electronic answer form online (members only, $60). Those who answer 80% of the questions correctly will receive an electronic statement of credit by e-mail within 24 hours. Those who do not pass can retake the test for no additional fee.

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The intent of this policy is not to prevent individuals with relevant financial relationships from participating; it is intended that such relationships be identified openly so that the audience may form their own judgments about the presentation and the presence of commercial bias with full disclosure of the facts. It remains for the audience to determine whether an individual's outside interests may reflect a possible bias in either the exposition or the conclusions presented.

80% The pass rate for the Home Study Test is now 80% to be in alignment with ACRP professional development standards.

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The Association of Clinical Research Professionals (ACRP) is an approved provider of medical, nursing, and clinical research continuing education credits.

Contact Hours

The Association of Clinical Research Professionals (ACRP) provides 3.0 contact hours for the completion of this educational activity. These contact hours can be used to meet the certifications maintenance requirement. (ACRP-2016-HMS-002)

Continuing Nursing Education

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Proposed Revisions to the Informed Consent and IRB Regulations

PEER REVIEWED | David Forster, JD, MA, CIP | David Borasky, MPH, CIP

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In September 2015, the U.S. Department of Health and Human Services (HHS) released a Notice of Proposed Rulemaking (NPRM) to significantly revise the human subject protection and informed consent regulations known as the "Common Rule."[1] If enacted, it will be the first substantial change to these regulations since 1981. Including HHS, the NPRM would affect 16 federal agencies; however, of note, the Food and Drug Administration (FDA) is not included in the current NPRM due to its unique role and statutory framework. FDA's intent is to issue a separate NPRM after the final rule has been enacted, in order to harmonize its specific regulations with the overarching regulations of HHS (of which FDA is an agency) to the extent possible.

LEARNING OBJECTIVE
After reading this article, participants should be able to distinguish the key ways in which the Notice of Proposed Rulemaking differs from the current Common Rule regulations.

DISCLOSURES
David Forster, JD, MA, CIP; David Borasky, MPH, CIP: *Nothing to disclose*

The goal of the NPRM is to recalibrate protection of human subjects and administrative burden by reducing institutional review board (IRB) oversight of minimal-risk research, while simultaneously implementing stronger consent and data protection measures. If enacted, it will lead to changes for IRBs, investigators, institutions, and sponsors.

The HHS did an admirable job of couching the proposed changes within the framework of the historic Belmont Report[2] principles of respect for persons, beneficence, and justice in research involving human subjects. In this paper, we discuss seven of the most significant proposed changes, including those addressing biospecimens, new exclusions, revised exemptions, consent changes, IRB continuing review, extension of the Common Rule to nonfunded clinical trials, and the requirement for single IRBs for multicenter research.

Biospecimens

The most far-reaching and significant proposal in the NPRM is that all human biospecimens will be considered to be identifiable, even if they are de-identified or anonymized, and thus research with biospecimens will always be considered to involve human subjects. It would no longer be possible to remove identifiers and then conduct research without IRB oversight or consent, as often occurs at present, except for "compelling research needs" that are expected to be "rare."

This approach is based on the premises that individuals in the U.S. want to control use of their biospecimens in research; that biospecimens are inherently identifiable due to the genetic fingerprint; and that, in order to maintain public trust, it is necessary to obtain consent for nearly all research with biospecimens. One important exception is that these requirements would not apply to secondary research use of a nonidentified biospecimen that is designed only to generate information about an individual that already is known, such as the development of a new cancer assay using biospecimens from individuals known to have cancer.

HHS has proposed that consent for future unspecified research will be obtained through a "broad consent" process, and plans to develop a template that can be used for this purpose. When an individual provides broad consent, researchers will be able to use existing data and samples at the institution, as well as obtain additional data and samples about that person for a period of 10 years. However, the research using the data and samples

will be able to continue for as long as described in the consent process, which can be indefinitely. (For children, the period covered is the shorter of 10 years or until they reach majority, at which time their new consent is required.)

If an individual refuses to provide broad consent, the refusal must be tracked and honored. The broad consent will include four elements of consent from the current regulations, including risks, benefits, confidentiality provisions, and contacts for questions. In addition, the broad consent must include:

- A statement that the subject's biospecimens may be used for commercial profit and whether the subject will or will not share in this commercial profit
- A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions
- An option for the subject or the representative to consent, or refuse to consent, to investigators re-contacting the subject to seek additional information or biospecimens or to discuss participation in another research study
- A general description of the types of research that may be conducted with information and biospecimens
- Information that is expected to be generated from the research
- Types of information or biospecimens that might be used in research
- Types of institutions that might conduct research with the biospecimens or information
- A clear description of the types of biospecimens or information that were or will be collected

Once broad consent has been obtained, biospecimens can be stored and used for research as long as two conditions are met: First, there is a limited scope, one-time IRB review, and second, new data security measures that HHS will devise are applied to the storage and use. However, if the investigator anticipates returning research results, then full IRB review and consent will be required.

Many will argue that the requirement for broad consent for all biospecimens weights the principle of autonomy too heavily at the expense of beneficence and the public good. It is foreseeable that in many healthcare settings there will not be the resources or incentives to obtain broad consent, particularly in institutions that do not receive federal funds to conduct human subjects research. If that is true, then large amounts of biospecimens that are currently available for use in research when stripped of identifiers would be no longer available for federally funded research, and perhaps for FDA-regulated research, depending on how FDA implements this requirement.

Consent Revisions

In addition to introducing broad consent for biospecimens collected for nonresearch purposes, the NPRM suggests several important revisions to the informed consent regulations. The rationale for the changes is a recommitment to the ethical principle of respect for persons, and a desire to promote greater transparency to the general public regarding the research enterprise.

The NPRM contends that consent forms have become information repositories that serve sponsors, institutions, and investigators at the expense of adequately informing the potential subject. To combat the trend toward long consent documents, the proposed rule requires that informed consent documents be limited to information required in the elements of consent and written in nontechnical language understandable to the average person.

All other information would be moved into an appendix to the consent document. Although the goals of improving the consent process and enhancing subject understanding are laudable, there is likely to be concern that the new appendix will become an unwieldy home to even more information than is currently contained in consent forms.

The proposal also includes minor changes to both the required and optional elements of informed consent. A new required element of informed consent would inform subjects of potential future research use of study data, and new optional elements address commercialization

The broad consent will include four elements of consent from the current regulations, including risks, benefits, confidentiality provisions, and contacts for questions.

Sponsors, knowing that the consent forms used to inform people about their research will be posted in a public space, will take greater care to ensure that consent materials are written in a clear, concise manner in a language that would be considered understandable to the lay public.

of biospecimens, the return of clinically relevant research results, and consent to future contact by the researchers.

Each of these changes addresses a current gap in the existing regulations, but also raises questions. For example, it is not clear what constitutes a "clinically relevant research result." Minor changes are also proposed to the criteria for a waiver of informed consent.

Continuing Review

One theme of the NPRM is a desire to calibrate the level of IRB oversight to the level of risk expected in the research. One way this is addressed in the proposal is through changes to continuing review requirements.

The draft policy proposes eliminating the need for continuing review for all research approved by expedited review, as well as any research that is in the data analysis phase or where the research interventions have concluded and data collection is limited to follow-up clinical data. Given that expedited research must be classified as being of a minimal-risk nature in order to be approved, this change is welcome.

It is not clear if this was considered for all minimal-risk research. Nevertheless, this will eliminate a large number of continuing reviews by IRBs. While traditional continuing review for these studies is eliminated, there is a requirement that the IRB receive annual confirmation that no changes have occurred that would require the IRB to conduct continuing review.

The elimination of traditional continuing review may reduce regulatory burden, but some of these gains may be offset by the annual confirmation process. This change will require IRBs to implement new administrative processes in order to accommodate the new annual confirmations.

Extensions of Clinical Trials

Critics of the current regulations have long pointed to the gap whereby a clinical trial that is neither federally funded nor regulated by the FDA is not subject to regulatory oversight. The NPRM attempts to reduce this gap by extending coverage to any clinical trial being conducted at an institution that receives federal research funding.

Research that is subject to regulation by the FDA is not impacted by this proposal. The proposed rule also provides a definition for the term "clinical trial" that is comparable to the definition used by the National Institutes of Health (NIH) and the International Committee of Medical Journal Editors.

Another change that applies to clinical trials is a new requirement related to consent. As part of the overarching theme of transparency to the general public, sponsors of all clinical trials covered by this policy will be required to post a copy of the informed consent form to a yet-to-be determined public website within 60 days of the close of enrollment. It is not clear that the informed consent appendices will have to be posted.

Some are likely to question the value of posting consent documents for studies that are no longer recruiting, and whether a consent form that is posted out of context truly benefits the general public. At the same time, it is possible that sponsors, knowing that the consent forms used to inform people about their research will be posted in a public space, will take greater care to ensure that consent materials are written in a clear, concise manner in a language that would be considered understandable to the lay public.

Single IRB

The NPRM proposes the use of a central IRB for all domestic multisite studies subject to Common Rule oversight, a concept that has also been proposed by a draft NIH policy[3] and the draft 21st Century Cures[4] legislation. The single IRB would be selected by the sponsor, and when research is not funded the lead site would select the IRB. Federal sponsors would have the authority to determine that a single IRB is not appropriate for certain studies, but such a determination would need to be justified.

However, numerous questions remain; for example, while it is clear that the sponsor will select the single IRB, it is not clear if there will be criteria for selecting the IRB. The HHS Secretary's Advisory Committee on Human Research

Protections[5] has previously identified multiple necessary attributes of single IRBs, including adequate electronic management systems, knowledge of state laws, and independent accreditation.

Further, with the sponsoring agency selecting the IRB, there are questions about what that process will look like. Concerns may be raised that some of the efficiencies gained through use of a single IRB would be lost if the selection process is mired in bureaucratic government contracting. Also, there will be concern about a "one-size fits all" process that treats a collaborative project between three institutions implementing a behavioral research project the same as a multisite clinical trial network.

Exclusions

The NPRM also proposes a new regulatory classification of "excluded research." Excluded activities do not have to satisfy any regulatory requirements, nor undergo any type of review process to determine this status, and there are no recordkeeping requirements for the IRB or institution. Eleven specific types of activities will be outside the scope of the regulations, falling into three general categories.

The first category includes activities that are not research (or might be research), but are part of inherently governmental functions. There are six exclusions in the first category, the most notable being oral history, journalism, biography, and historical scholarship activities; as well as quality assurance and quality improvement activities.

The second category includes low-risk research or research that is protected under other federal privacy protections, and thus does not need protection under the Common Rule. There are four exclusions in the second category:

- educational tests, survey procedures, interview procedures, or observation of public behaviors if subjects cannot be identified, or if disclosure would not reasonably place the subjects at risk, or the activity is conducted under other federal acts that provide protection of confidentiality;
- research involving the collection or study of information that has been or will be collected and is recorded such that the individuals cannot be identified;
- research conducted by a government agency using government-generated or government-collected data under a federal law providing confidentiality protections; and
- research that involves the use of protected health information by an entity covered by the Health Insurance Portability and Accountability Act.

The third and final category involves secondary use of nonidentified biospecimens when the research is limited to generating information about the subject that is already known.

By and large, the new excluded category appears to be a reduction in administrative burden balanced with appropriate protection of human subjects, and several currently uncertain activities are clearly placed outside the research framework.

Exemptions

Significant changes are proposed to the current Common Rule "exemption" categories (or "exempt research"), including increased oversight requirements. A few of the current exemptions are maintained, with minor changes, while other categories are new.

In contrast to the exclusions, records of an exemption decision must be maintained by the relevant IRB or institution. HHS will develop an electronic exemption decision tool allowing for an exemption decision to be made by entering information about the research. Use of the exemption tool will be considered a safe harbor, but an institution may alternatively choose to have a knowledgeable person can make the exemption determination, as currently occurs. (The NPRM asks for public input on whether investigators should be allowed to use the tool without any other review.)

There are two levels of exemptions—those described in the new .104(d) section that do not need additional controls, and those at the new .104(e) and .104(f) sections that contain exemptions that must meet the new privacy safeguards

There are two levels of exemptions—those described in the new .104(d) section that do not need additional controls, and those at the new .104(e) and .104(f) sections that contain exemptions that must meet the new privacy safeguards described in section .105.

described in section .105. HHS will publish a list of specific measures that will provide reasonable and appropriate safeguards to satisfy .105 after the NPRM is finalized.

Three of the new .104(d) exemptions are largely similar to current exemptions, while the fourth .104(d) exemption is new, and applies to research involving benign interventions in conjunction with the collection of data from an adult subject through verbal or written responses or video recording, if the subject prospectively agrees to the intervention and data collection, and either subjects cannot be identified or any disclosure will not harm subjects. This represents a significant improvement over the current exemptions, as these types of studies currently must be reviewed and approved under IRB expedited review, even though they represent no risk to subjects.

The next set of the new .104(e) exemptions require the application of the new .105 privacy protections in order to qualify for exempt status. The first is research involving the use of educational tests, survey procedures, interview procedures, or observation of public behavior where subjects can be identified in the records. This research can involve a risk of information harm to subjects due to the sensitive nature of the research, such as interviews about illegal behavior, because the .105 privacy protections provide protection in place of IRB review.

The second of the new .104(e) exemptions is secondary research use of identifiable private information (not including biospecimens) that has been or will be acquired for nonresearch purposes, if prior notice has been given to the individuals that such information may be used in research; and the identifiable private information is used only for purposes of the specific research project.

Finally, as previously mentioned in the section on biospecimens, the third set of the new exemptions at .104(f) involve the storage, maintenance, and subsequent use for secondary research of biospecimens or identifiable private information that have been or will be acquired for research studies other than for the proposed research study, or for nonresearch purposes.

Beyond the application of the .105 protections, as an extra protection the IRB must provide review using a new criteria for approval at .111(a)(9), which includes the requirement for broad consent.

It is difficult to judge the value of the proposed revised exempt categories of research for several reasons. First, HHS has not yet developed the exemption tool, the new .105 privacy safeguards, or the broad consent template, and thus their effectiveness and administrative ease cannot be assessed. In addition, there is concern that if investigators are allowed to make their own exemption determinations, accidental or intentional misapplications may expose subjects to research risks without IRB oversight. The NPRM is also silent as to whom the responsible parties are if such misapplications occur.

Conclusion

The proposals in the NPRM are intended to revise the regulations to better apply to this century's research environment, and enhance research subject protections while simultaneously reducing unnecessary administrative burden. The proposals are appropriately supported by use of the Belmont principles, and many of them will be welcomed by the research community as striking the appropriate balance.

However, because many tools have not yet been developed, it is difficult to assess whether the appropriate balance has been struck regarding biospecimens and the new exemption categories. They could end up transferring administrative burden from the IRB to other departments in institutions, and at the same time inhibiting valuable, low-risk research.

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INFORMED CONSENT: *Improving the Process*

PEER REVIEWED | Elizabeth Bankert, MA | Judith L. Forman, MPH

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Ensuring individuals are able to make an informed decision when deciding whether or not to enroll in a research study is a cornerstone of conducting ethical research. How do we ensure that the consent is valid, and that the signature on the document represents a truly informed study participant?

This article addresses the rational for obtaining valid consent, and describes an education program developed as a resource for research team members involved in the consent process.

Ethics of Informed Consent

Informed consent should be thought of as a process, and not as a document. It remains incumbent on the clinical research staff to engage prospective participants in discussion about their potential role in the study, and then provide them enough time for reflection before they decide whether to enter the study. Initial and subsequent interactions serve as opportunities to build a trust-based rapport with the prospective participant.

As described in the Belmont Report,[1] three key components of the informed consent process are information, comprehension (information provided in a way that is understandable), and voluntariness. Consent addresses the ethical concept of respect for persons by allowing people to make autonomous decisions about whether the potential risks and benefits of study participation are acceptable to them personally. Although informed consent must be obtained before participation in the study begins, the process should be thought of as ongoing throughout a study, with subjects being made aware that they are always free to withdraw consent and leave a study.

Many research centers rely heavily on the consent form to provide information to prospective participants. This dependency on a document without an additional means of evaluating level of comprehension may not be the most effective means of obtaining valid consent. The research community has long acknowledged the increasing complexity and length of consent forms, and the concern that the corresponding level of comprehension may actually be reduced rather than increased.

Obtaining valid consent has been a concern since at least 1966, when Henry Beecher wrote "Most codes dealing with human experimentation start out with the bland assumption that consent is ours for the asking. This is a myth. The reality is that informed consent is often exceedingly difficult to obtain in any complete sense... Nevertheless, it remains a goal toward which one must strive for sociological, ethical, and legal reasons."[2]

Now, nearly 50 years later, we are still concerned about the level of comprehension of prospective research participants. Researchers are responsible for educating potential participants, helping them consider their options, and ensuring that they understand the purpose of the research, the risks and potential benefits of participation, and what is expected of them.

LEARNING OBJECTIVE
After reading this article, participants should understand the importance of informed consent in research and be able to discuss the teach-back method as one potential mechanism for improving the informed consent process.

