

AMA Journal of Ethics

Formerly *Virtual Mentor*

December 2015

Volume 17, Number 12: 1103-1196

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American Medical Association Journal of Ethics

December 2015, Volume 17, Number 12: 1105-1107

FROM THE EDITOR

Revisiting the Ethics of Research on Human Subjects

The ethics of clinical research on human subjects has a rich history that belies its relatively recent development in the mid-twentieth century, marked by publications such as the Nuremberg Code [1], Henry Beecher's landmark 1966 paper "Ethics and Clinical Research" [2], the Belmont Report [3], and the Declaration of Helsinki [4]. In some universities and medical schools, ethics and professionalism courses can reduce medical ethics to the principles of beneficence, nonmaleficence, respect for persons, and justice [3]. A similar strain of reductionism happens when students are merely given historical examples of egregious violations of human decency, such as the US Public Health Service Syphilis Study at Tuskegee or the more recently exposed US Public Health Service Sexually Transmitted Diseases Inoculation Study of 1946-48, which took place in Guatemala [5]. Any tendency toward this kind of reductionism should be resisted, however, because a rich and full understanding of research ethics requires contextualization within historical, social, and cultural frameworks. The enterprise of biomedical research continues to be shaped by modern challenges, expectations, and social values. In this issue of the *AMA Journal of Ethics*, several authors explore current ethical issues in research and cull important lessons from the past to inform the future of biomedical research design and clinical practice.

I had the privilege of speaking with Robert Levine, MD, co-author of the Belmont Report and consultant for landmark regulations guiding the ethics of research on human subjects. In [the podcast](#), Dr. Levine shares his experiences as the chair of various committees and his opinions on ongoing issues in the field of clinical research ethics. We discuss how the overemphasis in the literature on conflicts of interest, a phenomenon seen previously with informed consent, gives a false impression to new scholars in the field that this is the only topic of importance in modern clinical research ethics.

Several articles this month do discuss informed consent, particularly issues that stem from legislative or technological changes. In [the health law piece](#), Richard Weinmeyer, JD, MPhil, MA, gives an overview of changes proposed to the Common Rule [6], which confers regulatory protections to research subjects who are members of vulnerable populations. Concisely, the proposed changes suggest new standards for informed consent processes and suggest how research review processes might be streamlined and made more efficient [7]. In the [policy forum section](#), Stephanie Alessi Kraft, JD, Kathryn Porter, JD, MPH, Benjamin S. Wilfond, MD, and the Research on Medical Practices Group explore unintended implications of the Office for Human Research

Protections (OHRP) draft guidance redefining research risks surrounding informed consent.

One reason informed consent is discussed so frequently in this issue is that research has always relied on the participation of volunteers, often healthy subjects who are assuming some risk to themselves, or, in some cases, their loved ones. The cases in this issue explore the tensions between mitigating risk to individual subjects and maximizing benefit to the broader population of future patients. Spencer Phillips Hey, PhD, and Robert D. Truog, MD, [comment](#) on the case of a guilt-ridden physician who questions her decision to encourage a patient to enroll in a clinical trial. This highlights the value and necessity of the principle of clinical equipoise—the medical community’s genuine uncertainty as to the efficacy of each arm of a clinical trial—for considering whether and when it is ethically justifiable for patients to become subjects. Erin P. Williams, MBE, and Jennifer K. Walter, MD, PhD, MS, [explore](#) the issues of justice and coercion in a case in which researchers must decide how much to compensate subjects for trial participation. In their case commentary, Armand H. Matheny Antommaria, MD, PhD, and Kristen Stanley Bramlage, MD, [discuss](#) conflicts of interest and therapeutic misconception when enrolling pediatric patients in a clinical trial.

As with the patient-physician relationship, unchecked paternalism is now regarded as inappropriate in researcher-subject relationships. As our contributors explain, in recent decades public responses to the research enterprise have changed. Susan Lederer, PhD, [explores](#) changes in media representation of research-associated deaths, contrasting former attitudes with recent highly publicized cases that have shaken public trust in clinical research. Elizabeth Bromley, MD, PhD, Loretta Jones, MA, ThD, Marjorie S. Rosenthal, MD, MPH, Michelle Heisler, MD, MPH, Julie A. Sochalski, PhD, RN, Deborah Koniak-Griffin, RNC, EdD, Cristina Punzalan, MPH, and Kenneth Wells, MD, MPH [discuss](#) the new National Clinician Scholars Program’s focus on multidisciplinary teams and community-based participatory research, which addresses health needs in communities and incorporates nonmedical leadership into the setting of research priorities. And Paige E. Finkelstein [provides](#) an overview of the Food and Drug Administration’s expanded access process, through which people with life-threatening illnesses can apply for access to investigational drugs.

Another ethical issue in research is how study results are discussed among scientists and whether or not they are publicized. Daniel L. Shaw and Joseph S. Ross, MD, [analyze](#) new policies aimed at increasing transparency about clinical trial results and discuss the benefits of promoting a culture of open data and collaboration among researchers. Turning to how results are communicated to the public, Ivan Oransky, MD, [shares](#) his views on the irresponsible media representation of medical research outcomes and the incentives that lead both journalists and researchers to overstate claims of significance.

These and other challenges are a result of the adaptation of clinical research ethics to changing regulations and scientific and cultural norms. This issue of *AMA Journal of Ethics*

attempts to raise awareness—and spark dialogue—about how clinical research ethics is transforming.

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Acknowledgment

I would like to thank all the contributors, for their time and thoughtful work, and the editorial staff at the AMA for their assistance and for the opportunity to serve as a theme issue editor. Thank you also to my advisor Lydia Dugdale, MD, of the Yale School of Medicine, who was instrumental in providing advice and support throughout the process of taking the issue from conception to production.

The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.

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ISSN 2376-6980

American Medical Association Journal of Ethics

December 2015, Volume 17, Number 12: 1108-1115

ETHICS CASE

The Question of Clinical Equipoise and Patients' Best Interests

Commentary by Spencer Phillips Hey, PhD, and Robert D. Truog, MD

Dr. Malone is a primary care doctor in the student health clinic at a large research institution, and one of her patients, 20-year-old Charlie, was just diagnosed with stage 4 non-small-cell lung cancer. The five-year observed survival rate is 1 percent and the current standard of care is chemotherapy. The Food and Drug Administration has just approved a promising new drug called MX320 for clinical trials. A medical school classmate of Dr. Malone's is the primary investigator of an active-controlled, double-blind, randomized clinical trial at a local hospital. Promising early-phase investigations suggest that patients receiving the new drug are improving and, based on this information, Dr. Malone thinks Charlie would probably be a good candidate for the drug.

There is no guarantee that Charlie would be randomized to the experimental arm of the trial, but Dr. Malone and Charlie are hopeful that he would improve. As a result, Charlie enrolls. After some weeks, he has shown no improvement, and, while it may be too early to tell, Dr. Malone begins to wonder whether he was in fact randomized to the control treatment arm. As Charlie's physician, Dr. Malone feels responsible for possibly giving him false hope. She is aware of another clinical trial from which Charlie might benefit and is unsure whether she should voice her suspicions to Charlie, which might prompt him to leave the study, or keep her concerns to herself.

Commentary

Dr. Malone's dilemma in this case centers on one of the most influential—and controversial—concepts in [research ethics](#): clinical [equipoise](#). In its canonical formulation, clinical equipoise stipulates that a randomized controlled trial (RCT) is only ethical insofar as there exists, at the outset, a state of genuine uncertainty in the community of medical experts about the relative therapeutic merits of every arm in the trial [1]. In other words, if clinical equipoise holds, then all arms are equally likely to be beneficial and all are consistent with competent medical care.

Background

This conception of clinical equipoise—as rooted in the uncertainty of the community of medical experts—emerged in response to an earlier (and perhaps more intuitive) conception, proposed by Charles Fried. Fried had argued that a physician-investigator could ethically enroll her patients in an RCT so long as she *individually* was in the state of equipoise—that is, she had no justified belief that one arm of the study was any better than the others. In other words, if she was perfectly indifferent about which treatment

arm was best, then she could enroll her patients in the trial and leave their assignments to chance [2].

