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Proposed Revisions to the Informed Consent and IRB Regulations

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

[DOI: 10.14524/CR-15-0041]

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

[DOI: 10.14524/CR-15-0042]

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

[DOI: 10.14524/CR-15-0044]

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.