DISCLOSURES
Elizabeth Bankert, MA; Judith L. Forman, MPH: *Nothing to disclose*

Although informed consent must be obtained before participation in the study begins, the process should be thought of as ongoing throughout a study, with subjects being made aware that they are always free to withdraw consent and leave a study.

In September 2015, the Office for Human Research Protections (OHRP), based within the U.S. Department of Health and Human Services, proposed new rules for human subjects research.[3] According to the OHRP website, the proposed rules are meant to *"ensure the highest standards of protections for human subjects involved in research, while enhancing effectiveness of oversight."*

One of the proposed changes addresses issues surrounding informed consent, including the following language:

> *The prospective subject or the representative must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information. The information must be presented in sufficient detail relating to the specific research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or representative's understanding of the reasons why one might or might not want to participate.*

Current regulations do not include the language noted above. The impact may be to change the existing focus on the consent *form* to also include enhancements to the consent *process.*

Education Program for Obtaining Informed Consent

Time constraints, pressure from sponsors to meet enrollment goals, and increasingly complex consent documents are factors contributing to the concerns related to obtaining valid informed consent.

In an effort to respond to these ongoing concerns, a team comprised of researchers and institutional review board (IRB) staff at Dartmouth created the VoICE (Valid Informed Consent Education) program. VoICE includes an overview of the elements of consent, presents a discussion of health literacy, and advocates the use of the "teach-back" method,[4] a communication confirmation method used by healthcare providers to confirm whether a patient or caretaker understands what is being explained to them.

The project to develop the VoICE education program was awarded a Quality Improvement Grant from Dartmouth Hitchcock Medical Center. Sixteen study coordinators volunteered to participate in the pilot program. One goal was to determine if research staff could be taught to utilize the teach-back method in the consent process.

The pilot program included observation of the research staff having a simulated consent discussion before they attended the education program, and again one week and three months later. Each staff member used the same consent form—one that had been adapted from a real study.

The pilot project demonstrated research team staff we were able to learn the teach-back technique. More teach-back questions were used in both post-test observations, as compared to the observation session held prior to the education session.

Why Utilize the Teach-Back Method?

The team developing the education program chose to advocate the teach-back technique to assess understanding of prospective participants, as this technique has been used in clinical settings and has been shown to improve communication and patient comprehension.[5]

In teach-back, the prospective research participant is asked to confirm his or her understanding of the key elements of the research study by describing them in their own words to the research team member. Using this method, an opportunity for dialogue is created.

"Asking that patients recall and restate what they have been told" is one of the 11 top patient safety practices based on the strength of scientific evidence.[5] In one study, "[p]hysicians' application of interactive communication to assess recall or comprehension was associated with better glycemic control for diabetic patients."[6]

An extremely important concept of this technique is that it is not a test of the prospective participant, but rather a test of how well the researcher explained a concept. Using teach-back

During the education program, we present a video which has proved to be a powerful depiction of health literacy issues. Called "Health literacy and patient safety: Help patients understand."

rather than a test turns the tables by putting the responsibility of explaining on the research staff instead of it being solely the responsibility of the prospective subject to figure out the details.

The use of closed questions such as "Do you understand?" or "Do you have any questions?" will most likely be answered with a yes or no, and does not encourage dialogue; therefore, this tactic is not recommended during the consent process. Rather, the method of the researcher explaining a key concept, pausing, and using an open-ended phrase to encourage dialogue, such as:

- "If you call your sister tonight, tell me how you would explain the purpose of this study to her."
- "To ensure I am doing my job correctly in explaining this study to you, please tell me what you understand about the risks."

During the pilot program, it was determined that mastering the teach-back technique and the use of open-ended phrases takes practice. As such, part of the VoICE education program includes time to consider what the key concepts of a particular research study may be, and time to actually rehearse the teach-back method with colleagues.

Other VoICE Components

In addition to the teach-back method, other important components are presented in the VoICE education program in order to complete the comprehensive session, including a description of the elements of consent, a discussion of an appropriate consent setting, and information relevant to health literacy.

The Institute of Medicine defines health literacy as "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions."[7] Research shows that patients remember and understand less than half of what clinicians explain to them, and even well-educated people may become functionally health illiterate when in pain or confronted with a serious disease or new diagnosis.[7]

During the education program, we present a video which has proved to be a powerful depiction of health literacy issues. Called "Health literacy and patient safety: Help patients understand," the video is available at www.youtube.com/watch?v=BgTuD7l7LG8.

We found research staff to be extremely willing to consider improvements to the consent process as we developed the VoICE program. Staff members wanted to ensure patients understood the key elements; however, they had received no formal training related specifically to how to make that assessment.

Summary

Because of the undeniable necessity for, and potential complications stemming from, the informed consent process being part of the conduct of any ethical clinical trial, we recommend the use of an education program to assist research team members in understanding the history of and procedures for obtaining valid consent. Information related to the VoICE program can be found at www.dartmouth.edu/~cphs/tosubmit/teachback/index.html.

It is the responsibility of the research team to ensure the understanding of the study on the part of the prospective patient. Improving the consent process may require innovative options to confirm that prospective patients grasp the key elements of the research.

This conversation is ongoing in the research community. This paper serves as a reminder that "informed consent is often exceedingly difficult to obtain in any complete sense… Nevertheless, it remains a goal toward which one must strive."[2]

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The Ethics of Targeted Oncological Trials

PEER REVIEWED | Cecilia Nardini, PhD

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In the wake of the full sequencing of the human genome, great promise has been stirred around the prospect of "personalized" or "precision" medicine. This term denotes a collection of techniques that combine various "omics" data—genomics, proteomics, metabolomics, and the like—in order to produce situation-based treatment recommendations that are maximally effective and minimally harmful, because the treatment is tailored to the characteristics of a specific patient and disease profile. President Obama's recent Initiative on Personalized Medicine[1] stands in testimony to the high level of expectation and commitment surrounding this idea.

LEARNING OBJECTIVE
After reading this article, participants should be able to explain the most relevant differences between conventional therapy and personalized therapy, and to discuss the ethical issues that arise in the context of testing personalized drugs specifically.

DISCLOSURES
Cecilia Nardini, PhD:
Nothing to disclose

As with any innovative technology, precision medicine has specific ethical issues attached to it. One principal concern is, understandably, that of distributive justice: It is feared that precision medicine will become the "medicine of the few" that can afford it, and that great research expenditure in this area will result in a reduced amount of resources available for affordable care for everybody. Another issue concerns the privacy, appropriate use, and proper handling of biological data and the information they carry.

There is, however, a further ethical problem arising specifically due to the peculiarities of personalized medicine—one that has received little, if any, attention from either scholars or professionals in bioethics. This problem concerns the ethics of research involving human subjects (i.e., the phase of testing personalized drug agents clinically).

This article explores the testing of personalized anticancer agents as a case study within the context of clinical trials. As a first step, we present an overview of the concept of personalized drugs and review their mechanism of action; we consider personalized anticancer agents in particular, also called "targeted drugs."

This overview provides insights into the peculiarities of targeted drugs and, in the second part of the discussion, how these peculiarities affect the process of testing such drugs—in particular, the ethical aspects related to testing. In the final part of the paper, we present a full ethical discussion of these issues.

Personalized Medicine and Targeted Anticancer Drugs

The term "personalized medicine" refers to a new concept of therapy that stemmed from the completion of the Human Genome Project (HGP) in 2003. Prior to this watershed, the guiding idea in medical research was that of identifying treatments that worked best on a large statistical basis.

The completion of the HGP brought about an augmented knowledge of the genetic mechanisms of disease and response; this, in turn, created the possibility of identifying molecular mechanisms of disease and of designing compounds that could act specifically on such mechanisms. This new generation of treatments would be tailored to the genetic characteristics of a specific patient and his/her illness, and in this sense would be "personalized."

In the field of oncological research, in particular, the idea of personalized medicine has taken a specific meaning, due to the impressive molecular heterogeneity underlying common tumors. Genomic analysis has revealed that the cellular disregulation that causes cancer can result from a variety of molecular anomalies, and that identifying the anomaly at the root of a particular patient's tumor can make a difference in prognosis and cure.

Furthermore, it is now possible to develop molecularly targeted drug agents—compounds that target specific molecular pathways. Traditional therapies for cancer are based on cytotoxic drugs that attack, in a nonspecific manner, all rapidly dividing cells. In contrast, molecularly targeted agents act in a selective manner on the precise nodes of cellular pathways that are mutated or disregulated in cancer cells of a specific kind of tumor. Thus, novel tumor therapies developed in light of genomic knowledge are "personalized," in the sense of being tailored to the molecular profile of a tumor.

The two most renowned of these compounds are probably Gleevec (imatinib) in chronic myelogenous leukemia (CML) and Herceptin (trastuzumab) in breast cancers characterized by overexpression of a hormonal receptor (HER2).

Targeted drugs can act against a tumor by means of different mechanisms:

- Some agents, like trastuzumab, are antibodies that recognize and bind a molecule that is overexpressed by the cells of a specific tumor kind. Antibodies that recognize tumor cells specifically can be exploited either to elicit the patient's immune response against the tumor, or as probes, in order to direct onto the malignant cell toxic compounds that will kill it.[2]
- A second mode of action of targeted drug therapies is direct interference with cellular mechanisms involved in tumor growth and progression. The drug compound would interfere with cell growth signaling or tumor blood vessel development, or promote the specific death of cancer cells. Imatinib represents an instance of this approach. In CML, a tyrosine kinase enzyme in white blood cells is locked in its activated form due to a chromosomal mutation, and in this form it speeds up cell division. Following the discovery of this genomic mechanism, investigators screened chemical libraries to find an inhibitor of this enzyme, later developed into the drug Gleevec.[3]

There is significant hype around the promise of targeted cancer therapy; imatinib, for instance, has essentially turned CML from a fatal disease into a chronic, manageable condition.[3] Furthermore, targeted agents are at present considered the major way forward in cancer research.[4] This is due to the property such agents have of being *targeted*—antibodies like trastuzumab or selective inhibitors like imatinib affect in a specific manner only the cells in the tumor; they leave healthy cells mostly unharmed.

Thus, targeted agents have typically less harmful side effects than conventional chemotherapy, which instead attacks healthy and malignant cells alike. The efficacy of a traditional chemotherapeutic, a cytotoxic agent, is balanced on a knife-edge with its toxicity—the former cannot be augmented over that of currently available treatments without the latter becoming unbearable. Targeted agents, by their specificity against the cells of the tumor, appear as the only option for improving upon the present safety/effectiveness deadlock.

The term "personalized medicine" refers to a new concept of therapy that stemmed from the completion of the Human Genome Project (HGP) in 2003.

Testing Targeted Agents Clinically

Clinical trials rest on a delicate ethical balance. On the one hand, the aim of a trial is to advance medical knowledge and possibly to establish a new, more effective treatment option. On the other hand, it is clearly unacceptable (according to our ethical standards) that this benefit comes from an exploitation of the patients who are involved in an ongoing trial.

This implies that clinical trials are ethically acceptable under the requirement that patients participating in the trial are not receiving a treatment that is known to be inferior to another available treatment regimen. However, the vast majority of clinical trials are randomized; on entering the trial, participants are allocated at random to receive either the new treatment or the control. Randomization entails that, by entering the trial, the patient may receive the treatment that will eventually turn out to be inferior in the comparison.

The view that is currently prevalent in the ethical literature is that this ethical tension is alleviated if the medical community is in a state of equipoise between the new and the standard treatment used as the control. Equipoise means that there is a reasonable and informed disagreement among medical experts about which treatment is superior.[5] If equipoise is present at the beginning of a trial, patients are not harmed by the offer of randomization between the two treatments, because

If a trial is designed in a way that compromises its possibility of achieving a reliable result, its ethical stance is questionable.

uncertainty makes it "an equal bet in prospect."[6]

Hill, the celebrated father of the randomized trial methodology, was referring to a similar idea when he observed "Only if, in his state of ignorance, [the doctor] believes the treatment given to be a matter of indifference can he accept a random distribution of the patients to different groups."[7]

Equipoise provides an accepted ethical justification for clinical trials of conventional treatments; if we do not know before starting the trial which treatment will turn out to be superior, patients are not harmed by the chance of receiving one or the other. However, the situation for targeted agents is different, in a way that may compromise the ethical acceptability of trials for these agents.

As seen above, targeted tumor agents are characterized by their selectivity of action; trastuzumab, for instance, is only effective against breast tumors characterized by a specific molecular profile (i.e., overexpression of HER2 receptor). When trastuzumab is administered to breast cancer patients regardless to the molecular profile of their tumors (i.e., regardless of whether they have HER2 overexpression or not), the response can vary dramatically, to the point that not only the magnitude, but also the direction of the treatment effect may be different for patients who do not have the mutation.

The consequence is that the equipoise condition analyzed above may break down for trials of targeted agents if these trials are designed in a conventional manner (i.e., to enroll a large number of patients who are not screened for the molecular variant of their tumors). If these patients' malignancies do not harbor the matching molecular profile, trial entry is not an equal prospective bet for the patients, since the mechanism of action of the targeted treatment is expected to be totally ineffective for them. Thus, large, undifferentiated trials of targeted agents may ultimately lack ethical permissibility.

An alternative for testing targeted agents relies on small trials that are themselves "targeted" (i.e., that focus on the subgroup of patients that are more likely to respond to the targeted drug). In many cases, it is possible to single out patients who have the matching tumor profile via genomic analysis or molecular (biomarker) assay. A recent example of this approach is provided by the I-SPY 2 study,[8] a Phase II trial for the identification of new adjuvant agents in breast cancer therapy.

I-SPY 2 was planned to evaluate 12 different drugs and to follow multiple biological markers as possible predictors of response. It leveraged adaptive randomization across biomarker subtypes arms; treatments performing better within a subtype were assigned with greater probability to patients having the same subtype. In this way, better performing therapies could move through the process faster and have greater exposure to responding subtypes, potentially resulting in more accurate and faster drug development.[9]

On the other hand, small trials targeted at the subpopulation may not be the solution—the issue is with the reliability of the conclusions that can be arrived at through such trials. One concern is that the assay used to screen eligible patients may not be fully grounded. Ioannidis et al.[10] have recently questioned the reliability of claims of increased treatment effect for biomarker-filtered subgroups of patients.

A second, more important concern is that targeted trials are necessarily small. For example, Tursz et al.,[11] in relation to breast cancer, note that the population of patients exhibiting both mutations that are predictive of response to a particular molecular agent account for around 0.4% of breast cancer. They observe that "[t]he feasibility of large clinical trials in this population is questionable, as this equates to 250 patients overall per year in France, when the total number of newly diagnosed breast cancer cases in the country is 50,000 per year."

The problem with small trials is that they are likely to produce indecisive results, and thus possibly create the necessity of a repetition. A trial that fails to arrive at a conclusion has, in retrospect, subjected patients to the risks of trial participation in absence of any benefit for them or for society at large.

If a trial is designed in a way that compromises its possibility of achieving a reliable result, its ethical stance is questionable. For instance, a recent commentary in *Science* journal states that "It should be deemed unethical to enroll patients in a clinical trial that has a low probability of generating meaningful information, no matter how promising a new investigational therapy."[12]

It might seem, therefore, that testing personalized drugs in an ethically acceptable manner is impossible, but in concluding this paper, we point to a possible solution to this ethical issue.

Conclusion: Redefining Evidence for Personalized Medicine

In this article, we have analyzed the ethical issues that arise in the context of testing personalized drugs through clinical trials. Conventional trials that test treatment effectiveness on a large,

undifferentiated population of patients may lack ethical justification in the case of personalized treatments, since the treatment is expected to be ineffective on a large fraction of the participants. The alternative is that of conducting small targeted trials on a highly selected population of patients, but this alternative is ethically controversial as well, due to the fact that small trials are generally considered unreliable by the medical community.

A possible way out of this ethical conundrum consists in acknowledging that the classical criteria of reliability that are valid for conventional trials may not be adequate for judging trials for targeted agents; this is a position that has started to emerge among medical researchers in recent years. The statistical rationale behind the requirement of large samples is to allow for the detection of an effect that can be small with a sufficiently low error rate, but large samples have indeed already been deemed unnecessary to provide evidence of dramatic therapeutic effects in well-known cases such as penicillin for bacterial infections, smallpox vaccination, and insulin in insulin-dependent diabetes.[13]

Most molecularly targeted agents, too, are expected to show a dramatic effect—limited to the class of patients that harbor the targeted mutation—and this is indeed the reason for interest in them. In the case of targeted drugs, it is of primary importance to assess that the molecular mechanism of action works as planned within the human body and that, by interfering with the targeted disease pathway, it can improve patient-relevant outcomes.

Small-scale comparative studies performed on a highly selected sample of patients, when combined with laboratory findings, can suffice to prove this. Once the small-scale study has proven that the agent is effective through the hypothesized mechanism, the rationale—both pragmatic and ethical—for conducting large trials is questionable.[14] In line with these considerations, the U.S. Food and Drug Administration already provides a "fast track" to approval for molecular drugs that are highly likely, as compared to available treatments, to benefit patients with life-threatening diseases; this is the Accelerated Approval program Subpart H, launched in 1992.[15]

Clearly, small trials are unable to generate large safety profiles; this implies that an increased level of postmarketing surveillance will be needed for therapies approved through this process.