However, critics were quick to point out that this state of individual equipoise—and therefore the ethical acceptability of enrolling research participants—was too fragile. A physician-investigator’s beliefs might change suddenly in the midst of a trial—or before the trial began—perhaps in response to new emerging evidence, or even a “hunch” (similar to what Dr. Malone is experiencing) [3]. Yet whatever the reason for her change in belief, as soon as she was no longer indifferent, she would be ethically prohibited from encouraging future patients to enroll in the study. More to the case at hand, it would also obligate her to encourage any of her patients who were already enrolled in the study to withdraw.

In response to the fragility of individual equipoise, Benjamin Freedman proposed the concept of *clinical* equipoise. Under the principle of clinical equipoise, individual physicians may have beliefs about the superiority of one treatment over another in an RCT, but the trial is still ethical so long as there is no consensus in the community of medical experts. As Freedman put it:

Instead of emphasizing the lack of evidence favoring one arm over another that is required by [individual] equipoise, clinical equipoise places the emphasis in informing the patient on the honest disagreement among expert clinicians. The fact that the investigator has a “treatment preference,” if he or she does, could be disclosed; indeed, if the preference is a decided one, and based on something more than a hunch, it could be ethically mandatory to disclose it. At the same time, it would be emphasized that this preference is not shared by others [1].

Shifting the uncertainty about the better treatment from the individual to the medical community made for a far more robust epistemic threshold, one more accommodating to carrying out RCTs. If there is a state of clinical equipoise at the start of the trial, then a physician may ethically enroll her patients. Importantly, this remains an ethically justifiable action even if she has a suspicion that a patient of hers has been allocated to the supposed inferior arm, since the existence of clinical equipoise entails that the medical experts as a group *do not yet know* which arm is better.

The Story of Vemurafenib

A saga from oncology, which parallels Dr. Malone’s dilemma, is worth mentioning. The *New York Times* published a story in 2010 describing the plight of two cousins who were enrolled in an RCT comparing dacarbazine, the marginally effective standard treatment, to a promising new drug, vemurafenib, for the treatment of BRAF-mutated metastatic melanoma [4]. One cousin received dacarbazine and succumbed to his cancer. The other received vemurafenib and, at least at the time of the article’s writing, had survived.

As the author of the *Times* story noted, there was considerable disagreement about the ethical acceptability of this RCT. Vemurafenib had achieved an 81 percent response rate in early-phase melanoma trials for patients with the requisite BRAF-mutated tumors [5]. Therefore, some physicians argued, RCTs were unethical because vemurafenib was clearly superior to the standard of care for this patient population [4]. Proponents of the RCTs argued that, despite the dramatic response rate in the early-phase studies, clinical equipoise could not be overturned on the basis of a surrogate endpoint (i.e., tumor response rate) alone. Therefore, an RCT employing clinical endpoints was still needed to definitively determine which treatment was superior [4].

This controversy points to a subtle but important dimension of clinical equipoise: a given case—the treatments and procedures that clinical equipoise either allows or prohibits—is based on the state of scientific knowledge at the outset of the clinical trial. If, at the outset of the trial, sufficiently robust evidence exists to rule out the possibility that the two treatments are clinically equivalent, then the trial is unethical. However, if this robust evidence does not exist, then the trial can still be ethical.

Given that high response rates in early-phase oncology trials can regress in subsequent studies, it is reasonable to think that clinical equipoise had not yet been overturned in the case of vemurafenib. And, as it turned out, the observed response rates with vemurafenib did regress considerably over the course of testing: from 81 percent in phase 1, to 53 percent in phase 2, to 48 percent in phase 3 [6]. There are also legitimate concerns that promising results on surrogate endpoints (such as response rate) or sometimes even clinical endpoints do not straightforwardly support conclusions of superior clinical effectiveness [7]. These additional dimensions of uncertainty and variability in clinical development must be factored into judgments of clinical equipoise. In retrospect, it appears that the vemurafenib skeptics may have been right to insist on RCTs: the drug is certainly efficacious, but we now know that it is not overwhelmingly more beneficial than other drugs for the treatment of BRAF-mutated metastatic melanoma.

Hope and Uncertainty

Returning now to Dr. Malone's case, if clinical equipoise held for Charlie's RCT, then every arm in that study was consistent with competent care, which means that the fact that he is not seeing immediate benefit does not mean that he is being disadvantaged. To illustrate, let's assume that preliminary testing with MX320 suggests that it has a mean response rate of 40 percent. However, since this is based on preliminary data, there should be considerable uncertainty around the 40 percent estimate. This uncertainty can be represented formally with wide 95 percent confidence intervals, ranging from 15 to 65 percent, say. In other words, we are very confident that the true response rate of MX320 lies somewhere between 15 percent and 65 percent.

Let's also assume that the standard treatment is known to have a mean response rate of 25 percent. Since there is typically much more evidence about the standard treatment, there will also be less uncertainty around this estimate (e.g., 95 percent confidence interval ranges from 15 to 35 percent). We can thus establish that there ought to be a state of clinical equipoise: since the confidence intervals of our average effect estimates for these two treatments overlap, there is legitimate scientific uncertainty about which is better. Furthermore, since the interval for MX320 does not fall below the interval for standard treatment, then both are consistent with competent medical care.

If we assume the RCT is using an equal allocation ratio, then there was a 50 percent chance that Charlie would get assigned to the MX320 arm. Once Dr. Malone observes that he is not responding to therapy, it is now a slightly better bet that he is in the control arm. But this is still far from certain. Charlie may be a late responder, or the new drug may just not be effective for him. A valid RCT requires that, until the study is complete, we do not know the arm of the trial in which Charlie is enrolled. Additionally, the existence of clinical equipoise explains why it is ethically acceptable to let Charlie continue in the study.

Clinical equipoise should also alleviate some of the guilt that Dr. Malone is experiencing. Clinical trials necessarily involve uncertainty about the effectiveness of new agents. Indeed, this is why we do research—to reduce uncertainty. Moreover, it is a necessary scientific feature of RCTs that some patient-subjects are exposed to what is later discovered to be an inferior treatment. Yet, this does not mean that the hope of an effective treatment that Dr. Malone offered to Charlie was false. On the contrary, clinical equipoise [ensures](#) that the hope was justified—Charlie would be equally likely to benefit regardless of whether he enrolled in research. At the same time, it is the nature of research that the possibility of dramatic patient benefit (greatly surpassing the expectations with the standard of care) can only be a hope. If there had been certainty that he would see incredible benefit from the experimental drug, then the RCT would have been unethical to begin with. At the same time, participants must recognize that the experimental agent may also turn out to be harmful compared to the standard treatment. Indeed, robust safety data about an experimental intervention typically only becomes available in late-phase trials (and rare adverse events are typically detected in monitoring after the drug has been brought to market). Thus, the concept of clinical equipoise mitigates physicians' responsibility for patients' outcomes when those patients are assigned to the control group and when they are harmed by experimental agents.

The Problem of Knowledge Value

We have now shown how Charlie's not benefiting in the trial does not mean that he is receiving inferior care. Therefore, Dr. Malone does not have an ethical obligation, flowing from considerations of beneficence, to encourage him to withdraw from the study. Yet to say that beneficence is not a dominating principle in this case is not the same as saying

that it does not apply. So let us now consider the logical inverse of this obligation: whether it would be unethical for Dr. Malone to encourage him to withdraw from the study. As the scenario stipulates, she knows that there are other trials going on and suspects that Charlie could do better in one of those.

Yet, because Dr. Malone facilitated Charlie's involvement in the current study—let us call it "study A"—is she now obligated to encourage him to see it through? Or can she justify encouraging him to withdraw from study A and consider enrolling in study B? To be clear: if Charlie decides of his own accord that he no longer wants to participate—for whatever reason—this is his right, and there is no ethical tension. There is, however, an ethical tension between Dr. Malone's obligations to Charlie's best interest and to future patients and the research enterprise. Specifically, how would Charlie's withdrawal impact the knowledge value of study A?