The position presented here can, indeed, be justified also on a theoretical level. The centrality of statistical evidence from large trials is the focus of a movement advocating what is known as evidence-based medicine (EBM). According to EBM proponents, the most authoritative way to assess that a new treatment is effective is by testing it through a trial conducted on a large statistical basis.[16] However, it has been argued[17] that personalized medicine and the quest for personalized drug agents fall under a paradigm of evidence-generation that is distinct from, and complementary to, that of conventional treatments represented by EBM.

Personalized medicine has distinctive evidential needs that are not accounted for by the classical paradigm of statistically significant effects in large populations.

In conclusion, the ethical issue highlighted in this paper concerning the testing of personalized drugs through clinical trials ultimately rests on a problem of conflicting standards of evidence. Trials testing personalized treatments will remain on an uncertain ethical footing as long as such treatments are evaluated according to the same criteria as conventional ones.

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HOME STUDY HS

Ethical Issues at Sites and Beyond

OPEN BOOK TEST

This test expires on February 28, 2017

(original release date: 2/1/2016)

Proposed Revisions to the Informed Consent and IRB Regulations

1. Under the proposed rule, future unspecified research with human biospecimens will generally be allowed only when:

- **A.** An IRB has waived informed consent under 45 CFR 46.116(d)
- **B.** Prospective broad consent has been obtained from the individual
- **C.** The specimens have been completely de-identified
- **D.** A convened IRB has determined that there are adequate data safety protections

2. If enacted, the new rule would apply to:

- **A.** All human subjects research conducted or supported by any of the 16 departments and agencies that participate in the Common Rule
- **B.** All human subjects research conducted in the U.S., regardless of funding
- **C.** All human subjects research that is funded by the U.S. government or regulated by the FDA
- **D.** All human subjects research conducted at institutions holding a Federalwide Assurance

3. Three goals of the NPRM as outlined in this article are the:

1. Increased oversight of minimal-risk research
2. Reduction of administrative burdens
3. Improvement of informed consent processes
4. Enhancement of data protection measures

- **A.** 1, 2, and 3 only
- **B.** 1, 2, and 4 only
- **C.** 1, 3, and 4 only
- **D.** 2, 3, and 4 only

4. Under the proposed rule, human biospecimens would be:

- **A.** Considered identifiable, even if de-identified or anonymized
- **B.** Considered identifiable, unless de-identified or anonymized
- **C.** Exempt from the human subjects regulations
- **D.** Covered under a new proposed exclusion

5. The proposed rule would eliminate continuing review:

- **A.** For all behavioral research
- **B.** For all minimal-risk research
- **C.** For all exempt research
- **D.** For all research approved by expedited review

6. Under the proposed rule, all of the following activities would be excluded from the regulations except:

- **A.** Healthcare operations research
- **B.** Quality assurance and quality improvement activities
- **C.** Oral history, journalism, and historical scholarship activities
- **D.** Activities that are part of inherently governmental functions

7. Under the proposed rule, several new categories of exempt research require adherence to:

- **A.** Simplified informed consent requirements for surveys and interviews
- **B.** New privacy safeguards that will be produced by the government
- **C.** New de-identification standards for private information
- **D.** Standards required by the Health Insurance Portability and Accountability Act

8. The proposed rule would apply to any clinical trial:

- **A.** That is regulated by the FDA, regardless of funding
- **B.** Conducted at an institution that receives federal research funding
- **C.** Conducted or supported by a Common Rule department or agency
- **D.** Regardless of funding

9. Under the proposed rule, sponsors of clinical trials would be required to:

- **A.** Post a copy of the informed consent form to a public website within 60 days of the close of enrollment
- **B.** Provide all subjects with their individual study results
- **C.** Publish results from all studies in a peer-reviewed journal
- **D.** Publish all study data on ClinicalTrials.gov

10. Under the proposed rule, a single IRB would be required for:

- **A.** All domestic FDA-regulated clinical trials
- **B.** All multisite studies, regardless of funding
- **C.** All domestic multisite studies subject to Common Rule oversight
- **D.** All domestic multisite clinical trials

Informed Consent: Improving the Process

11. What are the essential components of the informed consent process?

1. Information for the participant
2. Consultation with a family member or friend
3. Ample time for the participant to consider participation in the study
4. Discussion between participant and the research staff

- **A.** 1, 2, and 3 only
- **B.** 1, 2, and 4 only
- **C.** 1, 3, and 4 only
- **D.** 2, 3, and 4 only

12. Which of the following is a true statement about the informed consent document?

- **A.** The consent form can serve as a vital framework and guide for face-to-face discussion.
- **B.** The consent form is an agreement between the prospective participant and the investigator.
- **C.** The consent form is proof that a thorough discussion about the study has taken place.
- **D.** The consent form's purpose is to remove the risk of therapeutic misconception.

13. Which of the following is a true statement regarding what Henry Beecher wrote about obtaining valid consent?

- **A.** Most codes dealing with human experimentation assume patients will largely refuse to participate in studies.
- **B.** A "complete" level of informed consent is often difficult to obtain.
- **C.** Informed consent is a relic of an outdated philosophy for conducting research.
- **D.** Other than legal ones, there are no real reasons for striving to obtain consent.

14. Which of the following is a true statement of how the OHRP Notice of Proposed Rulemaking addresses informed consent?

- **A.** The consent process should be shortened to improve efficiency.
- **B.** Consent forms should provide detailed lists of facts about the researchers conducting the study.
- **C.** The prospective participant must be provided with the information a reasonable person would want to have in order to make an informed decision.
- **D.** Paper consent forms should be phased out and transitioned to eConsent.

Find the most current online test at **www.acrpnet.org/homestudy**, including any revisions made after publication of this issue of *Clinical Researcher*.

15. **Factors contributing to concerns about obtaining valid informed consent include:**

1. Time constraints
2. Pressure from sponsors regarding enrollment
3. How far participants live from the study site
4. The complexity of consent documents

A. 1, 2, and 3 only **C.** 1, 3, and 4 only
B. 1, 2, and 4 only **D.** 2, 3, and 4 only

16. **As described in the article, which of the following is not included in the VoICE program?**

A. An overview of the elements of consent
B. A discussion of health literacy
C. Advocacy for use of the teach-back method
D. A national listing of patient advocacy organizations

17. **The purpose of the teach-back method is:**

A. To formally test prospective participants on their knowledge of the consent form
B. To determine a prospective participant's eligibility for a study
C. To confirm prospective participants' understanding of how a study has been explained to them
D. To determine whether or not the prospective participant has read the consent form

18. **Which of the following questions to a prospective research participant are consistent with the teach-back technique for assessment of comprehension?**

1. "My job is to make sure I explain the study so that you can understand it, so would you please explain to me what the purpose of the research is?"
2. "Tonight when you have dinner with your spouse and he/she asks you what the risks are if you participate in the study, what will you say?"
3. "Do you understand the risks of the study?"
4. "Can you explain to me what will happen when you come for your first study visit?"

A. 1, 2, and 3 only **C.** 1, 3, and 4 only
B. 1, 2, and 4 only **D.** 2, 3, and 4 only

19. **Which of the following is not described in the article as being among other important components presented in the VoICE program?**

A. A glossary of research terminology
B. A description of the elements of consent
C. A discussion of appropriate settings for consent
D. Information on health literacy

20. **According to the article, how much information given by clinicians during a clinical encounter is retained by patients?**

A. All of the information
B. 80% of the information
C. 60% of the information
D. Less than half of the information

The Ethics of Targeted Oncological Trials

21. **According to the author, which of the following are ethical issues that arise in the context of personalized medicine?**

1. How to make personalized treatments fairly and widely accessible
2. How to handle properly the information contained in the genomic data of patients
3. How to test personalized therapy in an ethically acceptable way
4. How to define inclusion/exclusion criteria for receiving personalized treatments

A. 1, 2, and 3 only **C.** 1, 3, and 4 only
B. 1, 2, and 4 only **D.** 2, 3, and 4 only

22. **According to author, which of the following about personalized medicine are true?**

1. Personalized medicine was made possible by the achievement of the Human Genome Project.
2. Personalized medicine is "the medicine of the few."
3. Personalized medicine aims at providing treatment decisions that are tailored to the genomic data of a patient and his/her illness.
4. Personalized medicine aims at providing affordable care for everyone.

A. 1 and 3 only **C.** 2 and 3 only
B. 1 and 4 only **D.** 2 and 4 only

23. **According to the article, molecularly targeted oncological agents:**

1. Are more effective than conventional treatment because they are of the same size as molecules
2. Can act in a selective manner on a particular cellular pathway
3. Can recognize and bind to a specific molecule that is only expressed in tumor cells
4. Are less effective than conventional treatment because they don't act on all tumor cells but only on a specific subset

A. 1 and 2 only **C.** 2 and 3 only
B. 1 and 4 only **D.** 3 and 4 only

24. **The targeted drug trastuzumab:**

A. Can cure all forms of cancer
B. Can be used to treat all patients with breast cancer
C. Can be used to treat patients with breast cancers that have overexpression of HER2 receptor
D. Can be used to treat patients with breast cancers that have overexpression of HER2 receptor, provided that they have not received any previous treatment

25. **It is ethically acceptable to test a treatment on human subjects in a clinical trial if:**

1. All the participating physicians agree that the treatment will not harm the subjects
2. Patients agree to participate
3. The medical community is in a state of equipoise between the new treatment and the standard of care
4. There is a reasonable disagreement among medical experts about which treatment is more effective

A. 1 and 2 only **C.** 2 and 3 only
B. 1 and 4 only **D.** 3 and 4 only

26. **According to the article, targeted trials:**

1. Select eligible patients on the basis of the molecular profile of their tumor
2. Can apply adaptive randomization of patients to the best performing arm
3. Are conducted *in vitro* using biomarker assays
4. Select eligible patients on the basis of their response to the experimental treatment

A. 1 and 2 only **C.** 2 and 3 only
B. 1 and 4 only **D.** 3 and 4 only

27. **According to the author, the result of trials for targeted treatments may be less reliable than the result of conventional trials because:**

1. Trials for targeted treatments are usually conducted on a smaller population of patients.
2. Trials for targeted treatments do not have FDA approval.
3. Trials for targeted treatments often need to use biomarker-based screening that may be unreliable.
4. Trials for targeted treatments do not apply randomization of patients between a treatment and a control arm.

A. 1 and 3 only **C.** 2 and 3 only
B. 1 and 4 only **D.** 2 and 4 only

28. **According to the article, when testing targeted agents, it is important to establish that:**

1. The molecular mechanism of action works as expected
2. The drug can improve patient-relevant outcomes
3. The drug can work on a large statistical basis
4. The drug is effective against diseased cells

A. 1, 2, and 3 only **C.** 1, 3, and 4 only
B. 1, 2, and 4 only **D.** 2, 3, and 4 only

29. **According to author, if the FDA approves marketing of a new treatment based on the results of a targeted trial, the new treatment:**

1. Will create a state of equipoise in the medical community
2. May need increased postmarketing surveillance as compared to treatments tested in a conventional trial
3. Will need less postmarketing surveillance as compared to treatments tested in a conventional trial
4. May lack an adequate safety profile as compared to treatments tested in a conventional trial

A. 1 and 2 only **C.** 2 and 3 only
B. 1 and 4 only **D.** 2 and 4 only

30. **Based on the difficulties highlighted with testing targeted oncological drugs, what can be said about personalized medicine?**

A. Personalized medicine can never be evidence-based.
B. Personalized medicine may need evaluation criteria other than effectiveness on a large statistical basis.
C. Testing personalized agents clinically is too risky.
D. Personalized medicine can only be evaluated through expert judgment.

THE ACRP 2016 MEETING & EXPO:

Expanding Networks The Natural Way

We all utilize Skype, Google Chat, WebEx, and dozens of other apps designed to connect us with each other. Powerful tools all. Woven into our working lives, it's hard to imagine getting things done without them. However, they've got their limits. They're at their best when sharing data and other forms of raw information. None replace good old-fashioned face-to-face networking.

"Attending the conference raises the profile of our company. It's a great marketing tool."

There's something about meeting and talking with colleagues in person. You discover new peers who understand your opportunities and challenges in a way no one else can. You benefit from the opportunity to swap best practices—or to share a warning about something that's just not working. Human interaction generates its own unique and exciting synergy. Online tools simply cannot compete.

For Glenda Guest, CCRA, RQAP-GCP, TIACR, vice president of Norwich Clinical Research Associates Ltd. and the top-rated speaker from the ACRP 2015 annual meeting, getting together with colleagues in the same room is invaluable. "I meet bright colleagues, many of whom become friends. We've become a resource for each other," Guest says.

Guest enjoys keeping in touch throughout the year with colleagues she's met at past ACRP meetings to better swap ideas and answer each other's questions. Attending the Meeting & Expo (formerly known as the ACRP Global Conference & Exposition) is often the only time she'll get to reconnect in person. There are other benefits: "It raises the profile of our company," she says. "It's a great marketing tool."

Frequent attendee and speaker Stephen Sonstein, PhD, director of clinical research administration at Eastern Michigan University, couldn't agree more. "It's such a nice networking format at the conference," he says. "It's a unique learning environment in which to share ideas."

At the 2016 Meeting & Expo in Atlanta, Ga., Sonstein and Guest will lead interactive sessions designed to bring professionals together to improve problem-solving skills and advance the clinical research profession. Sonstein, active in the Joint Task Force for Clinical Trial Competency, looks forward to helpful and vital feedback from colleagues. "We need validation" that the task force's recommendations are relevant and viable, he says.

During one of her sessions, Guest will create working groups to dissect and prepare effective responses to U.S. Food and Drug Administration (FDA) Warning Letters. "We help each other understand that there isn't just one way to handle Warning Letters," she says. "You can be assertive and defend your position to the FDA."

However, it isn't always easy to understand the nuances when making your case to the agency, Guest stresses. Clinical trial practitioners are much more likely to learn those lessons working with an engaged team gathered around the same conference table. After solving the test case problem, the new team can take a coffee break together in a less formal setting to solidify new connections with peers.

Yes, WebEx and the like are helpful tools, but remember: They can't generate that unique human sense of real connection. Oh, and they can't serve coffee, either.

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>
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ACRP 2016 Meeting & Expo At-A-Glance

FRIDAY, APRIL 15

8:00am-12:00pm (Half-Day Workshops)

- Marketing for Your Clinical Research Practice
- Composing Source Documents: Pain or Gain?
- Insights, Implications, Impact and Implementation of Risk Management in Trial Conduct

1:00-5:00pm (Half-Day Workshops)

- Risk Management: Scalable Adaption in GCP for All!
- Insurance Coverage: How the ACA Changed Access to Clinical Trials
- Investigator-Initiated Sponsored Research

8:00am-5:00pm (Full-Day Workshops)

- Tools to Help Clinical Sites Optimize Performance and Maintain GCP Compliance
- Best Practices to Become a Preferred Site
- Good Clinical Practice Auditing Techniques

SATURDAY, APRIL 16

9:00-10:30am (Sessions)

- FDA Inspections: Understand the Process and Manage the Consequences
- Create an Onboarding Curriculum that Fits Your Budget
- Audits & Inspections: What to Expect and Corrective Action for GCP Compliance
- Four Generations, One Workplace (Back by Popular Demand!)
- Remote Monitoring and Access to Electronic Medical Records
- The Immortal Life of Henrietta Lacks: Applying Lessons Learned to Today's Informed Consent Process
- Results from the Joint Task Force Survey of Clinical Research Competence

10:45am-12:00pm (General Session)
Keynote Speaker Martine Rothblatt

12:00-3:00pm (Lunch, Exhibits & Poster Sessions)

2:30-4:30pm (Sessions)

- The Next Generation of Clinical Research: Developing Qualified Professionals
- Advanced Monitoring Visit Documentation: Global Regulatory Authority Inspections and Sponsors
- Implementation of the Joint Task Force for Clinical Trial Competency Framework
- Social Media in Clinical Trial Patient Recruitment
- Research Billing Compliance for Dummies
- Global Perspectives on the Informed Consent Process
- Clinical Trial Study Management Plans: The Architecture of a Quality Clinical Trial

KEYNOTE SPEAKER: Martine Rothblatt, PhD, MBA, JD

Saturday, April 16

Hear the inspirational story of Martine Rothblatt, noted entrepreneur, medical ethicist, and founder of Sirius Satellite Radio (now Sirius XM). When her daughter Jenesis was diagnosed with the rare disease pulmonary hypertension in 1994, Rothblatt left Sirius in search for a cure, ultimately founding United Therapeutics, which developed Remodulin, a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension.

SUNDAY, APRIL 17

8:30-10:30am (Sessions)

- Using Personalized ePortfolios to Demonstrate Professional Competency in Clinical Research
- Around the World in 120 Minutes: A Discussion of Global Research
- I Think I Can: Ethical Considerations for the Cognitively Impaired
- Standardization, Collaboration and Technology: A Global Site and Industry Perspective
- Regulatory and Ethical Considerations for Clinical Research Involving Mobile Technology
- Patient-Centric Medication with Direct-to-Patient Shipping
- Site Performance Report Cards: What's Fair?
- Requiring Good Clinical Practice Training for Investigators and Study Personnel

10:45-11:45am (Sessions)

- Ethical Research Involving Children Hinges on the Risk Benefit Relationship
- Keeping the Spark Alive During Long-Term, Multi-Center Trials
- Quality by Design: The Value of CRF Mapping
- Current Regulatory Scenario for Global Clinical Trials Program in India
- Collaboration in Patient-Centered Medical Device Innovation and Regulation
- Before RBM was in Vogue: How NIH Managed Efficient Monitoring
- CDER BIMO Compliance and Enforcement: What You Need to Know!

12:00-3:00pm (Lunch, Exhibits & Poster Sessions)

2:30-4:00pm (General Session)
Keynote Speaker Kai Kight

4:15-5:15pm (Sessions)

- Battle of the Clinical Trial Agreements: Sponsor versus Site
- PI Oversight: Making It Real
- Dealing with Unanticipated Problems Involving Risk in Clinical Research
- Inspection Findings Related to the Informed Consent Procedure: Lessons Learned
- Humanitarian Use Devices: It's Not That Complicated!
- Decoding the New Drug Good Clinical Practice Regulations: An Approach
- Using an Electronic Site Visit Report to Streamline Visit Reporting
- FDA-CDER: Three Topics from 2015 Conference Attendees

MONDAY, APRIL 18

8:30-10:00am (Sessions)

- Pregnancy Prevention During Trials: Beyond the Birds and the Bees
- Managing Time, Tasks and Relationships: Focusing on What Matters Most
- Communicating from the Heart
- Portal Technology: The Next Significant Innovation in Clinical Research
- Design Thinking and the Human Factor: Creating Effective and Efficient Systems
- Training Across Generations
- Three Perspectives: Conducting an Investigator-Initiated Multi-Center Clinical Trial

10:15-11:45am (Sessions)

- So You Have Been Chosen for an FDA Inspection: Guidance from a Former Auditor on How to Prepare, Host and Follow Up for a Site Inspection
- CAPA Isn't Just a Compliance Tool: Maximizing Site Performance Applying CAPA Principles
- It's Your Career: Own It!
- Making the Complex Compelling: Communicating Technical Information Effectively
- Conflict Resolution: Helping Teams Manage Through Conflict
- Unlocking the Positive Value of Ethics Using Educational Games
- So, You Want to Be an Investigator: The Other Side of the Coin
- Quality Essentials: Monitoring Visit Report Review Plans

12:00-3:00pm (Lunch & Exhibits)

2:30-3:30pm (Sessions)

- Clinical Trial Forecasting and Budgeting for Sites
- Vulnerability: Do You Know It When You See It?
- Real-World Study Planning
- EU Clinical Trials Regulation: Live in 2016?
- How a Clinical Trial Liaison Can Make Enrollment and Study Compliance Successful at a Site
- An Idea Whose Time Has Come: Next Steps in the Professionalization of Clinical Research
- Learning in the Digital World
- Inside the FDA: Drug Good Clinical Practice Regulations Compliance

3:45-4:45pm (Sessions)

- Cannabinoid Clinical Trials: Current Review, Problems, Pitfalls and Solutions
- Reverse Engineering 483s and Warning Letters to Improve Your QA Program
- Creating Accountability: A Step-by-Step Approach
- The Crossroad: Clinical Research Career Development & Site Endorsement
- Technical Data Review in IVD Studies
- Eliminating Shadow Charts from Your Study Site
- Is My Monitoring Adequate?
- 2016 Update: U.S. Healthcare Changes and How They Affect the Clinical Research Industry

TUESDAY, APRIL 19

9:45-10:45am (Sessions)

- Brain Tumors Under Attack: The "Shock and Awe" of Oncolytic Viruses
- Building a Better Budget: How Budget Improves Clinical Trials
- Mobile Technologies in Patient Engagement and Retention
- A New Data Collection Model to Streamline Data Flow, Traceability and Transparency
- Performance Evaluation Monitoring Visits: The Art of CRA Training and Assessments
- Special Considerations in Pediatric Trials for CRAs
- Clinical Trial Agreements for Medical Device Sponsors
- Standardizing Principal Investigator Delegation Records: An Alternative Approach for Sites
- Interpreting Clinical Regulations: Precautions and Warnings

11:00am-12:00pm (Sessions)

- The Metrics Evolution: Use Better Metrics to Improve Clinical Trials
- The Impact of Social Media Communities on Clinical Trials
- The True Costs of Site Regulatory Compliance and Improvement Opportunities
- Effective Employee Training for a Multi-Generational Workforce
- Improving Communication Between Researchers and Nurses Caring for Study Participants
- Efficiency Practices to Compete as a Small Clinical Trial Site
- Enrolling Critically Ill Children in Research: Opportunities and Challenges
- Bench to Patient: The Device Regulatory Process
- Subject-Centered ICF: A Research Nurse's Perspective

**All Session and Workshop Schedules Subject to Change*

KEYNOTE SPEAKER: Kai Kight

Sunday, April 17

A classical violinist turned innovative composer, Kai Kight inspires individuals and organizations to compose paths of imagination and fulfillment. Inspired by his mother, who when diagnosed with cancer revealed regrets of not bringing her ideas to the world, Kai's mission is to spark a global mindset shift that makes ingenuity the norm, not the exception.

@KaiKight

ACRP 2016 MEETING & EXPO

ATLANTA
APRIL 16-19

NETWORKING & SPECIAL EVENTS

FRIDAY, APRIL 15

All Day	Atlanta Tours (additional registration fees apply)
5:30-7:00pm	Academy Volunteers Reception (invitation only)
5:30-7:00pm	2016 M&E Volunteer Reception (invitation only)

SATURDAY, APRIL 16

6:30-7:30am	Medical Heroes Appreciation 5K Run & Walk (additional registration fees apply)
8:15-8:45am	Attendee Orientation Session
4:45-6:30pm	Exhibit Hall Opening Celebration
6:30-7:30pm	Speaker Appreciation Reception (invitation only)
7:00-9:30pm	Certification Milestone Recognition Ceremony (invitation only)

SUNDAY, APRIL 17

6:30-10:00pm	Clinical Researcher of the Year Gala (additional registration fees apply)

TUESDAY, APRIL 19

8:30-9:30am	ACRP/Academy Membership Business Meeting
12:00-3:30pm	Facility Tours

**All Networking Event Schedules Subject to Change*

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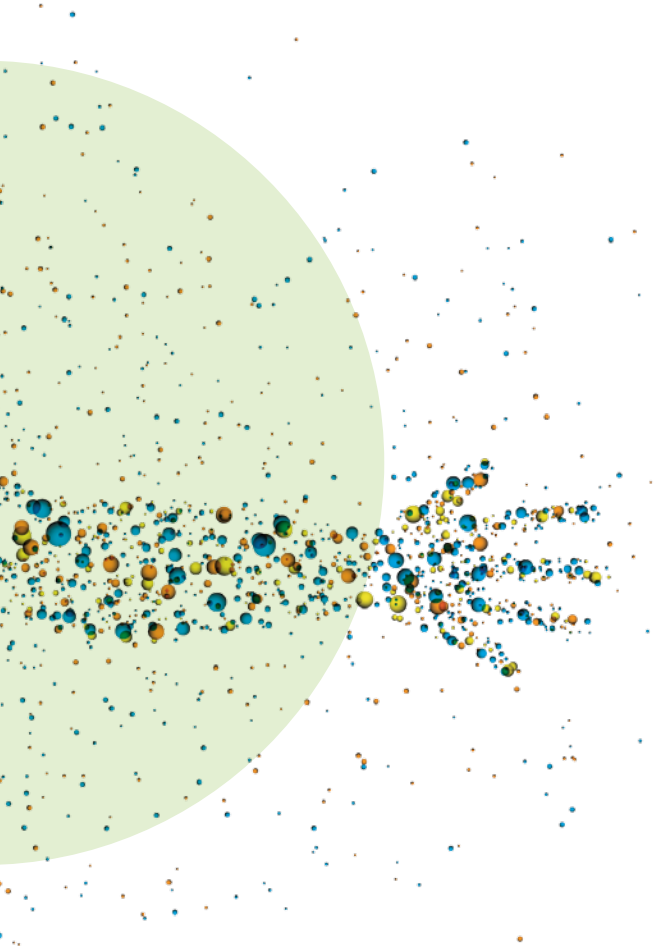
Designing Clinical Trials for New Drugs:

Ethics, Governance, and Reputational Challenges

PEER REVIEWED
Jennifer Miller, PhD
Arthur Caplan, PhD
Alessandro Blasimme, PhD

[DOI: 10.14524/CR-15-0045]

Much has been written about the ethics of healthcare innovation and the role of pharmaceutical companies in innovation. Rightly or wrongly, the scholarship and media coverage has been disparaging. Many commentators fear that the biopharmaceutical sector no longer serves patients' interests; they see it as more focused on shareholders' financial interests.



For instance, such commentators maintain that pharmaceutical companies are testing drugs for first-world problems on third-world populations that might not need them, or who cannot afford them. Others have documented cases of drug companies and medical journals failing to publish unfavorable clinical trial results, noting that selective publication compromises the quality of medical evidence and patient care. More recently, attention has escalated around drugs prices, partly because of high-profile cases like that of Martin Shkreli, who bought the rights to an antiparasitic drug and raised its price by 5,500%.

Despite the glut of scholarly and media attention on the ethics of clinical trials and the role of pharmaceutical companies in healthcare innovation, not much attention has been paid to the ethics of clinical trial design itself. This is strange, since ethical clinical trial design is foundational to the topics mentioned above. After all, it is unethical to recruit research subjects to participate in an intentionally biased clinical trial.

Moreover, also failing to address unintentional biases shows a lack of ethical concern for the fact that research participants are being exposed to risks not compensated for by significant gains in terms of *generalizable* medical knowledge. Additionally, biased trials can compromise medical evidence, thereby leading to suboptimum care.

Randomized Controlled Trials

Randomized controlled trials (RCTs) are considered the most accurate way to test if a novel drug or treatment is safe, effective, and better overall than already available alternatives. These trials are held in such high regard because they possess some of the defining features of a sound scientific experiment. First, they have an experimental arm and a control arm—possibly a placebo—helping to prevent errors in the interpretation of results. Moreover, the fact that many RCTs are blind or double-blind and/or randomized can help minimize investigators' biases and preserve the objectivity of data. These features account for a clinical trial's internal validity.

Based on these premises, many people in drug development and healthcare believe RCTs provide the chief method for generating credible scientific evidence for the efficacy of any treatment. As a consequence, other types of trial designs and data-analysis techniques (e.g., observational, historically controlled studies, adaptive trials) have been regarded as less reliable and thus less desirable.

It is therefore to RCTs that we currently turn in deciding whether a new drug deserves to be licensed for marketing; and, second, in deciding which medical intervention is best for a patient.

Ethical Concerns About Clinical Trial Design

A key concern about the ethics of how clinical trials are designed is the risk for bias. Critics worry that if trial sponsors or researchers have vested personal or institutional interests in producing favorable trial outcomes, they may be tempted to intentionally bias the designs of trials to achieve those outcome.

There are at least three fundamental ways critics worry trial design biasing can occur: cherry picking research subjects (the people upon whom a drug is tested), cherry picking research settings (the trial sites), or cherry picking the selection and dosing of comparators (the ingredient against which a drug is compared in a multiarm study).

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Unfortunately, critics often fail to distinguish between two types of biasing—intentional manipulations versus less blameworthy external validity limitations shared by many, if not most, trials.[1] *Intentional* biasing is motivated by lack of ethical and scientific integrity, and it might be geared toward generating "good advertising material," whereas *unintentional* biases might result from regulatory, scientific, or payer requirements.

Looking at the data, it seems drugs are often tested on patients who are far younger and healthier than would be the eventual patient consuming approved medicines. Take myocardial, COPD, and NSAID drugs as examples. Myocardial drugs are frequently tested on younger patients; "a review of 214 drug trials in acute myocardial infarction found that over 60% excluded patients aged over 75 years."[2] Similarly, COPD and NSAID drugs have been tested on atypically healthy patients without comorbidities, when the average patient has multiple health complications.[3,4]

Peter Rothwell, a professor of clinical neurology at the University of Oxford, argues that monitoring for clinical trial design bias generally falls outside the purview of every gatekeeper, be it the U.S. Food and Drug Administration (FDA), medical journal editors, or institutional review boards (IRBs).[2]

Responses to the Ethical Concerns

SCIENTIFIC AND REGULATORY REQUIREMENTS

The first two rationales for why research participants often represent specially curated populations are that scientific and regulatory systems largely mandate it. In terms of science, to clearly show cause and effect, one needs to limit confounding variables; a "clean" baseline is essential in order to detect adverse events and to insure that positive responses are attributable to the active agent. In other words, in order to see whether a particular drug is effective for a particular condition, it is helpful to limit comorbidities, and thus not test drugs on people with five other health problems taking five other drugs. This explains why many drugs are tested on patients who are far healthier than the eventual average users.

Additionally, Congress and the FDA helped produce the system of testing new drugs on highly specialized populations in highly controlled settings, largely in response to the thalidomide disaster in the 1960s. To aid in preventing this type of tragedy, Congress passed the Kefauver-Harris amendments to the Federal Food, Drug, and Cosmetic Act of 1938. The amendments created many new requirements for drug manufacturers, including that they provide "substantial evidence" of effectiveness based on "adequate and well-controlled studies" (i.e., clinical trials).

According to experts, "the law did not define a well-controlled study, (however) testimony before Congress made it clear that it included, as a minimum, the use of control groups, random allocation of patients to control and therapeutic groups, and techniques to minimize bias including standardized criteria for judging effectiveness."[5] In other words, the law responding to the thalidomide disaster was partly responsible for the Phase I through III, highly controlled trials in highly specialized populations seen today.

Moreover, some drugs need to be tested on treatment-naïve patients (those who haven't taken any other drugs). For instance, once a person has been exposed to an HIV medicine, one's immune system can change as a result of the antiretrovirus medicine, which can in turn change the effects of a second-line medicine. Similarly, cancer drugs can select for drug-resistant tumor clones, thus affecting reaction to investigational drugs.

PHASE IV STUDIES

A third defense for the current clinical trial regime pertains to FDA requirements to conduct post-approval Phase IV studies, which assess a drug's safety and effectiveness in the general population, and often in ordinary care settings.

Some argue that these Phase IV studies sufficiently round out the data collected from specialized populations in Phase I–III trials, and in fact represent the best time to collect generalized data, because doing so prior to approval could slow the approval process and, therefore, general patient access to drugs. Further, when access to potential life-saving therapies is a priority, why would anyone delay a drug's approval, and therefore broad patient access, until it has been tested on every major patient population?

THE ROLE OF THE FDA

The FDA reviews all trial data submitted in a New Drug Application to determine whether to grant marketing approval. This may include assessing whether the trial data are generalizable. If the agency has concerns, it can ask drug sponsors for further studies. Companies generally comply with FDA requests to help get their drugs approved.

THE ROLE OF PAYERS

Payers often request trials in special populations before granting coverage. They may, for example, wish to understand how a drug studied primarily in

45-year-olds works in 75-year-olds, and may refuse to pay for the drug unless a trial is run in populations other than those already targeted in studies.[6,7]

Similarly, countries may also request trials in certain locations. For example, China's regulatory body may request a trial in China to approve a drug or device if it doesn't see enough data on the drug's efficacy in Chinese populations.[8]

TRIAL AND EVIDENCE: ADVANCING REAL-LIFE CLINICAL INVESTIGATION

Addressing intentional and unintentional biases in clinical trial design is an ethical and public health priority; the question is how to do so. Ethical persuasion and incentive design mechanisms like indices, ratings, and rankings might be helpful. These types of programs help signal what the best practices are, what they can and should look like, and where there are areas ripe for reform. They also reward good performance.[9,10] Certainly, promoting full transparency and disclosure of trial results (both positive and negative) is essential in mitigating intentional biases.[11]

As to unintentional biases, it is the design of clinical trials that could be targeted. In particular, we may have to look at novel forms of clinical investigation—possibly reconsidering some of the assumptions that confer RCTs their privileged status—in order to overcome known problems with external validity. This is reflected in an upheaval of interest for trial designs that aim at generating evidence also from real-life data on the use of a drug or clinical protocol.

These novel models can be grouped under the heading of "pragmatic trials." Whereas explanatory interventional trials (RCTs) are used to test the *efficacy* of a drug under ideal experimental conditions, pragmatic trials aim at testing the *effectiveness* of the drug, that is, its benefit under ordinary clinical conditions.[12]

At least three types of pragmatic approaches are currently receiving a good deal of attention for their presumed capacity to perform better than RCTs in terms of external validity: efficacy-to-effectiveness (E2E) trials and adaptive licensing pathways, both in the field of drug licensing, and superiority trials, or comparative effectiveness research (CER), in the domain of clinical practice.