Recruitment targets for late-phase clinical trials are typically determined on the basis of a statistical "power calculation." That is, one can calculate how many participants would be needed in order to reject the null hypothesis (i.e., that the two treatment arms are equally effective) with statistical significance if there is indeed a real difference between the experimental treatment and the control. The goal is then to recruit an adequate number of participants, so that whatever the trial's outcome, it is possible to make a valid causal inference: if the experimental treatment was superior to the control, then we can reject the null hypothesis and conclude that there is evidence of effectiveness, or if the difference was not statistically significant, then we can reject the alternative hypothesis and conclude that the experimental treatment is no better than the control. However, if a trial does not recruit—and retain—an adequate number of participants, then it is said to be "underpowered," meaning that it increases the chance of not rejecting the null hypothesis when one of the treatments is, in fact, better than the other.

Thus, in a world of limitless human and material resources, this statistical cost of Charlie's withdrawal might not matter so much. Study A might lose a bit of statistical power from his missing data points, but it might still have enough remaining participants to answer the investigators' primary research question. (And if too many patients drop out of the study, that fact itself can be sufficient to determine whether the experimental agents are effective.) If so, then Dr. Malone's dilemma would perhaps not be so difficult: if she has justified doubts about study A, then she should encourage Charlie to look into study B. After all, study B is also asking an important research question, and study B needs participants too!

Unfortunately, we do not live in a world of limitless resources for research. Once recruitment on a study has ended, dropouts might not be able to be replaced. Given that research risks for trial participants and research costs for society are supposed to be offset in part by the scientific knowledge generated (which will hopefully help future patients), every lost data point, in effect, worsens the ethical profile of the trial (by

increasing the likelihood of a faulty inference) and contributes to inefficiency across the research enterprise [8]. Consistent inefficiencies in research can also diminish public trust in the value of medical research. Thus, although any single patient's withdrawal from a study might not seem like a great waste when considered in isolation, it is important to consider the larger, social context and social cost of research when thinking about sound ethical guidelines for physician and patient decision making.

Further, as the vemurafenib case showed, experimental agents can generate promising results in early phases of research, only to lose some of their promise in later phases. Moreover, according to one recent study, there is only about a 1 in 10 chance that a new agent entering clinical testing will be proven to be effective [9]. Although the prospect that a struggling patient-subject may benefit in a different trial can be a tantalizing one, it must be considered realistically, in the broader context of the scientific process and in the long view of evidentiary standards for determining what constitutes an innovation.

Therefore, in discussing future options, Dr. Malone should explicitly explain this dilemma to Charlie, acknowledging his absolute right to withdraw and switch to the other study if he so chooses (since he may not share her commitment to improving the care of future patients). She should also discuss the realities of experimental medicine, explaining that research is uncertain by nature, and that the majority of new drugs fail in development [9]. Once that is said, if the shift from study A to study B can still be supported by a sound argument—explaining why switching to study B offers a better prospect of a good outcome than continuing on in study A and how switching still does not guarantee that Charlie will receive the experimental drug—then this expression of patient-centered care and beneficence might mitigate worries about scientific validity and efficiency. But the burden of proof should fall heavily on this explanation.

Can We Do Without Equipoise?

In closing, we should acknowledge the critical perspective that sees clinical equipoise as, at best, an inappropriate standard for ethical research [10] and, at worst, an incoherent concept [11]. In its place, critics have proposed that informed consent can do the proverbial heavy lifting in research ethics. That is, so long as a patient-subject is informed of, understands, and accepts the risks of participation, the research is likely ethically acceptable.

Although it would take us too far afield here to canvass the various arguments and counterarguments in this debate [12], it is worth noting that the ethical analysis of Dr. Malone's dilemma would look different without the concept of clinical equipoise. Her feelings of guilt, for example, are rooted in the fact that she is not in a state of *individual* equipoise. She truly believes that the experimental intervention in these studies is better than the control, and so (naturally enough) she feels responsible for Charlie's not responding well in the trial (and assumes that he has probably been assigned to the control arm).

Although Charlie's valid, informed consent might allow us to say that Dr. Malone should not feel guilty (because enrolling was his autonomous decision), the concept of clinical equipoise illuminates precisely *why* this guilt is misplaced: it is not her state of belief that makes Charlie's participation in the study ethically acceptable or unacceptable; it is the state of belief in the community of experts. When she presents a patient the option of enrolling in a study, she can honestly inform him or her about the state of her beliefs. She thinks MX320 is better than the standard treatment, and these trials provide access to that agent. However, there is no consensus in the community of medical experts that MX320 *is actually* better than standard treatment. Some of her colleagues might believe it is the same or even worse. Therefore, she thinks it would be reasonable for him to enroll.

The fundamental point is that clinical equipoise does more for the physician-investigator and the research enterprise than restrict the domain of acceptable scientific comparisons. It is also a concept for critical reflection, and, as Freedman notes in the block quotation above, it should be the beginning of a conversation between the physician and patient contemplating trial participation, which can include questions like these: *What is the state of medical knowledge? Why is this trial asking an important question? How does the likelihood of benefiting in study A compare with that of benefiting in study B or with the standard of care?* These questions are at the heart of genuinely informed consent, and their answers are illuminated through clinical equipoise.

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ISSN 2376-6980**

American Medical Association Journal of Ethics

December 2015, Volume 17, Number 12: 1116-1121

ETHICS CASE

When Does the Amount We Pay Research Participants Become “Undue Influence”?

Commentary by Erin P. Williams, MBE, and Jennifer K. Walter, MD, PhD, MS

Susan is a member of an institutional review board (IRB) at an academic institution in a large city. A phase 3 protocol is up for its annual review. The multi-center study, sponsored by a large pharmaceutical company, is designed to assess the safety of a new medication for the treatment of asthma. This is one of the soundest protocols Susan has come across during her time on the IRB: the aims are well-defined, the study design is scientifically valid, the informed consent form is clear, the risks-to-benefit ratio is good, and no adverse events have been reported to date. The study entails three full-day sessions, and the risk involved is classified as greater than minimal due to blood draws necessary to study the pharmacokinetics of the drug. Participants are paid \$25 for the initial screening visit with a physician and \$75 for each subsequent day-long session, for a total compensation of \$250 to those who complete the entire study.

After the first round of recruitment, Susan notices that the majority of the participants are of a lower socioeconomic status (SES). This trend continues during the second round of recruitment. Susan becomes even more concerned when a colleague mentions that some of the study participants are homeless. When she mentions her concern to the full IRB committee, one of her colleagues remarks that studies have shown that the highest prevalence of asthma is associated with the lowest socioeconomic status, so it is appropriate, indeed ethical, for many people from this group to incur the research risks; they stand to benefit most from it.

Troubled by this answer, Susan wonders whether the monetary compensation for the study exerts an undue influence on those who would otherwise not consent to participate in it. Given the demographics of the city, with a large socioeconomically vulnerable population, she wonders whether the participants are being paid too much.

During a conference call with a colleague at another urban study site, Susan is alarmed to hear that participants are being compensated twice as much, all other things being equal. What if the participants at her institution are being paid too little for their time? How can the IRB pay participants enough to compensate them for exposure to the study risks without paying them so much that the payment constitutes undue inducement? Susan also wonders whether there are merits to a sliding scale of payment that depends

on the socioeconomic status of the participants and whether this practice is ethically justifiable.

Commentary

Undue Inducement

Payment for participation in research makes many IRB members nervous because of their concerns about why we pay study participants and whether it could lead to harm [1, 2]. *Coercion* in this context is best described as a person's being forced into a decision that might leave him or her in a worse position than if he or she never encountered the offer. Luckily, due to stringent regulatory guidelines, coercion, strictly understood, does not often occur in clinical research because people are technically able to choose not to participate [3]. *Undue influence*, however, is more complicated; it occurs when the compensation or incentive is sufficient to induce prospective participants who otherwise would not enroll to enter studies in which there might be significant risks. The worry is that people with limited resources are more susceptible to inducements to act against their own best interests, or that, worse, they could be targeted for recruitment because they are easier to influence with smaller sums of money.

There are many interpretations of what constitutes undue influence. According to Ruth Macklin, an inducement is undue if it encourages participants to lie or conceal information in order to participate or prompts participants who otherwise would not participate to enter a study that poses significant risks [4]. She also argues that an inducement may be undue if participants could have been recruited for less compensation [4]. Similarly, Neal Dickert and Christine Grady argue that undue inducement occurs when an incentive is so attractive that it causes people to ignore their personal values or preferences in order to participate in the research [5]. Yet another definition of undue inducement, described by Ezekiel Emanuel, includes four elements: (1) an offered good (2) of excessive value, making it extremely compelling, (3) which encourages participants to exercise poor judgment (4) while taking on risk of serious harm [6].