EFFICACY-TO-EFFECTIVENESS TRIALS

In E2E trials, an effectiveness study starts immediately after efficacy data have been collected in an RCT, thus generally after Phase III.[13] This model, therefore, is intended for a pre-release phase of drug development.

The aim here is to test the result that the trial has generated with a homogeneous sample of participants on a more varied population that better reflects the real clinical care setting. This is primarily intended to prevent the effects of artificial cohorts described earlier, thus enhancing the regulators' capacity to predict the real effect of a drug early on, before approving a new drug for marketing.

Although early effectiveness trials may represent an added cost for developers, such costs could be compensated by the fact that this design relaxes the originally narrow eligibility criteria, thus broadening the number of potential beneficiaries beyond the initial indication. Moreover, this design may help isolate subgroups of well-responding patients, thus allowing a treatment to survive in spite of negative findings concerning its general effect.

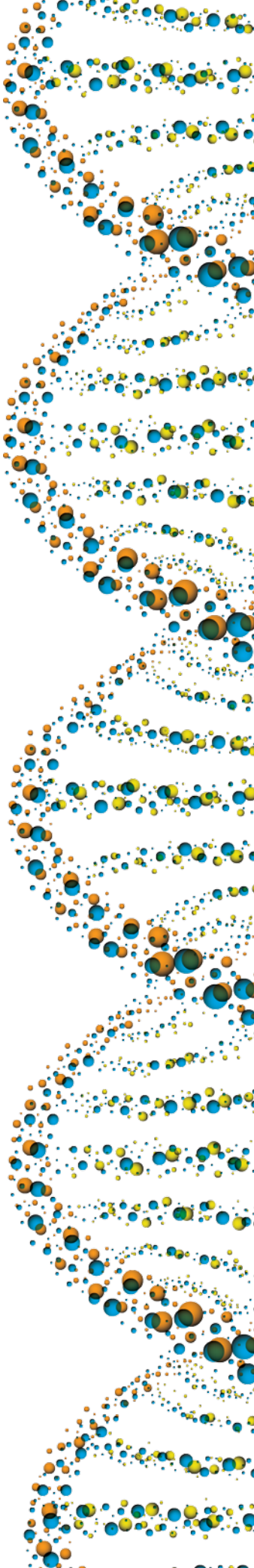
ADAPTIVE LICENSING PATHWAYS

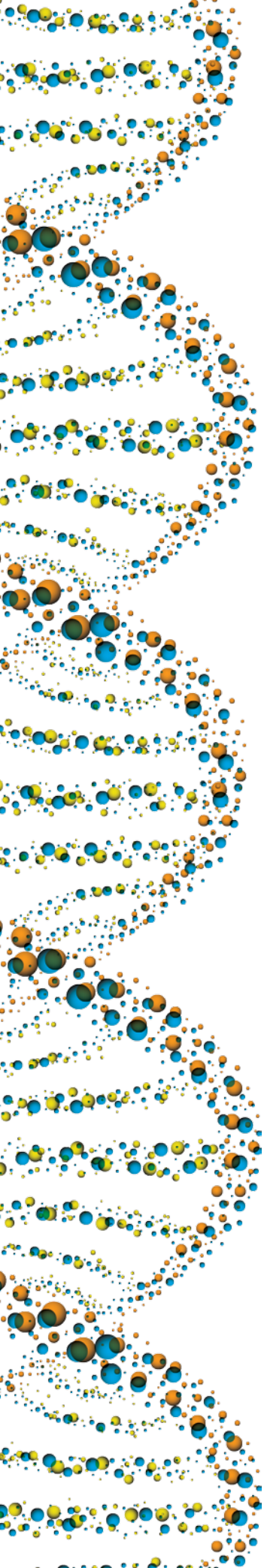
Adaptive licensing, or adaptive pathways, indicates a novel way of conceiving drug licensing, whereby the release of a drug is anticipated right after Phase II.[14,15] In this way, efficacy data are collected directly from clinical use, whereas the scope of the initial license gets adapted by regulators according to the accruing evidence about the use of the drug in actual clinical conditions. At the end of a monitoring period, regulators can either issue a definitive license or withdraw the drug.

Again, the idea behind this model is to test the new drug on a natural population and check for signs of effectiveness early on in the pipeline. Additionally, this model could make it much harder for sponsors to hide negative results or to selectively report efficacy data. Some also argue this practice could help transition to a type of "learning healthcare system." Moreover, since they are conducted in real-life conditions, adaptive licensing (like E2E) may do better than RCTs in ruling out biases due to inclusion criteria.

COMPARATIVE EFFECTIVENESS RESEARCH

CER represents an earlier kind of pragmatic trial design,[12] and is aimed at two possible outcomes. On the one hand, CER can be used to resolve medical uncertainty about the comparative value of two or more existing treatments. On the other, it can be used to compare the cost effectiveness of multiple treatments for the same condition in view of a more efficient allocation of resources in coverage decisions.





CER can be randomized if genuine clinical equipoise occurs, but it can also be just observational.[16–18] Moreover, CER can be the basis for adaptive decisions of the kind described in the previous model. Also in the case of CER, inclusion criteria are much less strict than in a conventional RCT, which again is supposed to ensure greater predictive power.

Further Considerations

What the three above paradigms have in common is that they all rely on real-life data, generated in the course of normal clinical care—as opposed to data generated under tightly controlled conditions. Therefore, whereas for explanatory interventional trials internal validity is the primary virtue, pragmatism in clinical research stresses the importance of external validity. The challenge for pragmatic and adaptive designs is to ensure statistical consistency in spite of more heterogeneous samples. The challenge for regulators is to accept more *uncertainty* to gain information in wider, more realistic patient cohorts.

Although intriguing from a methodological viewpoint, these pragmatic approaches call for dedicated ethical scrutiny. In E2E and adaptive licensing, a drug of yet unproven efficacy is provided to a larger population than would be the case for a late-phase clinical trial. Therefore, while in the assessment of conventional RCTs the focus is on the amount of known risk that it is ethical to accept, in these pragmatic models the focus should rather be on the amount of uncertainty that it is ethical to tolerate in view of its progressive reduction. We should thus have standards in place to understand under which circumstances this can be taken to be ethical.

One of the ways to render this feature of pragmatic trials ethically plausible is to say that this design could be limited to patients with unmet medical needs. Interestingly, this suggests that the ethical basis of these novel forms of drug development is being carved out from the ethics of compassionate use or expanded access programs.

The assumption here is that, for those who lack other therapeutic options, gaining access to an experimental drug that is still under development may represent an opportunity more than a risk. In effect, proponents of these models—such as patients' advocacy groups—often point at excessively paternalistic standards of clinical research ethics as an unjust limitation for patients who seek access to a wide array of therapeutic alternatives.[19]

On the other hand, it has been noticed that clinical investigation based on real-life settings blurs the distinction between research and practice—as is apparent, for instance, in CER aimed at comparing two already existing clinical interventions. This line of separation between generating clinical knowledge and providing a therapeutic intervention has played an important role in bioethics, since it demarcates activities that require IRB oversight (clinical research) from activities that fall under the responsibility of medical professionals guided by decisions about the standard of care (clinical care).

Other than creating governance issues, pragmatic research also poses issues that are ethical at heart. For example, it is not clear whether informed consent of the kind that is used in research—with its emphasis on therapeutic misconception—is appropriate in pragmatic settings, particularly if randomization occurs on the institution rather than the patient level.[20] Also unclear from an ethical point of view are the notions of patients' hopes and preferences with respect to access to new drugs.

Possible Solutions

Trial sponsors, researchers, the FDA, and other stakeholders recognize there is a need for flexibility in the area of clinical trial design, and many of them are exploring adaptive clinical trial designs and the other strategies outlined above. Notwithstanding, companies and trial sponsors argue they cannot easily move away from the highly controlled format of clinical trials until the FDA does. For now, they say they need to maintain the status quo to meet FDA requirements or their products won't be approved.

Below we highlight four interrelated topics stakeholders can consider in addressing concerns about biased clinical trial designs and limited clinical trial data generalizability. In particular, they can begin or further consider the role of:

- **Phase IV studies**, or postmarketing studies, in understanding how drugs work in routine clinical practice;
- **pragmatic clinical trials** in understanding how new drugs compare to existing standards of care;
- **superiority trials,** as part of a larger strategy of understanding the *effectiveness* of a new intervention, not just the *efficacy* for various patient populations; and

Although early effectiveness trials may represent an added cost for developers, such costs could be compensated by the fact that this design relaxes the originally narrow eligibility criteria, thus broadening the number of potential beneficiaries beyond the initial indication.

- **clinical trial transparency and data-sharing** as well as **health data-sharing,** more generally, for better understanding drug reactions and interactions in targeted populations.

Moving forward in any of these areas requires ethical scrutiny to address topics such as confidentiality and privacy protections; this is already under way in many forums.

Conclusion

The prevailing view in the literature is that explanatory and pragmatic trials should not be seen as antagonistic. Rather, they can and should coexist along the same regulatory continuum as more traditional trial designs. What is hard to deny, however, is that the two models embrace rather distinct concepts of what counts as sufficient evidence and of what counts as ethical treatment of those involved in clinical investigation. This means that more work is needed to actually bring about the integration of experimental and pragmatic research.

Repeated calls for "learning healthcare systems," "big data and digital health," "precision medicine," and, more in general, "clinical translation" are already pushing drug development in a more pragmatic direction. It is therefore imperative that bioethics continues to engage with this novel area of real-life clinical investigation to develop appropriate ethical and governance standards.

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New Opportunities and Threats in the Realm of **Informed Consent**

James Michael Causey

[DOI: 10.14524/CR-16-4005]

Informed consent errors have fallen to sixth from first place as cited in most common clinical investigator findings by the U.S. Food and Drug Administration (FDA) over the past five years. While that suggests clinical researchers and sites have gotten better at handling this critically important set of tasks, it may not tell the whole story, say a number of speakers at the upcoming ACRP 2016 Meeting & Expo and other thought leaders.

"I'd like to think we've gotten better," says independent clinical research consultant Janet Holwell. "We still have a long way to go. This is a critical piece as it relates to human subject protections." One of her concerns? Relatively new issues such as eConsent could present unanticipated challenges. The FDA released a draft guidance document last year regarding eConsents, but this may be a new area to many sites and present new challenges to develop tools and tactics for adequate processes.

Observations from the Trenches

Deborah Rosenbaum, a consultant with Sarrison Clinical Research, sees two additional areas of concern: Gene therapy and human genomes. Both will require new ways of guaranteeing everyone's eyes are wide open during the conduct of informed consent.

Technology and new ideas aside, the biggest obstacle to implementing and maintaining a robust informed consent standard operating procedure (SOP) remains the human factor, says Claudia Christy, an independent nurse consultant based in North Carolina. It takes time to build the relationships that are the foundation of properly performed informed consent, she adds.

It's also important to stress that informed consent is an ongoing process—not a simple box to check and forget about. Further, it is critical for sites to show they can adjust their SOPs to different patient populations (e.g., trials involving children or adults with Alzheimer's).

New hires and even relatively seasoned clinical research coordinators (CRCs) don't always understand the *why* of what they're being asked to do, Christy says. That's problematic because it can result in sloppy work.

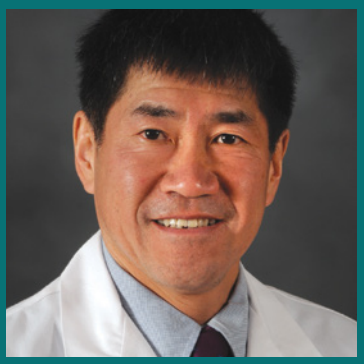
For example, Christy was a potential subject in a large study with no serious potential of danger. She was vetted by a young summer hire, she says, adding, "He told me to sign the form and then take it home and read it."

Obviously, it should be the other way around, but the youngster didn't know that was an issue. He treated the form as more of a *pro forma*. Another mistake: He didn't read it closely and missed that the trial required a follow-up a year later.

Pursuing Best Practices

Because of how easily misunderstandings and mistakes can occur, Christy urges clinical researchers to make sure a potential subject really understands what he or she is signing up for. Specifically, she recommends:

- Asking the subject to tell you how they'll describe the trial to their family.
- Using short quizzes to double-check understanding.
- Ask the subject if they understand the basics of eConsent, if appropriate.



I often talk to potential trial subjects...and connect them with past trial participants, too.

— Nathan Wei, MD

Despite changes in technologies and the way potential subjects view trials, there are several informed consent shortcomings that have remained constant over the years.

— Janet Holwell

Ask the subject to tell you how they'll explain this to their family.

— Claudia Christy

Don't overestimate the power of the "white coat." Gone are the days of the "patriarchal" view that doctors were all-knowing entities never to be questioned by mere mortal patients, Christy notes. Today, patients more often make their own decisions, she says.

However, used strategically, that white coat can be a big help, says Nathan Wei, MD, at the Arthritis Treatment Center in Frederick, Md. His team has had success with several approaches, including:

- A clear explanation of potential side effects. It's a bit of a balancing act, Wei admits. His team will remind subjects that they are required to highlight any side effects, even if there is a 1/10,000 occurrence rate.
- An assurance that Wei will be on hand to discuss the trial parameters and specifics at any time. "I often talk to potential trial subjects," he said.
- Connect past trial participants with new subjects. Wei likes to find former trial subjects and have them address a group of prospective ones. "It can take away that 'guinea pig' fear," he says.
- Adjust how you handle subjects. Their experiences are across the board, Wei notes. Frequent volunteers are usually "ready to roll," while others of course need more hand holding.

Wei often mails informed consent forms to patients prior to their coming in for the formal informed consent process. It's helpful...up to a point. "Since they already have gone through the informed consent, they don't want to have to go through it again," Wei says. "Unfortunately, our SOPs as well as the SOPs for our sponsors mandate that the informed consent be conducted when the patient comes in for the baseline visit."

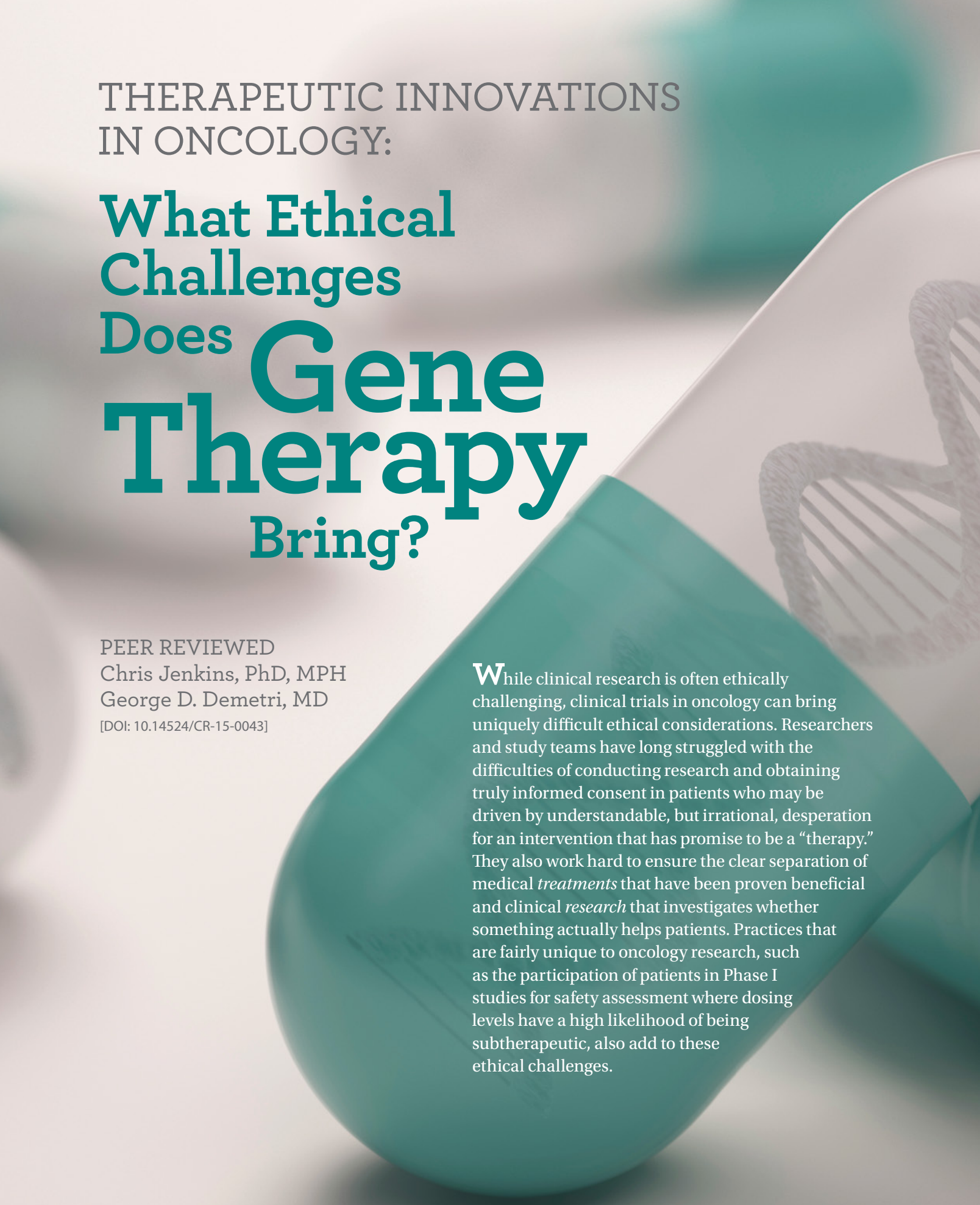
Finally, Holwell reminds that, despite changes in technologies and the way potential subjects view trials, there are several informed consent shortcomings that have remained constant over the years. She called out two for special attention:

- **Version control.** Too often, a CRC or investigator will use an old version of a consent form. Holwell advises using headers and footers to keep things straight. She also advocates a color coding system (e.g., first version on white paper, second on green, etc.). "It's another visual clue, another safeguard," she says. Destroy obsolete blank consent forms to avoid using an incorrect version.
- **Failure to properly document informed consent via missing signatures or dates.** There should be a standard operating procedure for obtaining informed consent. Investigators or persons eliciting consent might miss signing the consent form at the same time with the subject. This can be an honest mistake with serious consequences resulting in findings of noncompliance.

THERAPEUTIC INNOVATIONS IN ONCOLOGY:

What Ethical Challenges Does Gene Therapy Bring?

PEER REVIEWED
Chris Jenkins, PhD, MPH
George D. Demetri, MD
[DOI: 10.14524/CR-15-0043]



While clinical research is often ethically challenging, clinical trials in oncology can bring uniquely difficult ethical considerations. Researchers and study teams have long struggled with the difficulties of conducting research and obtaining truly informed consent in patients who may be driven by understandable, but irrational, desperation for an intervention that has promise to be a "therapy." They also work hard to ensure the clear separation of medical *treatments* that have been proven beneficial and clinical *research* that investigates whether something actually helps patients. Practices that are fairly unique to oncology research, such as the participation of patients in Phase I studies for safety assessment where dosing levels have a high likelihood of being subtherapeutic, also add to these ethical challenges.

In recent years, the rapid advances in cancer therapies have brought new ethical complications, as well. Before the 20th century, surgery was virtually the only approach to cancer therapy. However, the past century brought many advances, including radiation therapies to treat various cancers, cytotoxic ("cell killing") chemotherapy drugs capable of curing childhood leukemias and sarcomas, the cell therapies of bone marrow and stem cell transplantation permitting tolerance of high-dose chemoradiotherapy with a nontargeted immunologic action, therapies targeting hormonal signaling, and the administration of selected lymphocyte cell therapies pioneered at the National Cancer Institute by Dr. Steve Rosenberg.

The end of the last century and the dawn of the 21st century have brought us a panoply of high-impact new therapeutic tools, including targeted therapies such as monoclonal antibodies (rituximab in lymphomas or trastuzumab for breast cancer) and pills such as imatinib, and EGF-receptor inhibitors such as erlotinib and others. One cannot pick up an issue of the *New York Times* or *USA Today* without seeing content trumpeting breakthroughs like immune activators such as nivolumab and pembrolizumab.

Further, the promise of genetically modified T-cell therapies with so-called "CAR T-cells" (and even the cleverly named "Armored CARs") has lifted the wave of enthusiasm to impressive heights, and the world awaits data to show exactly how many cancers may benefit from these complex and highly sophisticated interventions with multiple variables. In the years ahead, Nobel-quality science such as CRISPR (clustered regularly interspaced short palindromic repeats) gene editing systems brings hope—as well as fears—of unforeseen consequences in a brave new world of scientific perturbations of the natural world in search of genetic and epigenetic therapies for cancer and other genetic diseases.

FEAR, HYPE, AND EVENTUAL ACCEPTANCE OF NEW TECHNOLOGIES

Gene therapy is a field with a roller-coaster history from both ethical and scientific perspectives. Initially perceived as a revolutionary new technology with the promise to cure almost any disease with a genetic or molecular basis, setbacks and unforeseen side effects tempered expectations and enthusiasm waned as the hoped-for cures did not manifest immediately.[1] The

The message to be extracted from the cycles of enthusiasm and disappointment is that the future success of gene therapy will be founded on a deeper understanding of vector biology and cellular pharmacology.

tipping points seemingly were related to technologic limitations based upon the "molecular vehicles" used to deliver the therapeutic genes to the target tissue without the required efficacy, safety, or specificity. In early trials, the vehicles, or "recombinant viral vectors," were inefficient and failed to persist in the targeted cells, and this led to inadequate expression of the genetic information.

Then, in 1999, a severe adverse patient reaction to an adenovirus vector during a Phase I trial led to the realization that inadequate understanding of the biology of vector interactions with the human immune system could have fatal consequences.[2–5] This emphasized urgently that more effort to understand risks was necessary before these tools entered "prime time" standard care.

The ups and downs of this field continued; in the year 2000, the first gene therapy successes were noted in three children who were cured of a fatal immunodeficiency disorder. However, the therapy was subsequently linked to causing a leukemia-like disease in two of the 11 patients who had participated in this gene transfer clinical trial. Other similar cases were subsequently reported from other gene transfer trials. Such severe blows risked overshadowing the substantial progress that had been made in the development of gene-transfer technologies over recent years.

The message to be extracted from the cycles of enthusiasm and disappointment is that the future success of gene therapy will be founded on a deeper understanding of vector biology and cellular pharmacology.

Over the past few years, intense efforts have been concentrated on understanding the molecular basis of how viruses and viral vectors interact with the host. We are now beginning to see these efforts translate into more clinical trials with earlier and more profound levels of success than ever before; this applies both to directly injecting the therapies into a human subject (*in vivo* gene therapy), as well as procedures that take biological materials from the subject or another source, modify them outside the human body with vectors, and introduce them into a human subject (*ex vivo* gene therapy). Both methodologies carry inherent benefits and risks, but a fundamental issue is shared; this revolves around the issue of how one should *evaluate* and e*xplain* risk when the risk level is unknown, for example when introducing a virus or genetically modified cell into a human subject.

ASSESSING RISK WHEN THE RISK IS UNKNOWN

The challenge in human gene transfer studies is to assess risk when it may be nearly impossible to account for all of the variables involved, and when very few subjects are present from whom to draw evaluable data. Risk is an inescapable aspect of clinical research, and is increasingly pertinent to the gene transfer field as the number of clinical trials increases exponentially.

Because of the previously noted occurrences of serious adverse events (SAEs) in early gene therapy studies, there has been heightened fear in public perceptions of gene therapy, especially for metabolic genetic diseases outside cancer.

Although it is essential to be cognizant of the risks involved in gene therapy research, there is a danger of the pendulum swinging so far that the approach to the truly promising science of gene therapy may become excessively and irrationally risk-averse. If the field is to make progress, it is necessary to understand how risk is defined in gene therapy research, how understandings of risk differ, how risk is assessed, how decisions about risk are made, and how gene therapy risks are communicated to subjects and research participants during the informed consent process.

In addition to minimizing the risks of clinical research through extensive preclinical safety studies and careful control of processes, attention should be given to how decisions about risk and risk acceptability are made by researchers and subjects, and to the methods used to communicate risks to patients. Critical attention to risk will help ensure that the safety of subjects is held paramount, while also enabling research to develop better treatments for patients.

What we do know about one very unique risk of certain types of gene therapy is that there is a chance of inducing cancer or cancer-like neoplasia, through insertional mutagenesis. In short, insertional mutagenesis is changing the normal DNA sequence by the insertion of one or more bases. Insertional mutations can occur naturally,

can be mediated by virus or transposon, or can be artificially induced for research purposes in the lab. Recently, in gene therapies, unusual forms of leukemias have developed as complications following retroviral transfer of potentially therapeutic genes into hematopoietic cells. A crucial component in the pathogenesis of these complications was the upregulation of a normal cell gene (called a *proto*-oncogene) by random insertion of the retroviral gene transfer vector, which essentially turned on a cancer-inducing gene by chance alone.

There are other safety and ethical concerns about tampering with the human germ line (cells that can give rise to transmission to other generations directly). However, another unique safety and ethical issue of human gene therapy lies in the potential risks to caregivers, family members, and even the general population. What is the risk to others besides the research participant of giving a vector containing a gene with the intent of having that viral vector reproduce and then spread through the research participant's breathing, sneezing, sweating, or excreting other biological fluids?

Shedding is the release of the viral or the bacterial progeny from the patient after the patient receives a virus or a bacterial vector, and it successfully reproduces in that patient. You want it to reproduce, so that it actually infects the patient's cells. However, is the patient going to shed genetically modified viruses, and what's the risk to family members from that? Are there any special concerns for vulnerable populations, such as infants or children in the household, or even in the general population?

The depth and breadth of these questions are compelling and important to ensure that the public as well as the professionals in this field are thinking about all relevant aspects of this complex biology and research in humans.

ETHICAL ISSUES IN NEW TECHNOLOGIES

In the earliest days of gene therapy, there was so much excitement around the science that the efforts to understand ethical issues surroundings these tools were perhaps overshadowed. More recently, as we understand gene therapy involves making changes to the body's set of basic instructions, it has raised many unique ethical concerns, including:

- How do we assess the balance of potential risks and benefits of research in a technology that we are still working to understand?
- How do we consider the potential risks to others—the research staff, the family of the research participant, the general public—in therapies that include factors like the potential for viral shedding?
- Can we all agree on limits to what constitutes reasonable research? For example, should any gene editing of the human germline be permitted?

When gene therapy moves out of the clinical research space and into clinical practice or other uses, expanded ethical issues appear:

- How can "good" and "bad" uses of gene therapy be distinguished?
- Who decides which traits are normal, which are acceptable, and which constitute a disability or disorder?
- Will the high costs of gene therapy make it available only to the wealthy?

Current gene therapy research has focused on treating individuals by targeting the therapy to body cells such as bone marrow or blood cells. This type of gene therapy cannot be passed on to a person's children. However, gene therapy could be targeted to egg and sperm cells (germ cells), which would allow the inserted gene to be passed on to future generations. This approach is known as germline gene therapy.

The idea of germline gene therapy is hugely controversial; while it could spare future generations in a family from a devastating genetic disorder, it might affect the development of a fetus in unexpected ways or have long-term side effects that are not yet known. Because people who would be affected by germline gene therapy are not yet born, they can't choose whether or not to have the treatment. Further, if something goes grievously wrong, the human who received the treatment cannot simply be destroyed, but could suffer long-term consequences.

Because of these ethical concerns, the U.S. government does not allow federal funds to be used

> The challenge in human gene transfer studies is to assess risk when it may be nearly impossible to account for all of the variables involved, and when very few subjects are present from whom to draw evaluable data.

for research on germline gene therapy in people. However, we're entering a brand-new world of germline genetic editing (see the April 2015 coverage in the *New York Times* on "Chinese Scientists Edit Genes of Human Embryos Raising Concerns"[6]). As seen in the Chinese research, the aforementioned genetic editing tools such as CRISPR are really game-changing. Using part of the bacterial immune system (an enzyme called Cas9), these tools have the capability to literally go in and edit every piece of DNA in the body, including germline genes. Any changes could get passed on to future generations.

The ethical interests here are amazing, as are the practical interests. The Chinese report generated so much controversy because it was the case that, as Gina Kolata reported, these experiments were dreaded yet widely anticipated. It is a nearly irresistible temptation for scientists who want to change the world to propose editing genes in an embryo to permanently alter the DNA, but what would happen when that person was born?

The Chinese researchers were hoping to fix one gene and alter that gene in every cell, but not do any other damage. However, this experiment failed with the current version 1.0 of CRISPR technology. Although this did not lead to human suffering, one can imagine alternative scenarios with gruesome results. What if some misguided scientist looking for fame and glory were trying to actually fix a gene in an embryo that could turn into an actual human? What if that human was born with DNA damage wrought by the experiment?

Since 2015, the whole idea of CRISPR germline editing and its implications have reverberated through the biotech industry and throughout the scientific community. Two Nobel Prize winners, David Baltimore and Paul Berg, wrote an editorial in the *Wall Street Journal* saying essentially, "let's hit pause before altering humankind."[7]

First of all, there's often an imprecise understanding of the actual mechanisms and implications of what might happen in a human, combined with difficulty in terms of predicting the risks purely using animal models. However, balancing the risks and benefits when the risks are so unclear is an important ethical discussion and distinction. In addition, informed consent is challenged by the highly imperfect information, as discussed above, especially when this communication is compounded by the "hype" over potentially curative gene therapies that is being presented to the lay public by biased sources.

> In the earliest days of gene therapy, there was so much excitement around the science that the efforts to understand ethical issues surroundings these tools were perhaps overshadowed.

It is important to emphasize the current state of knowledge and avoid therapeutic misconception. For the most part, the benefits of gene therapy remain on the theoretical side, but the bar shifts rapidly toward reality in the case of some cancers, such as advanced childhood leukemias that are resistant to other treatments, but which have had exceptional responses to genetically modified chimeric antigen receptor-bearing T-cell therapies. Thus, the benefits are sometimes clear, yet the risks remain somewhat obscure.

Nonetheless, carefully applying scientific process, careful observation, transparent reporting, and appropriate ethical controls should allow us to feel more comfortable about applying the promise of gene transfer–activated immunologic therapies to patients with life-threatening cancers and other diseases. There is the potential, certainly, to address the root cause of specific genetic diseases, and to fix disease pathogenesis for good rather than merely manage symptoms.

The U.S. National Cancer Institute website refers to some of the CAR T-cell approaches that use genetically engineered immune cells as a "living drug,"[8] because the infused engineered cells from the patients are the therapy, along with the patient's own response to the cells themselves. This is a dynamic, interactive, evolving therapeutic and risk equation in which the therapy is not only the living drug, but also invokes the evolution of a host response to those cells and to the targeted cancer cells. It is like solving a higher order calculus equation with multiple variables and insufficient information; only scientific observations and experimentation can provide the answers we all seek to apply this technology and ensure safety and proper assessment of efficacy and toxicity.

OVERSIGHT OF NEW THERAPIES

In partial response to the challenges they present, there is also very complex regulatory oversight of human gene transfer studies. What exactly constitutes that oversight? Certainly, the U.S. Food

and Drug Administration (FDA) has the responsibility for overseeing drug safety and efficacy, but in this case, one might wonder what is "the drug" if we refer to CAR T-cells as a living drug. Is there one actual drug? Is it the agent that infects the patient's own cells with the chimeric antigen receptor gene? Is it the culture solution in which they are kept?

"The drug" actually represents a composite of many, many variables, both external to the patient and patient-specific host factors. This represents huge complexity for the FDA (in particular the biologics branch of the FDA), which recognizes this as a *process,* not just a *drug.*

Although the capitalization of the human gene therapy companies has been unprecedented in size, scope, speed, and scale for biotech, this remains an area that is very complicated to understand, since each academic center and each company might be doing things just a little bit differently, but small variations might make huge differences in safety and/or efficacy. As we watch these trials move into larger, multicenter studies out of the rarified environment of single-center, top-tier academic centers, there is tremendous concern about how this field can keep the quality control high, keep the patient risk in an acceptable range, and figure out what the regulatory oversight is on the local as well as the national and even international level.

Locally and centrally, there are institutional review boards (IRBs), which fundamentally have the protection of the rights and welfare of the human subjects as their focus at the site level. In addition, institutional biosafety committees (IBCs) are extremely important for institutions to think about establishing in order to protect the welfare of everyone around the subject—the study team members themselves, the doctors and nurses, the family, the rest of the facility staff, and even in terms of the public health, random people the patient might be exposed to in daily life.

How such considerations are taken into account, and how an institution complies with all of the relevant U.S. National Institutes of Health (NIH) guidelines are serious matters, indeed. Even the most sophisticated research centers can reel under the weight of these important questions, and in the face of the variety of important logistical factors that must be put into place to conduct this research safely and ethically.

IBCs are required to be in place at institutions receiving funds directly from the NIH for research with recombinant DNA or for studies conducted on behalf of NIH-funded sponsors. The IBC's role is to ensure compliance with the NIH guidelines, to approve specific research protocols, and to work in tandem with IRBs. Note that this is the group that is responsible for setting bio-containment levels; there are different levels of safety that have to be recognized and then respected for the institution to process these tools and procedures safely.

Similar to the structure of IRBs, IBCs comprise experts on the relevant research topics and protocols, as well as representatives of the institution and local members of the public not affiliated with the institution. However, an IBC provides strictly local review; there are no central, regional, or for-profit IBC boards, as can be the case with IRBs for some of the other ethical issues. This has to be a much more "logistical boots on the ground" local review. The important role then of the IBC is to deliberate and to vote on specific research proposals at convened public meetings.