From the information presented in the case scenario, the phase 3 clinical trial for asthma medication has been thoroughly reviewed and approved by the IRB at Susan's institution. Most importantly, the risks-to-benefit ratio has been determined to be good and no adverse events have been reported, suggesting that those enrolled in the trials are not exposed to serious or significant harm.

Is undue influence a potential problem in this case? It is important to note that when an IRB is determining the safety of a clinical trial, the research is judged independently of payment or incentive to try to get an accurate assessment of the true benefits and risks of the study. The main risk cited in this case scenario is necessary blood draws, which are generally not considered extremely risky. If we accept that the harm-to-benefit ratio of

the study is good, then no one would be considered to have been unduly influenced, since it would be reasonable to expect that none will experience more harm than benefit from participation. Without this key component of serious harm or risk, even if the payment or incentive is excessive, this case could not qualify as one of undue influence according to both Macklin's and Emanuel's definitions. Additionally, because there is no evidence suggesting that people are participating in the study despite their personal values or preferences, the case fails to meet the criteria for Dickert and Grady's definition of undue inducement.

Issues of Justice

When we talk about undue inducement, we are often actually concerned about justice in research. This case brings to light the fairness of both sliding payment scales (unequal payment) and participant selection.

Compensation. To explore the ethics of paying participants for research, we must determine the motivation of the researchers in offering payment. Dickert and Grady argue that there are four main models for offering payment to participants: the market model, the wage-payment model, the reimbursement model, and the posttrial appreciation model [5], each of which has merits and drawbacks.

In the market model, payment is adjusted according to the principle of supply and demand—if research is risky, incentives increase, whereas if participation is desirable or low-risk the incentives decrease [5]. This model has a high potential for undue influence if high incentives are offered for risky research. We trust IRB review to reject research protocols that would expose participants to serious harm or risk. However, different people have varying degrees of risk aversion and risk tolerance, leading them to weigh risks differently. The incentives might be just high enough to induce a person to participate in research in which he or she would not otherwise partake.

In the wage-payment model, participants are compensated for work and paid a standardized wage that is close to the regional unskilled labor wage, with the possibility of pay bumps or bonuses for variables such as increased discomfort or longer commitments [5]. This model is hypothesized to attract a disproportionate number of [people from a lower SES](#) because the compensation is not sufficient to interest those with more wealth.

In the reimbursement model, participants are either compensated for expenses incurred during research or for loss of earned wages due to trial participation [5]. Compensation for loss of earned wages is commensurate with each participant's primary income. This model has the potential to attract participants with higher incomes and is difficult to implement due to the need to determine individual compensation for every participant.

Finally, the posttrial appreciation model awards payment in recognition and appreciation of participation [5]. It can be challenging to determine an objective and appropriate magnitude of award. The little data that exists on research payment models documents a wide range of payments for similar tasks with little or no justification [7]. Because payments are almost never broken down by hour, it is hard to ascertain if posttrial, award-style payments even meet the expectation of the minimum wage standard of the wage-payment model [7]. Since there is no basis on which to determine the magnitude of the award, participants might not be fairly compensated for their time.

In the case presented, the study seems to follow a wage-payment model. After the initial screening, the participant receives \$25, and for each of the next three daylong visits he or she receives \$75. Assuming an 8-hour workday, the rate of pay is about \$9 per hour (just above the federal minimum wage). Despite Susan's concerns about overrepresentation of participants of a lower SES, it is important to note that, in a nationally representative sample, participation in research varied little among SES groups [8]. Additionally, when asked how much payment would have to be offered for them to agree to participate in a hypothetical low-risk medical trial, people from the lowest and the highest SES groups did not request significantly different amounts [8].

Susan also worries that the study participants are not compensated highly enough. She could increase the amount of money offered overall in the study, perhaps to \$400, ensuring that all participants are paid closer to the \$15 per hour living wage. This would encourage people of a higher SES to participate without skewing compensation in their favor as the reimbursement model does.

Susan also considers a sliding scale of payment dependent upon participants' socioeconomic status. Macklin has argued that a sliding scale is unethical because (like the reimbursement model) it encourages unequal pay for equal work, which violates the principle of justice [4]. This approach may attract participants from a higher SES but alienate those from a lower SES and could result in participants' lying about career and salary to increase compensation. For Macklin, unequal payments would constitute an undue inducement because there would be strong encouragement to participate. However, if higher compensation can induce particularly reluctant members of low-income, [underrepresented minority groups](#), like Hispanics, to participate in research, unequal payments may actually promote equality in distribution of the potential harms and benefits of research [8].

Participant selection. Selection of participants should neither target [vulnerable populations](#) for risky research nor favor affluent groups in research on promising treatments [9]. The scientific goals of the research should take priority in participant enrollment, and groups or individuals should not be excluded unless they do not meet the scientific criteria of a study or are susceptible to excessive risk (e.g., excluding men

from a hormone therapy trial for menopause or pregnant women from a drug trial that might not be safe for the fetus) [9]. Fair participant selection requires that “groups and individuals who bear the risks and burdens of research should be in a position to enjoy its benefits, and those who may benefit should share some risks and burdens” [9]. If the research mentioned in the case aims to benefit those with asthma from the lowest SES group, then members of that group may take on some of the risks and burdens of this research trial. To address the concern that the future cost of the drug would be out of range for the average participant in the study, so that those who take on its burdens will not enjoy its benefits, the study may stipulate that, if the drug is determined to be effective, all participants will receive it for free or at a reduced cost. Additionally, the drug should be available to those in their communities at a reduced cost or reasonable price.

Scientific validity also requires testing the efficacy and side effects of a medication for all the groups who will use it, rather than merely extrapolating results from the trial group to others. The inclusion of members of groups at risk for the disease both improves scientific validity and promotes a fair distribution of benefits and burdens; therefore, those of a lower SES, including the homeless, should not be excluded from the trial in the name of protecting them. However, great care should be taken in screening them, as there is a greater potential for undue inducement if the risk-to-benefit ratio is less favorable.

Conclusion

It is essential that researchers and regulatory bodies like IRBs ensure that research participants are not being exploited. They can do this by requiring researchers to optimize risks-benefit ratios, as was done here, and to recruit from populations who could benefit from the research. Although ideally participants should be paid equally, there might be some circumstances in which difficulty enrolling participants makes increased payment for underrepresented groups ethically acceptable or even necessary.

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ISSN 2376-6980**

American Medical Association Journal of Ethics

December 2015, Volume 17, Number 12: 1122-1126

ETHICS CASE

Enrolling Research Participants in Private Practice: Conflicts of Interest, Consistency, Therapeutic Misconception, and Informed Consent

Commentary by Armand H. Matheny Antommara, MD, PhD, and Kristin Stanley Bramlage, MD

Dr. D'Amato is a partner in a nonacademic gastroenterology clinical practice. One of his patients is Matthew, a 17-year-old with type 2 diabetes, nonalcoholic hepatosteatosis (NASH, or fatty liver), dyslipidemia, and obesity. Dr. D'Amato has been following him for the past three years, and, despite nutritional and exercise counseling, Matthew has been unable to change his dietary habits and lose weight. Dr. D'Amato's biggest concern is treating Matthew's fatty liver, which is leading to elevated liver enzymes, inflammation, and possibly cirrhosis. Currently, the most effective treatment for NASH is weight loss. There are a few phase 2 and 3 clinical trials testing the safety and efficacy of vitamin E and other novel therapies.

At a recent clinical visit, a liver needle biopsy revealed inflammation but no signs of cirrhosis for Matthew. Dr. D'Amato stresses to Matthew the importance of losing weight and adopting a healthy lifestyle before he shows signs of developing cirrhosis. Matthew tells Dr. D'Amato that he has heard about a phase 3 clinical trial for a new monoclonal antibody. He asks Dr. D'Amato about the possibility of enrolling in the trial.