SUMMARY

Human gene transfer, or gene therapy, remains in its infancy. The promises are real, but so are the perils. This is true of most exceptionally interesting new technologies in science and medicine. With the proper education, expertise, and sensitivity to differing needs, this can be approached rationally and responsibly to ensure that risks can be assessed properly and communicated to patients, families, caregivers, and the general public, and to keep this field moving forward while minimizing actual or perceived risks that might be dangerous or onerous.

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[DOI: 10.14524/CR-16-4003]

Grant Gorr reflects on a decade of experience as a top talent recruiter and president of the ACRP Kansas City Chapter

The demand for research professionals has grown dramatically. CRO, pharmaceutical, biotech, and university settings all have increased their research activities, and all have increased their demands on top talent.

Q: How did you first become interested in clinical research, and can you describe the career path you've followed?

A: I first became interested in clinical research in 2005. I work in business development for Aerotek, a company that focuses on clinical research staffing, and it had been fielding many requests from our customers to help with resourcing the clinical research associate skill set. I had just started recruiting this skill set and only knew a few things about it. We brought in a monitor we had known from a global contract research organization (CRO), and she spoke to a small group of us, basically providing the full scope of her work and how it impacts research. I was immediately captivated.

Q: How about your involvement in ACRP? When did you first get involved, and what type of benefits have you reaped from being a member?

A: A few years ago, I was approached by two friends in the industry who wanted to start up an ACRP chapter in Kansas City—both had earlier worked on the West Coast, and had exposure to and activity with the Northern California Chapter. The three of us worked together for about six months, and were granted permission to start our own chapter. As we close out year three, we are sitting at a healthy 60 members.

I have met so many wonderful people over these three years, from members to guest speakers and more. I attended the Global Conference the last two years and was able to speak to other chapters. I was able to bring back some best practices that have really strengthened our Kansas City Chapter.

Q: Since your career has spanned several years and you have no doubt seen many changes, what is the most significant change (or top changes) you have seen? How has this affected the industry, either positively or negatively?

A: The biggest change over the last 10 years that I have seen is the sheer volume of positions needed. The demand for research professionals has grown dramatically. CRO, pharmaceutical, biotech, and university settings all have increased their research activities, and all have increased their demands on top talent. While that is positive, the demand is so much greater than the supply; it has been a challenge for organizations to grow at the rate they would like.

Q: What advice do you have to share with other clinical research professionals, in terms of professional development and advancement?

A: The best advice I can give someone is to always stay connected to what is going on outside his or her current role. What I mean by that is, no matter how happy you are in your career, I believe you should continue to educate and network and to stay close to the world beyond your immediate job duties.

The best place to start, in my opinion, is ACRP! Read the *Clinical Researcher,* sign up for events, volunteer. I work very closely with employers in this industry, and very often they are interested in what candidates are doing to better themselves OUTSIDE the workplace. Of course, it does not hurt to get to know a variety of people, and ACRP events offer up a fantastic opportunity to network and learn about people and the jobs they do.

Q: What about your personal goals? Where do you see your career path heading?

A: I would like to continue to learn more of the technical side of clinical research to better understand the roles I am filling. That will ensure that Aerotek remains a leading partner in the industry. Ultimately, I want to be an invaluable resource for both the clinical and staffing industries.

Q: As you think about the future generation of clinical research professionals, what three "lessons learned" would you like to share?

A: 1) It's important to network; 2) Be a student of the industry—continue to learn and educate yourself; 3) The industry is ever-evolving, so be ready! Be adaptable, agile, and open to change.

Q: Do you have any closing thoughts you would like to share?

A: I have been so fortunate over the years. I love my job. It's a rewarding career because we are helping people find employment in an industry that focuses to advance medicine and, ultimately, to fix, heal, and save lives. Each day is special to me. I am grateful for Aerotek and grateful for all the people who have helped me learn my way in this fantastic industry. Finally, ACRP is the glue for me; it keeps me current and keeps me connected.

It's a rewarding career because we are helping people find employment in an industry that focuses to advance medicine and, ultimately, to fix, heal, and save lives.

Jamie Meseke, MSM, CCRA, (jamie.meseke@ppdi.com) is a clinical trial manager for PPD, Inc., and a member of the ACRP Editorial Advisory Board.

OPINION

Serious Adverse Events:

How to Interact with Clinical Trial Participants When They Need You the Most

PEER REVIEWED | Michael Noss, MD

[DOI: 10.14524/CR-15-0036]

I had a 44-year-old subject in a clinical trial in which I was the principal investigator (PI) call our office and leave a message informing us she experienced a stroke several weeks earlier that almost killed her. She said that she had been previously healthy, and indeed, the only thing she told us about in her medical history was seasonal allergies. She said after three weeks of hospitalization, she was left with residual speech impairment, left-sided weakness, difficulty walking, and lethargy.

Because of this, the subject wanted to discontinue the study, adding that she wouldn't be able to come in for any more visits. She said she previously had been going to the gym every day and was very active, but this event had turned her life upside down.

She stated the only thing that was different in her life that could have caused her stroke was the study product we gave her. She said she saw in the study's informed consent document that there were funds available for injuries caused by the study product, and indicated that she would be willing to settle without the help of a lawyer.

An All-Too Common Scenario

I am sure many of you have been in similar situations; if you haven't, but continue to do clinical trials, you surely will. I have had several encounters like this over my 20-plus years as a PI, and have counseled numerous other PIs over the years in my role as a corporate medical director.

As PIs and research staff, we are repeatedly trained on how to fill out the many forms that go along with serious adverse event (SAE) reporting, but we are never trained on how to actually interact with the study subject who is affected.

Many times, as research staff, our first instinct is to get defensive. The subject in this example received the study product in August and had her stroke in November, so how could the study medication have caused that? She signed an informed consent that clearly stated the known risks and mentioned unknown risks, so that protects me from liability.

The subject is mad and blaming me, so hopefully she will calm down over time. Maybe I'll just wait several weeks and then call her back. …Actually, why should I call her back at all and get yelled at? I'll have the research coordinator do it.

A Better Strategy

However, getting defensive is the exact wrong way to handle this situation—or any similar situation—in my experience. This is a cry for help from this subject, and just because she is a research subject that may be insulated from you by informed consents, protocols, and faceless sponsors and governmental agencies, you as a PI should engage her as quickly and compassionately as possible.

Though you may think the study product had nothing to do with her stroke, how do you know for sure? You might be wrong and she might be right.

We are blinded in most clinical trials exactly for this reason. It is not our job at this point to know for sure if the adverse event (AE) is related to the study product or not. Instead, as a PI, it is our job to communicate with the subject and fill out the AE form, or in this case the SAE form, as accurately and quickly as possible and send it to the sponsor and institutional review board (IRB) if necessary for safety considerations.

Additionally, as PIs and clinical research staff, we need to speak with our study subjects, because if they can't speak with us, their only hope of getting support and answers may come from people who don't really understand the clinical trial they were involved in (or worse yet, from a lawyer). We all know study subjects have little hope of getting specific answers by contacting the sponsor, the Food and Drug Administration (FDA), or even the IRB listed in their study's informed consent.

On the Front Line

The reality is that YOU—the PI and study site personnel—are the best hope for these subjects to get the information they desire. My mindset in these types of situations is to think of myself as an advocate for the subject, and not as the subject being my adversary.

When such situations arise, I will quickly review the subject's chart, have the lead coordinator present to answer any logistical questions that may arise, and call the subject back immediately. The anticipation of how they are going to react—will they be mad at me, will they blame me—is very nerve wracking, and I have lost sleep wondering what might happen.

The reality is that YOU—the PI and study site personnel—are the best hope for these subjects to get the information they desire.

Thankfully, my anxiety has always been overblown in my experience after I have taken the time to speak with the subjects. My first message is empathy, and telling them how sorry I am that this event happened to them. The reason I start out with this message is because it is truly how I feel.

We must keep in mind that no research subject has to take part in our trials. I have so much respect and gratitude for anyone who volunteers to do a research project with me, because I know they don't have to, and I make a point to tell them that.

I feel so bad for subjects who have AEs and SAEs, whether from anything to do with the trial or not, just because I hate to see human suffering. I especially feel bad for research subjects who experience AEs and have the added stress of wondering if their decision to participate in the study caused or contributed to their suffering. Just listening to them is the most powerful tool we have—taking in the details of what happened when the event occurred, their trials and tribulations at the hospital, and how they are coping at home.

Taking Time to Do it Right

I make sure I have plenty of time set aside to have this conversation with the subject. I don't want him or her to feel like I am rushing the talk or to give the impression that what they have to say isn't important. I take notes so I can accurately detail our conversation in the subject's progress reports. I answer all of their questions as truthfully as possible, and try to explain complicated issues at a level they can understand. If I don't know an answer to a question, I tell them so, but I also tell them I will try my best to get answers and follow through.

Many times when subjects have experienced such serious events as strokes, heart attacks, or the onset of cancer, or you are speaking with a family member of a research subject who passed away, they want to know if the same event happened to anyone else. I tell them I have no problem calling or e-mailing the physician (medical monitor) in charge of the study at the sponsor to let him or her know what happened and to ask if similar cases have been reported with other study subjects.

My experience has been overwhelmingly positive with medical monitors being very interested in my subjects' cases, very insightful about other safety issues they have seen during the study, and excellent at following-up to see how my subject is progressing. I make it a point to relay this information to the subject with each conversation I have with the sponsor.

Following the Trail (if There is One)

The last thing I want to do is tell subjects I don't think their SAE had anything to do with the study product, even if I truly believe it didn't, because it doesn't really matter at this point. What matters is telling them how important it is to get all of the details about what happened to them recorded as accurately as possible, and that we are going to relay that information to the sponsor and IRB as quickly as possible. This information will be used to make sure that there is not a trend with similar events happening to other subjects elsewhere in the study.

I explain to subjects how important it is to have hospital records so everyone knows exactly what happened to help prevent similar occurrences to other participants. I also explain that, even if the subject can't physically come to our office, we would really appreciate it if we could call them from time to time to update their records and help us answer any questions that might come in from the sponsor or IRB.

You would be surprised how positive most subjects respond when they feel that their suffering isn't in vain, and that their information will be used to help address safety issues in the study. I have had subjects personally drive to the hospital and sign a medical release form, and one subject even delivered a box full of his medical records to our office for us to make copies.

Not infrequently, the sponsoring company will make additional requests, such as new tests or follow-ups with specialty physicians, depending on the circumstances of the SAE.

In the case I have been presenting, the protocol asked for additional lab work for any embolic events. Several days later, I called the subject back to discuss this. I informed her that I knew she said she would be unable to come to our office for any more visits, but I felt that it was important for her to know what the sponsor wanted to do in follow-up. I added she still had every right to refuse, and explained that per the protocol, the sponsor wanted to do blood clotting studies to see if she had a genetic predisposition for clotting.

The subject seemed reluctant, and alluded that this information could be used against her. I explained to her how this information would be used—that she could have copies of all the results to share with her personal physician, and how this could help regulators decide if the study product was actually contributing to clotting events or not.

Hesitant, the subject said she would like to talk to her family about it first, and I told her to take her time and just let me know when she decided. Several days later, I was happy to hear from her that

she was willing to come in for the blood clotting studies, because ultimately she wanted to contribute as much information as possible to the study to help prevent similar events from happening to anyone else.

Guidance Through a Gray Area

Another area where it pays to be proactive is helping research subjects understand the section of the informed consent that talks about compensation for injury while participating in a study.

The first point is that, in the vast majority of clinical trials, compensation for injury has to be a direct result of the study product being tested or some component directly related to study participation. Often, this is a very gray area. Though the study subject may think the study product caused his or her injury, how do we really know for sure, who makes this determination, and when is it made?

In many cases, subjects think the PI makes these determinations. In the case I am presenting here, in terms of whether the study product possibly contributed to the stroke, I explained how this complicated process usually evolves. I also explained what my limited role was as just one PI among many at numerous study sites involved in the trial.

In such situations, I also explain that I only get to see firsthand what is happening to subjects I enrolled at my office, but that the sponsor and any data and safety monitoring board used for the study are able to see trends for all study subjects involved.

In rare events like this—where no obvious trend is detected during the study—sponsors will usually wait as long as possible to collect as much safety data as possible to be absolutely sure that there is a connection to the study product or not. Then who makes the final determination, when that determination is made, and how subjects will be compensated is something we as PIs have no way of knowing and little control over.

In the past, I have contacted sponsors with these very questions, and have gotten very mixed results—everything from proactive responses in more obvious cases to being totally ignored. As a PI, it is wise to relay these frustrations to your study subjects, to show them that you will remain at their side to get these questions answered, and to support them in what can become a long, drawn out process.

Being the Middleman

Many years ago, I had a case—and more recently assisted another PI with a similar case—in which the subject or a family member was asking questions only the sponsor could answer, and the sponsor was asking questions only the patient could answer (dealing more with payments for medical tests, hospitalizations, etc.). This is a very burdensome kind of situation in which the research site and the PI become involved as middlemen.

Again, by taking a proactive approach and being an advocate for the research subject, in both cases, we were able to connect the subject or family member with the responsible party at the sponsor. Not only did this seem to encourage the study subjects that they weren't dealing with some big, faceless pharmaceutical company, but it also relieved me of the pressure of trying to accurately relay in a timely manner numerous messages to both sides.

In Search of Happy Endings

The outcome of my study subject who had a stroke was that she ultimately came in for her blood clotting studies several days later. When I entered the exam room, we didn't have to say a word; instead, we just gave each other a big hug. She knew I empathized with the trials and tribulations the stroke had caused her, and I realized she knew I thought of her as more than just a number on a chart related to an event that had caused me a lot of paperwork.

I still don't know for sure if the study product ultimately caused her stroke, but I know that by being proactive and open with this subject, I have collected the best data possible in a timely manner so that the sponsor, FDA, and others involved can make the best determination if this product is safe or not.

I don't know for sure if the subject will yet hire a lawyer and sue me, but I know it will be less likely since I took the time to listen to her, kept her engaged in the safety aspects of the study, and put a human touch to what can be a very cold and confusing process when doing clinical research. Ultimately, the subject decided to continue to come to our office for the protocol-specific safety visits and never even missed a visit window. She continues to improve physically and mentally, and I continue to sleep better at night knowing we are both going to be okay.

> You would be surprised how positive most subjects respond when they feel that their suffering isn't in vain, and that their information will be used to help address safety issues in the study.

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5 Proposals to Ponder in the New Year

As we head into 2016, clearly there are some significant issues and changes pending and under review regarding the conduct of clinical research following the tenets of good clinical practice.

As we begin another year and not too many questions have been coming in to answer in the usual Q&A format of this column, I thought it would be useful instead to summarize some of the significant changes in good clinical practice (GCP) that have been made recently, or are pending in 2016.

1

The first change is the long-awaited update to the landmark GCP guidance known as the International Conference on Harmonization (ICH) E6 Good Clinical Practice Consolidated Guidance. The update—in the form of an Addendum—is proposed to modernize ICH E6 to enable implementation of innovative approaches to clinical trial design, management, oversight, conduct, documentation, and reporting that will better ensure human subject protection and data quality. Check out the ICH website at www.ich.org as well my column from the October 2015 issue of *Clinical Researcher* for further details.

2

The second topic is the long-awaited update to the U.S. Department of Health and Human Services (HHS) regulations regarding institutional review boards (IRBs) and informed consent. In September 2015, HHS released the draft changes to the Federal Policy for the Protection of Human Subjects (the "Common Rule") (see www.hhs.gov/ohrp/humansubjects/commonrule/) as a Notice of Proposed Rulemaking. This proposal represents the first changes to the Common Rule (published in 1991) and the most substantive revisions to the core regulation governing federally funded research in the United States since their establishment in 1981.

This proposed rule offers a number of broad and sweeping changes. It is summarized and explained in more than 130 pages of three-column, small-print, government language, so there is a lot to digest. The major highlight of these proposed changes is summarized in the Ethically Speaking column in the December 2015 *Clinical Researcher*

The long-awaited update to the U.S. Department of Health and Human Services regulations regarding institutional review boards and informed consent represents the first changes to the Common Rule (published in 1991) and the most substantive revisions to the core regulation governing federally funded research in the United States since their establishment in 1981.

by Dr. Elisa Hurley, the executive director of PRIM&R (Public Responsibility in Medicine and Research), an organization dedicated to ethical research oversight and administration.

The third topic is the draft proposal from the U.S. Food and Drug Administration's (FDA's) Office of Good Clinical Practice from March 2015, relating to the use of electronic informed consent in clinical investigations. The draft guidance provides recommendations on how to use electronic media and systems to obtain informed consent in studies involving FDA-regulated products.

The guidance covers a number of questions and suggestions on how to use electronic tools to facilitate the informed consent discussion and document informed consent from subjects. The use of computers and electronic tools is becoming ubiquitous, so this represents a logical next step (see www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM436811.pdf).