As it happens, Dr. D'Amato and his colleagues are recruiting eligible participants for this trial run by a pharmaceutical company. The pharmaceutical company compensates Dr. D'Amato for the care of enrolled patients during their participation and also gives him \$5,000 for each patient he suggests who ends up being eligible and enrolling in the trial. Dr. D'Amato thinks that Matthew may be eligible for the trial, but he does not know to which arm—standard treatment or experimental treatment—Matthew would be assigned.

Matthew's mother, who has been extremely supportive of her son throughout his illness, does not want him to enroll in the study. If there is a way to reverse the NASH through weight loss, then she does not want to expose her son to the risks associated with the clinical trial. Dr. D'Amato agrees with Matthew's mother, but, given the seriousness of his condition and his past history of noncompliance with his weight loss regimen, there might be a chance that if Matthew were randomized to the drug arm of the study, he would benefit.

Commentary

This case highlights the importance of managing conflicts of interest; enrolling patients consistently; minimizing therapeutic misconception; and evaluating potential benefits, risks, and alternatives of enrolling in a clinical trial.

NASH is the most severe form of nonalcoholic fatty liver disease (NAFLD) and can progress to advanced fibrosis, cirrhosis, and liver failure, requiring transplantation. NAFLD is associated with obesity but is also believed to be influenced by genetic factors and environmental exposures. As noted above, the current standard of care for the treatment of NASH is weight loss [1]. Nobili and colleagues, for example, conducted a study of children with NAFLD in which all children were prescribed lifestyle intervention and were randomized to either alpha-tocopherol (vitamin E) and ascorbic acid (vitamin C) or placebo. Both groups demonstrated a significant improvement in liver histology at 24 months, but there was no significant difference between groups [2].

For the sake of argument, let us assume that Dr. D'Amato has offered Matthew and his family a comprehensive multidisciplinary weight loss intervention that includes long-term dietary modification, decreased sedentary activity, moderate daily exercise, and behavior change skills [3]. In spite of these efforts, Matthew has been either unwilling or unable to lose weight or to maintain his weight loss.

Managing Conflicts of Interest

Dr. D'Amato should seek to prevent his interest in advancing the knowledge in his field and his commitment to individual patients from [conflicting](#) and, if they do, the latter should generally take precedence. Dr. D'Amato is being compensated for enrolling participants in a clinical trial. This compensation should cover Dr. D'Amato's additional expenses of enrolling participants rather than induce Dr. D'Amato to refer potential participants. Compensation should be consistent with Dr. D'Amato's usual professional fees. The pharmaceutical company [should not](#) offer, and Dr. D'Amato should not accept, an inappropriate level of compensation, and clearly excessive payments may be considered "kickbacks," and would be illegal [4].

Enrolling Patients Consistently

Matthew has become aware of a clinical trial in which Dr. D'Amato is enrolling patients. If Matthew fulfills the inclusion criteria, Dr. D'Amato's withholding information about the trial from him would be inappropriate. It would be paternalistic for Dr. D'Amato not to offer Matthew the opportunity to enroll in the trial because he is concerned that enrollment might be a disincentive to Matthew to continue to try to lose weight. Not offering the option to all of his patients who fulfill the enrollment criteria might inappropriately bias the sample.

Minimizing Therapeutic Misconception

If Matthew is eligible for the trial, he needs to be aware of the differences between research and clinical care. Dr. D'Amato should address any therapeutic misconception—the false belief that the primary purpose of the trial is to provide medical benefit to the participants or that the research procedures are individualized to them [5]. It is particularly important for Matthew and his mother to understand the concept of randomization and the possibility that he will not receive the investigational agent.

Evaluating the Potential Benefits, Risks, and Alternatives

Dr. D'Amato, Matthew, and his mother should also [discuss](#) the potential benefits, risks, and alternatives of participation. In terms of potential benefits, monoclonal antibody treatments have proven effective in treating other gastrointestinal diseases, such as Crohn disease and ulcerative colitis [6]. If Matthew were assigned to the experimental treatment arm, he might see some improvement in his NASH.

The potential risks of participating in the trial should also be discussed. Characterization of the risks should be based on the results of animal studies, phase 1 trials, and experience, if any, with the investigational drug for other indications. For example, infliximab, a monoclonal antibody used to treat Crohn disease and ulcerative colitis, carries such risks as serious infections, including tuberculosis and invasive fungal infections; malignancies, including lymphoma; severe hepatic reactions; and hypersensitivity reactions [6]. The agent may also have unknown or unanticipated risks that may only become apparent during the trial or in postmarketing surveillance. Finally, there may be risks associated with the study procedures.

The alternatives available to Matthew would include not participating in this specific trial or participating in another trial. As of May 2015, for example, adolescents with NASH were being recruited for a controlled trial comparing weight loss surgery/vertical sleeve gastrectomy and a comprehensive lifestyle intervention [7].

Because Matthew is a minor, his mother would have to provide her permission, and he would have to provide his assent to enroll in the trial. When he turns 18, Matthew would have to give his consent to continue to participate. If Matthew's mother's concerns cannot be adequately addressed and she withholds her permission, Matthew cannot enroll until he turns 18 (if the trial includes participants of that age).

Conclusions

NASH has become more frequent with the increasing prevalence of obesity [1]. Treating obesity is difficult, and pharmaceutical alternatives or adjuncts may be attractive to patients. Dr. D'Amato should seek to balance his interest in advancing the care of patients with NASH and his commitment to Matthew, and he should not accept undue inducements to enroll patients in clinical trials. It is reasonable for Matthew to be

interested in enrolling in this trial and for Dr. D'Amato to be concerned that enrollment might undermine Matthew's weight loss efforts. Dr. D'Amato's concern is not, however, a sufficient reason to withhold information about the trial from Matthew. In seeking Matthew's assent and his mother's permission, it is important for them to be aware of the goals of the trial and its potential benefits, risks, and alternatives.

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ISSN 2376-6980**

American Medical Association Journal of Ethics

December 2015, Volume 17, Number 12: 1127-1135

MEDICAL EDUCATION

The National Clinician Scholars Program: Teaching Transformational Leadership and Promoting Health Justice Through Community-Engaged Research Ethics

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Introduction

National health care reform, including expanded insurance coverage under the Affordable Care Act of 2010, has focused attention on both developing effective health care systems with expanded access and improved quality and achieving health care and public health goals through cooperation among health and community-based agencies, such as social service and faith-based programs [1, 2]. For clinician leaders, such reforms create new opportunities at the intersection of evidence-based practice, quality improvement, health-services research, and community engagement [3]. Among many training opportunities for clinicians interested in these areas, one of the most influential has been the Robert Wood Johnson Foundation/US Department of Veterans Affairs Clinical Scholars Program (RWJF/VA CSP) [4, 5]. This program, which has focused on health services research since its inception in 1972, incorporated an emphasis on community-engaged research in 2003 [6, 7]. Under this expanded framework, 310 physicians have been trained at four sites: University of Pennsylvania, Yale University, University of Michigan, and University of California, Los Angeles (unpublished data).

After the announcement of the planned 2017 closure of the current RWJF/VA CSP, leaders at the four institutional sites developed a new program, the National Clinician Scholars Program (NCSP), which builds upon lessons learned from the CSP [8]. Unlike the CSP, the NCSP will train both physician and nursing scholars in partnership with local community-based agencies, with the support of public and private health care systems as well as academic institutions and the VA. As described below, it aims to develop leaders with expertise in research and community partnering who transform health care systems and academic medical centers, and it aims to do so via co-leadership among team members and community and health system partners. This article reviews the goals and structure of the NCSP and the opportunities for ethics training stemming from its community-engaged research focus.

Learning Ethics through Community-Engaged Research

Community-engaged research can provide the means to design, implement, and sustain

interventions that fit community needs; reduce inequalities in health status and in access to health care services; enhance community capacity; and inform policy [9–11]. In community-engaged research, academic researchers like NCSP scholars and community stakeholders—patient advocates, community members, clinicians, and policymakers—are equal partners in each phase of research processes, from [design](#) and implementation to [results dissemination](#) [12, 13]. Today many US funders, including the National Center for Advancing Translational Sciences, the Patient-Centered Outcomes Research Institute, and the Agency for Healthcare Research and Quality, require some degree of community engagement in research [14, 15].

Through prioritizing consensus-building, shared control and interpretation of data, attention to cultural humility, and nurturing inclusive and meaningful partnerships, community-engaged researchers follow the principles and practices of research integrity described in the Belmont Report while underscoring the value of community and academic co-leadership [16–18]. Working with an awareness of contemporary and historical injustices, community-engaged researchers pay heightened attention to ethical research methods [19], employ practices that promote two-way knowledge exchange, and establish fair procedures for direct community benefit [20]. As Fraser and colleagues say, “collaboration is less an option than an ethical obligation” [21]. Whereas protocols to uphold research integrity are typically [approved](#) in advance, community-engaged researchers view conducting ethical research as an iterative, evolving process; they review challenges, address [conflicts](#), and share perspectives with community stakeholders to guide investigators’ and others’ courses of action throughout the duration of a project [22, 23]. Community-engaged researchers also recognize the need to adapt ethical guidelines to local priorities, since what might be perceived as ethical in one community might not be in another [24, 25]. The NCSP structure provides scholars with opportunities to learn how to navigate these kinds of ethical considerations [26].

Overview of the NCSP

Each current RWJF/VA CSP site, with extensive feedback from program partners and alumni, has developed a legacy program coordinated through a leadership committee. The training seeks to develop clinicians who will lead transformative change in health care delivery, public health, and community health through (1) excellence in health care delivery sciences (health services research, health policy, translational and implementation sciences, and community-based participatory research) and (2) completion of research, quality improvement and policy evaluation projects within and in partnership with health care, public health, and community systems. To provide enhanced opportunities for cross-fertilization among disciplines and sites, scholars have access to academic and community nursing leaders and their community agency networks in addition to existing RWJF/VA CSP mentorship and program site networks [27].

Scholars at all sites are supported for two years. Their training includes graduate-level coursework in research methods, health policy, and health systems organization; seminars and experiences in leadership in health care; a focus on strategies for planning, initiating, and nurturing partnerships for community-driven interventions; and clinical or teaching service, typically at a sponsoring site, as appropriate. During the program scholars identify and undertake a mentored research project and might have the opportunity for a one-to-two month placement with local, state, or national agency.

Community-Engaged Research within the NCSP

Scholars' projects utilize various models of community engagement. Some NCSP sites emphasize community-based participatory research that seeks community-defined solutions for community-prioritized issues, with academic support in program implementation and evaluation. Other sites use the model of community-partnered participatory research, which engages members of the community in adapting, implementing, or disseminating evidence-based approaches, combined with community insight, to address issues of importance to both community and academic stakeholders. To build capacity and ensure relevance, projects must (1) fit the interests of scholars and partners, including agency partners, community leaders, and other representatives of under-resourced communities and (2) support two-way knowledge exchange and co-leadership and yield value for science and the community. Projects typically aim to mitigate disparities in health and health care and might address social risk factors, such as homelessness, poverty, incarceration, and violence, which might exacerbate those disparities, within a public health framework.

For example, an NCSP site might introduce scholars to potential partners in a summer orientation and facilitate scholars' visits to individual sites and meetings with faculty mentors and partners. Scholars with interests in community groups not represented in the main network of partners are supported in exploring new partnerships. This might be followed by a course in community partnership in health research that includes topics such as ethical principles underlying community partnership research, how to establish and nurture partnerships, how to generate ideas for projects, and how to collaboratively and respectfully conduct research within specific communities. Integral to such courses are both large-group discussions with academic and community co-leaders and smaller meetings with community and academic mentors. Scholars might also participate in projects that build community capacity to address community priorities such as reducing violence or mitigating consequences of trauma.

Ethical Principles Underlying the NCSP

Equity and equality. A primary goal of NCSP projects is motivating health justice by reducing disparities in health and health care through research and the practice of equitable and equal partnering and power sharing with systems and communities. Equity indicates the practice of fairness and impartiality; equality means that status, rights, and

opportunities are similarly distributed. The program structure supports equality through co-chairing of advisory boards by academic and community leaders, co-mentorship of scholars, and co-leadership of projects. The focus on equity means that community agencies strongly represent themselves in policy advisory boards and that partners with fewer available resources are supported.

Respect. Practicing respect in community-engaged research projects means valuing all partners' experiences, perspectives, and priorities; and interacting in culturally sensitive ways. To cultivate respect, scholars learn about historical antecedents of inequalities such as discrimination. Scholars are encouraged to spend time in partners' neighborhoods and with community members, and to elicit partners' views on factors underlying disparities in health and access to health care, in order to more fully understand their perspectives. At times, this inclusive approach can generate conflict among team members or between system and community stakeholders, since a team that is receptive to multiple viewpoints would expect to encounter disagreements [28]. Scholars receive explicit training in identifying and resolving conflicts and gain skills in using conflict effectively to advance partnerships. For example, they learn strategies for working productively with conflict by identifying similarities and differences between priorities (finding the "win-win"), accepting differences as markers of increased network diversity, and establishing shared goals for progress (e.g., agreeing to disagree).

Patient and community-centeredness. NCSP training emphasizes patient and family leadership, promoting such leadership with sensitivity to patients' health conditions and power differentials between clinicians and patients. For example, patients with mental illnesses might not wish to be identified as mentally ill, but rather as patients or community members with an interest in mental health promotion. Patient and community-centeredness also means protecting the autonomy of individuals and communities to prevent exploitation and coercion. In the NCSP program at the University of California, Los Angeles, community engagement exercises are used to "level the playing field" by promoting awareness of different kinds of expertise; for example, expertise gained through lived experience [29] is recognized as equally important as scientific expertise.

Beneficence and nonmaleficence. One meaning of *beneficence*, or doing good, in the context of community-engaged research is that community members realize and enjoy an equitable distribution of the benefits of research. One meaning of *nonmaleficence*, or avoiding harm, in the context of community-engaged research is that scholars have regular feedback sessions with community partners to listen and to identify unexpected or known harmful effects, such as program features that could exacerbate inequalities (e.g., levels of affordability or access to services). Additionally, program activities and solutions are framed in resilience or strength-based ways to avoid the harm of labeling a community as deficient (e.g., "underserved," "poor," "high-risk").

Transparency. Scholars learn to collaborate with partners in ways endorse that transparency and cultivate shared understandings, including ethical implications [30] of courses of action. For example, in an exercise called “Feet of Clay,” scholars and community partners share a moment of vulnerability from their pasts. In consequence, clinician-scholars, who are often trained in formal and hierarchical environments, learn to express more fully their own perspectives as a way of establishing and maintaining common ground and relationships with partners. This kind of learning is designed to build scholars’ collaborative leadership skill.

Conclusion

The National Clinician Scholars Program is a new legacy program that builds on and enhances the successes of the RWJF/VA CSP by linking clinician-scholars to local health systems through community-engaged research. The NCSP approach offers promising strategies for training transformative, collaborative leaders. Scholars learn scientific rigor and innovation while helping build community capacity. Through rigorous research training coupled with experience partnering with community organizations, scholars gain skills needed to improve practice, execute research in the area of health justice, and motivate policy changes that more fully integrate health care with public health goals and, over the long term, hold promise to reduce disparities in health and health care. The program also provides scholars with unique ethics training: core ethics principles of equity, equality, respect, patient- and community-centeredness, beneficence, nonmaleficence, and transparency are central parts of the program’s curriculum. The ethical dimensions of scholars’ learning prepares future leaders to value equitable, respectful engagement with communities as a priority in health service delivery and research and to ensure community voices are represented at the policymaking table.

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Acknowledgements

The authors thank the Robert Wood Johnson Foundation and collaborators at each of the four National Clinician Scholars Program sites. This work was supported in part by grants from the Robert Wood Johnson Foundation (71897, 72719, 71898, 72720, 70987, 71899) and the National Institute of Environmental Health Sciences (R21ES02293). The authors would like to extend their gratitude to important CSP and NCSP partners for their long-standing support and co-leadership: Natasha Ray, MS, New Haven Healthy Start Core Services Manager, The Community Foundation for Greater New Haven; Zachary Rowe, BBA, Executive Director, Friends of Parkside; Anthony Singleton, President/Chief Executive Officer, Educators 4 Education. The authors also thank Dmitry Khodyakov, PhD, RAND Corporation, for contributions to the manuscript.