The fourth proposal is from April 2015, and relates to the acceptance of foreign clinical data for medical device clinical studies conducted outside the U.S. (see www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM443133.pdf). This proposal relates to FDA's policy on accepting scientifically clinical valid data from foreign clinical studies for medical devices.

This guidance describes the implementation of Section 569B of the FDA Safety and Innovation Act regarding the acceptance of foreign data. The draft guidance describes how FDA plans to review and accept foreign data submitted in support of marketing applications for medical devices. The FDA also issued a proposed rule in 2013 (78 FR 12664) that, when finalized, would require that foreign studies in support of device clinical trials be conducted in accordance with the tenets of GCP.

The final proposal released in 2015 relates to a draft guidance from November 2015 from the FDA and the HHS Office for Human Research Protections on the keeping of meeting minutes for institutions and IRBs. The guidance describes what the agencies consider to be best practices for meeting the regulatory requirements for maintaining meeting minutes for IRB meetings.

Included is the kind of information that should be documented in the meeting minutes and expectations on the level of detail that should be captured in the minutes. Since this is only a draft guidance at this point, the agencies have requested comments and feedback from industry on the proposal (see www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM470154.pdf).

Conclusion

Clearly there are some significant issues and changes pending and under review as we head into 2016. Stay tuned for more developments.

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Draft guidance from November 2015 from the FDA and the HHS Office for Human Research Protections on the keeping of meeting minutes for institutions and IRBs describes what the agencies consider to be best practices for meeting the regulatory requirements for maintaining meeting minutes.

IS YOUR CAPA SYSTEM EFFECTIVE?

PEER REVIEWED | Susan Muhr Leister, BS, MBA, PhD, CQA, CSSBB

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A corrective and preventive actions (CAPA) system is an essential component of any quality management system, and is an approach intended to correct and prevent problems from recurring or prevent them from ever happening. This article describes key components of a CAPA system, highlights key elements of a CAPA report, and reviews some methods for root cause analysis. Also discussed is the need for implementing a risk-based approach when reviewing CAPAs, and the benefits of setting up a CAPA program.

Some Terminology

A corrective action (CA) includes steps taken to eliminate the cause of an actual problem, which should prevent the problem from recurring. Corrective actions are easier to develop than preventive actions. Per ISO 9000:2015, a CA is defined as an "action to eliminate the cause of a nonconformity and to prevent recurrence."[1]

A preventive action (PA) includes steps taken to prevent the occurrence from ever happening. Therefore, a CA is a reactive measure, and a PA is a proactive approach. ISO 9000:2015 states that a PA is "action to eliminate the cause of a potential nonconformity or other potential undesirable situation."[1]

Having PAs is highly desirable in terms of reducing costs when compared to spending time and money to fix ("react to") a problem; in short, preventing problems up front is where organizational leaders should strive to spend their resources.

Components of CAPA

Writing the CAPA report can be a step-by-step process (see Table 1), including the problem statement, a root cause analysis, a proposed solution, details on the implementation of the solution, and an effectiveness check.

Where Do the Data Come From?

Data for CAPAs can come from many places. Most data can be acquired from internal sources; however, there are several external sources that can be beneficial for a CAPA program. For example, internal and external audits can provide valuable information for opportunities for improvement.

In addition, consider observations from a regulatory inspection to be entered into the CAPA program. Customer feedback, especially critical complaints, can contain valuable information for a CAPA with nonconforming work products or services.

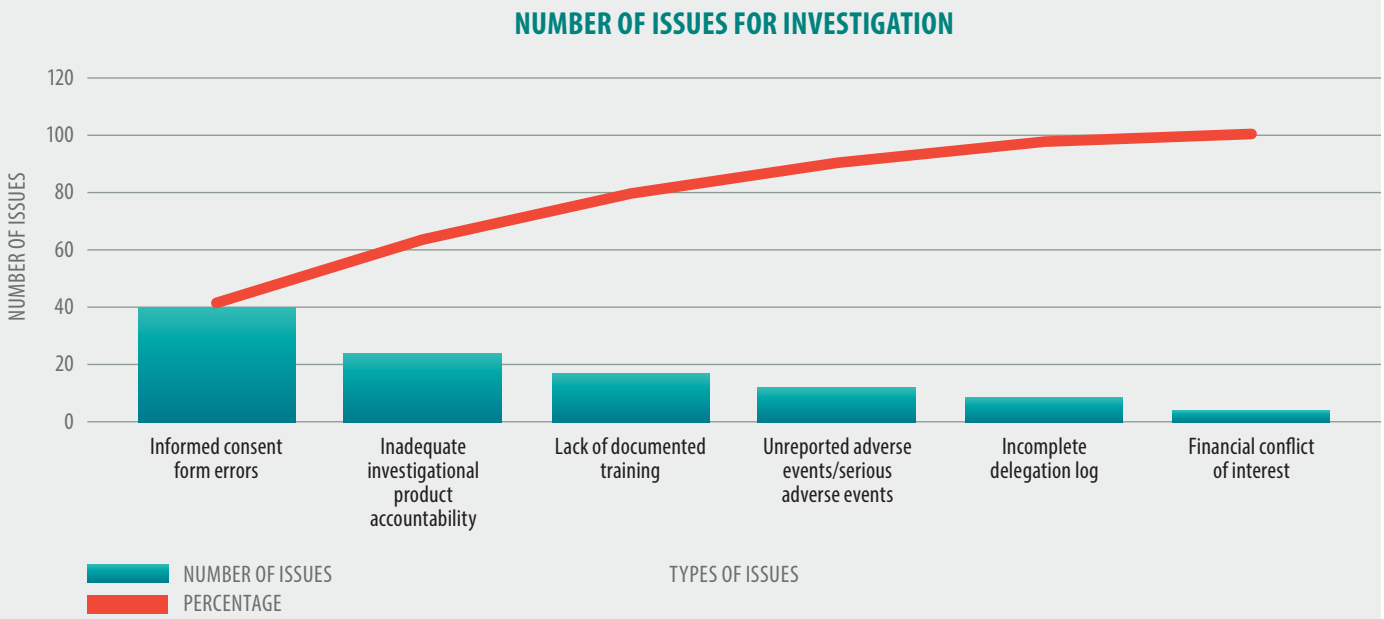
Any issue can move into a CAPA program via management direction. Observations from staff are very important because they are the closest to the task at hand and can provide invaluable information, which should not be overlooked.

Remember that all CAPA data need routine analysis from the key players. One widely used approach is the Pareto analysis technique developed by Joseph Juran.[2] This technique is used to identify, evaluate, and prioritize nonconformities. Pareto analysis can summarize many data such as impact, error, defect, delays, and cost.

TABLE 1: Components of CAPA[3]

STEP 1 Problem Statement	STEP 2 Investigate the Cause/ Root Cause Analysis	STEP 3 Propose a Solution	STEP 4 Implement the Solution	STEP 5 Effectiveness Check
Develop a well-written problem statement that provides measurable and objective evidence answering the questions of who, what, where, when, how much, and how many, but does not suggest solutions. Avoid poorly written problem statements, because these can lead to ineffective resolutions.	Identify applicable causes that could explain why the problem has occurred. Use a root cause analysis tool to investigate the cause and determine the scope of the problem. Root cause analysis aids in determining whether the problem is, for example, a process issue, procedural issue, or human error. If possible, identify why the problem was not noticed at the time it occurred. Any cause should be verified.	Choose one solution over others, confirm the choice will not have an adverse effect on the process/ product, and verify the solution can eliminate the root cause. Once the proposed solution has been validated and verified, the solution can be implemented.	Implement a solution while managing three critical, but different, areas: technology, project management, and organizational change management. • Technology focuses on equipment, software, and any laboratory process. • Project management focuses on scheduling, managing resources, communicating, and implementing the change. • Organizational change management includes the process of change, dealing with resistance to change, and the need for some facilitation to make the change successful.	Follow up to check if the implemented solution was effective before the CAPA report is closed.

FIGURE 1: Pareto Chart Example



The outcome of a Pareto analysis is typically in a chart. A Pareto chart allows a team to count the number of times (frequency) each category occurs (see Figure 1). This arrangement allows the most significant problems (categories) to be identified quickly. The ability to organize data helps to focus and handle one issue at a time. Also, the organized data suggest to stakeholders where resources must be used.

Once an issue is resolved, the organization can apply resources to the next unresolved root cause.

Setting CAPA Triggers

Regarding data analysis, there are a few things to consider. Review the data on a routine basis and define the frequency and volume of data, so trending can be performed at appropriate intervals. Regarding data trending, include the organization's audit schedule and scope to eliminate redundancy in data review and trending efforts.

The goals of data analysis are to capture a baseline of the data and help in establishing action limits (thresholds). This helps to justify the data, and identify when data are truly outliers so the item of concern can move into the CAPA process, but not overburden the CAPA program.

For data trending, use appropriate methods to ensure the data can be analyzed properly. Consider tools such as scatter diagrams, histograms, and the Pareto analysis to help in reviewing data.

Remember not all CAPAs are created equal. Therefore, it is necessary to establish a method for categorizing CAPAs based on risk level (e.g., critical, major, and minor). Using a risk-based approach filters and prioritizes CAPAs, which can communicate a sense of urgency to management.

Writing the CAPA report can be a step-by-step process, including the problem statement, a root cause analysis, a proposed a solution, details on the implementation of the solution, and an effectiveness check.

Each department should work to identify its critical processes (areas of interest), and consider evaluating any processes which are high-risk or have critical vulnerabilities (such as regulatory file management). Focus on the "vital few, not the trivial many."[4] Work to set tolerance levels by asking how much down time can the department withstand if something happened. If a tolerance level is met, this will trigger the need to create a CAPA.

In addition, management can use its discretion and request a CAPA for any high-risk failure. It is imperative that problems with greater potential impact, such as issues related to regulatory compliance and human subject protection, receive appropriate attention.

Repeat failures can be interpreted as a lack of due diligence for how to design, produce, and deliver reliable products and/or services. To reduce any confusion and uncertainty, ensure CAPA risk levels are well-defined and included within the appropriate standard operating procedures.

The Rigors of Root Cause Analysis

The root cause analysis step involves investigating the cause and determining the problem. Root cause analysis aids in determining whether the problem is, for example, a process issue, procedural issue, or human error. There are countless approaches and quality tools available for root cause analysis.[5]

Consider developing a flowchart to document a new process or to further analyze a current process. Flowcharting provides a visual depiction of any potential bottlenecks, weaknesses, or other concerns with the process using various symbols. Keep the beginning narrow, internal, logical, and focused with clear boundaries to avoid scope creep. Avoid going outside the organization, and do not assign blame.

Once boundaries are established, a flowchart can be created for better understanding of the process. Flowcharts can identify who should or should not be involved in the process. Also, flowcharts demonstrate steps that may have contributed to the problem, help identify data collection points, and help show drilldown points.

Brainstorming techniques such as the "Five Whys" and "Cause and Effect," discussed in more detail below, are two other root cause analysis tools to consider.

Brainstorming provides no root cause, but is useful in combination with other problem-identification tools. Brainstorming is used in a small, controlled group to explore many possibilities of the root cause; the effectiveness depends on the group and its leader.

Having a leader help guide the team through a nonbiased discussion will help identify many potential causes to the problem. A leader should not try to interject his or her own opinions or desires, but guide the discussion in a healthy manner. If the session becomes stagnate, the leader serves as a facilitator to move the conversation along.

Brainstorming will not solve the problem, but encourages open thinking and generates ideas. Toward this goal, "Five Whys" is an easy and quick analysis tool for use with a small team when causes might be confusing and when a team prefers a visual tool. Visual tools might also include flip charts, post-it notes, or a computer. Ask "Why" at least five times to make sure a fundamental answer has been reached. When used properly, the "Five Whys" can uncover the root cause.[2]

The "Cause and Effect" diagram, also known as a Fishbone diagram, is another helpful tool for root cause analysis with a small group. It is a highly visual technique that aids the process of defining the elements of a problem or event and determining how it probably occurred.[6] Such diagrams capture the use of manpower, machines, materials, environment, and methods that could cause the problem (see Figure 2). The problem or effect is placed in the box on the right side of the diagram, and the potential major causes are inserted in the boxes directing to the main problem.

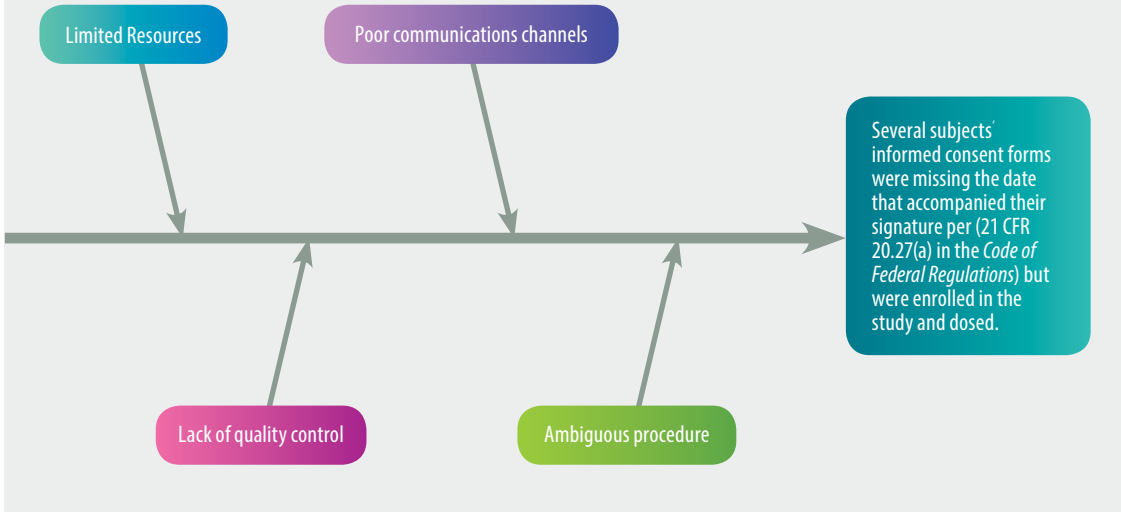
Figure 2 has been populated with an example scenario. The diagram focuses on defining the problem and can be used for preventive action analysis.

Elements of an Effectiveness Check

The effectiveness check should be completed at least 30 days after the proposed solution has been implemented, to allow adequate time for the change to take effect. The check is documented as the final step on the CAPA report before the CAPA is closed.

Most data can be acquired from internal sources; however, there are several external sources that can be beneficial for a CAPA program.

FIGURE 2: Sample Cause and Effect Diagram



Remember not all CAPAs are created equal. Therefore, it is necessary to establish a method for categorizing CAPAs based on risk level (e.g., critical, major, and minor).

Sometimes, 30 days may not be enough time for a solution to deliver results, depending upon the process (i.e., equipment not frequently used). Effectiveness checks can also deem the attempted solution has failed for several reasons, including: the CAPA plan was not specific to the root cause, an incorrect root cause was targeted, or inappropriate data were used during the assessment phase.

If an effectiveness check fails, leave the CAPA open and re-investigate the problem; improper resolution means the problem will return over time, so it is better to spend the time up front resolving the issue. Further, if a CAPA will be open for an extended period, strive to document periodic "check-ins" and document the progress of the work to show if a regulatory inspection occurs.

An effectiveness check can be performed in a variety of ways, such as during a routine internal audit, remote audit, or a separate verification review. Make sure the process is flexible enough to allow the effectiveness check to be made by a variety of methods, so it is not a burden to staff and other resources.[7]

When All is Said and Done

Finally, make sure the CAPA report is complete. The CAPA report is a key component of a CAPA system and captures all relevant information in one place. There are key elements that a CAPA report should contain: a unique report number, a problem statement, a risk level, investigation methods, description of items/documents reviewed, results, an implementation plan, names and dates of the CAPA review team, and effectiveness check results.

Two other key components of a CAPA system are procedure(s) on the CAPA process and CAPA trending. Procedures on the CAPA process should cover documentation practices and the process, in terms of how to define the problem, categorize risk, identify root cause, determine the solution that is appropriate to the risk and root cause, and define implementation and completion of an effectiveness check.

Further, at a minimum it is essential to trend CAPAs annually. Trending CAPAs allows for a representation of any repeat problems, reoccurring tendencies in the same area, etc. Trending CAPAs may reveal another PA, which shows continuous improvement and forward thinking.

Challenges and Benefits of CAPA Programs

Some challenges may arise from staff rushing to close the CAPA prematurely, poor documentation of the root cause, overuse of the CAPA system (putting every problem into the system), lack of follow-up to closure, gradual obsolescence of the CAPA system, and use of multiple CAPA systems.

A clear sign the CAPA program is not working properly is when the same issues occur over and over. The team is constantly putting out the same fires.

The benefits to having an effective CAPA system include, but are not limited to reducing overall cost, meeting regulatory requirements, focusing on patient safety, having more efficient processes and procedures, and focusing on continuous improvement rather than on a reactive approach.

Remember, it takes time to establish a CAPA program that properly resolves the true root cause to serious problems. However, when implemented correctly, a CAPA program can be beneficial to every organization.

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