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ISSN 2376-6980**

American Medical Association Journal of Ethics

December 2015, Volume 17, Number 12: 1136-1141

THE CODE SAYS

The AMA *Code of Medical Ethics'* Opinions on Clinical Research

Opinion 2.07 – Clinical Investigation

The following guidelines are intended to aid physicians in fulfilling their ethical responsibilities when they engage in the clinical investigation of new drugs and procedures.

(1) A physician may participate in clinical investigation only to the extent that those activities are a part of a systematic program competently designed, under accepted standards of scientific research, to produce data which are scientifically valid and significant.

(2) In conducting clinical investigation, the investigator should demonstrate the same concern and caution for the welfare, safety, and comfort of the person involved as is required of a physician who is furnishing medical care to a patient independent of any clinical investigation.

(3) Minors or mentally incompetent persons may be used as subjects in clinical investigation only if:

(a) The nature of the investigation is such that mentally competent adults would not be suitable subjects.

(b) Consent, in writing, is given by a legally authorized representative of the subject under circumstances in which informed and prudent adults would reasonably be expected to volunteer themselves or their children as subjects.

(4) In clinical investigation primarily for treatment:

(a) The physician must recognize that the patient-physician relationship exists and that professional judgment and skill must be exercised in the best interest of the patient.

(b) Voluntary [written](#) consent must be obtained from the patient, or from the patient's legally authorized representative if the patient lacks the capacity to consent, following: disclosure that the physician intends to use an investigational drug or experimental procedure; a reasonable explanation of the nature of the drug

or procedure to be used, risks to be expected, and possible therapeutic benefits; an offer to answer any inquiries concerning the drug or procedure; and a disclosure of alternative drugs or procedures that may be available. Physicians should be completely objective in discussing the details of the drug or procedure to be employed, the pain and discomfort that may be anticipated, known risks and possible hazards, the quality of life to be expected, and particularly the alternatives. Especially, physicians should not use persuasion to obtain consent which otherwise might not be forthcoming, nor should expectations be encouraged beyond those which the circumstances reasonably and realistically justify.

(i) In exceptional circumstances, where the experimental treatment is the only potential treatment for the patient and full disclosure of information concerning the nature of the drug or experimental procedure or risks would pose such a serious psychological threat of detriment to the patient as to be medically contraindicated, such information may be withheld from the patient. In these circumstances, such information should be disclosed to a responsible relative or friend of the patient where possible.

(ii) Ordinarily, consent should be in writing, except where the physician deems it necessary to rely upon consent in other than written form because of the physical or emotional state of the patient.

(5) In clinical investigation primarily for the accumulation of scientific knowledge:

(a) Adequate safeguards must be provided for the welfare, safety, and comfort of the subject. It is fundamental social policy that the advancement of scientific knowledge must always be secondary to primary concern for the individual.

(b) Consent, in writing, should be obtained from the subject or from a legally authorized representative if the subject lacks the capacity to consent, following: disclosure of the fact that an investigational drug or procedure is to be used; a reasonable explanation of the nature of the procedure to be used and risks to be expected; and an offer to answer any inquiries concerning the drug or procedure.

(6) No person may be used as a subject in clinical investigation against his or her will.

(7) The overuse of institutionalized persons in research is an unfair distribution of research risks. Participation is coercive and not voluntary if the participant is subjected to powerful incentives and persuasion.

(8) The ultimate responsibility for the ethical conduct of science resides within the institution (academic, industrial, public, or private) which conducts scientific research and

with the individual scientist. Research institutions should assure that rigorous scientific standards are upheld by each of their faculty, staff, and students and should extend these standards to all reports, publications, and databases produced by the institution. All medical schools and biomedical research institutions should implement guidelines for a review process for dealing with allegations of fraud. These guidelines should ensure that:

(a) the process used to resolve allegations of fraud does not damage science.

(b) all parties are treated fairly and justly with sensitivity to reputations and vulnerabilities.

(c) the highest degree of confidentiality is maintained.

(d) the integrity of the process is maintained by an avoidance of real or apparent conflicts of interest.

(e) resolution of charges is expeditious.

(f) accurate and detailed documentation is kept throughout the process.

(g) responsibilities to all involved individuals, the public, research sponsors, the scientific literature, and the scientific community is met after resolution of charges. Academic institutions must be capable of, and committed to, implementing effective procedures for examining allegations of scientific fraud. No system of external monitoring should replace the efforts of an institution to set its own standards which fulfill its responsibility for the proper conduct of science and the training of scientists.

(9) With the approval of the patient or the patient's lawful representative, physicians should [cooperate with the press and media](#) to ensure that medical news concerning the progress of clinical investigation or the patient's condition is available more promptly and more accurately than would be possible without their assistance. On the other hand, the Council does not approve of [practices](#) designed to create fanfare, sensationalism to attract media attention, and unwarranted expressions of optimism because of short-term progress, even though longer range prognosis is known from the beginning to be precarious. With the approval of the patient or the patient's family, the Council, however, encourages the objective disclosure to the press and media of pertinent information. If at all possible, the identity of the patient should remain confidential if the patient or the patient's family so desires. The situation should not be used for the commercial ends of participating physicians or the institutions involved.

Issued prior to April 1977; updated June 1994 and June 1998.

Opinion 2.071 - Subject Selection for Clinical Trials

Ethical considerations in clinical research have traditionally focused on protecting research subjects. These protections may be especially important for those from socioeconomically disadvantaged populations who may be more [vulnerable](#) to coercive pressures. The benefits from altruism that result from participation in research, particularly for severely chronically ill persons, may justify equitable consideration of historically disadvantaged populations such as the poor. With these considerations in mind, the following guidelines are offered:

(1) Although the burdens of research should not fall disproportionately on socioeconomically disadvantaged populations, neither should such populations be categorically [excluded](#), or [discouraged](#), from research protocols.

(2) Inclusion and exclusion criteria for a clinical study should be based on sound scientific principles. Conversely, participants in a clinical trial should be drawn from the qualifying population in the general geographic area of the trial without regard to race, ethnicity, economic status, or gender.

If a subject's primary care physician determines that the subject received a clear medical benefit from the experimental intervention which is now moving towards marketing approval and chooses to seek authorization from the Food and Drug Administration (FDA) for continued use of the investigational therapy during the time period between the end of the protocol and the availability of the drug on the market, the investigator should work with the primary care physician, the product sponsor, and the FDA to allow continued availability of the product.

Issued June 1998 based on the report "Subject Selection for Clinical Trials," adopted December 1997.

Opinion 8.0315 - Managing Conflicts of Interest in the Conduct of Clinical Trials

As the biotechnology and pharmaceutical industries continue to expand research activities and funding of clinical trials, and as increasing numbers of physicians both within and outside academic health centers become involved in partnerships with industry to perform these activities, greater safeguards against conflicts of interest are needed to ensure the integrity of the research and to protect the welfare of human subjects. Physicians should be mindful of the conflicting roles of investigator and clinician and of the financial conflicts of interest that arise from [incentives](#) to conduct trials and to recruit subjects. In particular, physicians involved in clinical research should heed the following guidelines:

(1) Physicians should agree to participate as investigators in clinical trials only when it relates to their scope of practice and area of medical expertise. They should have adequate training in the conduct of research and should participate only in protocols which they are satisfied are scientifically sound.

(2) Physicians should be familiar with the ethics of research and should agree to participate in trials only if they are satisfied that an Institutional Review Board has reviewed the protocol, that the research does not impose undue risks upon research subjects, and that the research conforms to government regulations.

(3) When a physician has treated or continues to treat a patient who is eligible to enroll as a subject in a clinical trial that the physician is conducting, the informed consent process must differentiate between the physician's roles as clinician and investigator. This is best achieved when someone other than the treating physician obtains the participant's informed consent to participate in the trial. This individual should be protected from [the pressures of financial incentives](#), as described in the following section.

(4) Any financial compensation received from trial sponsors must be commensurate with the efforts of the physician performing the research. Financial compensation should be at fair market value and the rate of compensation per patient should not vary according to the volume of subjects enrolled by the physician, and should meet other existing legal requirements. Furthermore, according to Opinion 6.03, "Fee Splitting: Referral to Health Care Facilities," it is unethical for physicians to accept payment solely for referring patients to research studies.

(5) Physicians should ensure that protocols include provisions for the funding of subjects' medical care in the event of complications associated with the research. Also, a physician should not bill a third party payer when he or she has received funds from a sponsor to cover the additional expenses related to conducting the trial.

(6) The nature and source of funding and financial incentives offered to the investigators [must be disclosed](#) to a potential participant as part of the informed consent process. Disclosure to participants also should include information on uncertainties that may exist regarding funding of treatment for possible complications that may arise during the course of the trial. Physicians should ensure that such disclosure is included in any written informed consent.

(7) When entering into a contract to perform research, physicians should ensure themselves that the presentation or publication of results will not be unduly delayed or otherwise obstructed by the sponsoring company.

Issued June 2001 based on the report “Managing Conflicts of Interest in the Conduct of Clinical Trials,” adopted December 2000.

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ISSN 2376-6980**

American Medical Association Journal of Ethics

December 2015, Volume 17, Number 12: 1142-1146

STATE OF THE ART AND SCIENCE

Expanded Access to Investigational Drugs: What Physicians and the Public Need to Know about FDA and Corporate Processes

Paige E. Finkelstein

For many people, physicians included, the US Food and Drug Administration (FDA) seems like a black box. We know that the FDA regulates the obvious—food and drugs—but not much else. As a medical student, I certainly used to share this sentiment. I had no idea how the drugs I would one day be prescribing to patients were determined to be safe and effective. We simply write off determination of drug safety and efficacy as “the FDA’s job,” and all a good doctor has to be concerned with is complying with the FDA’s final recommendations regarding prescribing, dosing, and monitoring the side effects of drugs.

On the contrary, it’s not actually that hard to find out what goes on there. The FDA has tremendous outreach capability and a plethora of available resources on its website designed to assist physicians not only with food-and drug-related questions, but also with resources connected to cosmetics, medical devices, vaccines, tobacco, and even veterinary treatments. Exploring the website can give physicians some means by which to better understand what goes on behind the scenes in drug development. Doing so will also enable them to promote the safe use of available drugs and devices through training regarding certain medications, frequently updated safety information, and the latest science news.

I was an intern with the FDA’s Professional Affairs and Stakeholder Engagement (PASE) staff, which assists in the important expanded access/compassionate use process. The FDA’s website explains that the expanded access program “provides a pathway for patients to gain access to investigational drugs, biologics, and medical devices for serious conditions” [1]. For some patients, access to drugs not yet approved for the general market can be life-saving.

The [expanded access process](#) has been a topic of ongoing legislative debate. In 1987 and 1997 [2], respectively, the FDA made investigational drugs available through compassionate use processes and specified the situations in which it would allow expanded access. In 2009 [3], the FDA revised the Code of Federal Regulations again in order to raise awareness and knowledge about expanded access. In May of 2015 [4], the 21st Century Cures Act, which in part seeks to establish conditions for drug manufacturers to develop and publicize official policies on expanded access, was brought

to Congress. In July 2015, it was overwhelmingly approved in the House [5], and now it is being deliberated in the Senate.

The expanded access process is designed to help those who have no other therapeutic alternative. The patient must have a condition that is serious or immediately life-threatening for which there are no available therapies. These situations are evaluated by a physician; if the physician knows of an investigational drug he or she is willing to try with the patient, he or she will complete a two-step application for expanded access. The first step, applying to the FDA, requires a surprisingly small amount of paperwork, the instructions for which can be found on the FDA's website [6]. The FDA must reply to the request within 30 days, or even less, depending on the severity of the situation.

The FDA actually approved more than 99 percent of the requests for expanded access received during the 2010 to 2014 fiscal years [7]. However, the second step is applying for approval from the drug manufacturer itself, and this is where many requests are thwarted.

Subtitle E of the 21st Century Cures Act [4], "Expediting Patient Access," would require that drug manufacturers and distributors make publicly available all of the following information within 60 days of the bill passing into law:

1. contact information to facilitate communication about expanded access
2. procedures for requesting expanded access
3. criteria that must be met to approve expanded access requests
4. the length of time needed to consider expanded access requests

The bill does *not*, however, require that drug companies provide access to investigational drugs. This loophole raises unresolved practical and ethical questions regarding expanded access. While the bill would help expedite *access to information* from the FDA and the manufacturers, it does not actually promote *access to the experimental agents*. If patients can get information, but aren't actually likely to get the drug from manufacturers, an open ethical question remains: should such legislation really be promoted as helpful to patients?

Often, manufacturers do not grant access to the investigational drug; in April of 2014, only 86 of 32,304 clinical trials offered expanded access programs [8]. Neither the FDA nor any current or proposed piece of legislation (even the 21st Century Cures Act) can force a manufacturer to provide an investigational drug to a patient seeking expanded access.

There are several legitimate reasons why it may not be possible for a manufacturer to provide the drug:

1. There is not enough of the drug available for both the clinical trial patients and the expanded access patients. Many drugs, so early on in their development, are

not produced in large quantities [8]. If only a small amount of the drug is available, the manufacturer must prioritize patients participating in the clinical trials.

2. The drug company and physician must create a special protocol for the expanded access patient's use of the investigational drug, which can take hundreds of hours to do. Some manufacturers, especially smaller ones, do not have the manpower to complete this task within a reasonable amount of time.
3. Since the drugs in question are not approved by the FDA, insurance companies may not cover them. Small companies may not have the financial resources to supply drugs to patients who cannot afford them.
4. If an adverse event occurs for an expanded access patient, it must be reported to the FDA regardless of whether it was caused by use of the investigational drug. This requirement, in turn, can put the ongoing clinical trial at risk and make the manufacturer liable for damages.

Unfortunately, the opportunity for patients to try these investigational drugs happens infrequently, for the reasons listed above.

Conclusion

Every so often we see a heartwarming story about a new investigational drug being given to a patient and prolonging his or her life. The case of Sarah Broom, for instance, was covered in the *New York Times* in 2013 [9]. Broom had advanced lung cancer and had run out of treatment options, so she pled with Novartis for access to a compound that she had heard about from an oncologist. After Novartis denied the request, Broom decided to appeal to the humanistic side of the company's executives and sent a package of letters written by her young children asking to let their mother try the drug. She was finally granted access, and the drug gave her an additional year of life with her children and family before she ultimately died.

For patients who have been denied expanded access, the next best step they and their families can take is getting involved with their disease advocacy groups. Advocacy groups are instrumental in raising awareness about a disease and raising funds to further scientific research. One example would be the Amyotrophic Lateral Sclerosis (ALS) Foundation's Ice Bucket challenge that saturated social media for several months in 2014. How many more people are aware of ALS today because of that social media campaign? About 17 million people uploaded videos in which they dumped ice water on themselves to raise awareness for ALS, and these videos were watched by 440 million people [10]. From August through September 2014, the ALS Foundation raised \$115 million dollars [11]. As demonstrated by the ALS Foundation, we must not only continue to work together as a community to find the ethical and humanitarian balance of support for medical science for future patients, but also spread compassion for today's patients who have run out of options.

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ISSN 2376-6980**

American Medical Association Journal of Ethics

December 2015, Volume 17, Number 12: 1147-1151

HEALTH LAW

New Developments in Human Subjects Protections: Proposed Updates to the Common Rule

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The history of [human subjects research](#) in the United States is checkered with horrifying examples of exploitation that demonstrate the need for overarching protections for research participants. From the US Public Health Service Syphilis Study at Tuskegee, in which poor African American men in rural Alabama were denied treatment for their syphilis so that federal researchers could study its natural progression [1], to Willowbrook, where institutionalized mentally disabled children were deliberately infected with hepatitis in order to develop treatments for the disease [2], researchers have time and again trampled upon the legal and ethical rights of vulnerable populations in the name of science. To address these egregious violations, scientists, ethicists, academics, and politicians in the 1970s and 1980s developed a body of regulations to oversee biomedical and behavioral research involving human subjects in the US, known today as the Common Rule.

Based on the ethical principles elucidated in the Belmont Report and the work of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, the Common Rule was published by the Department of Health and Human Services (HHS) in 1991 and codified by fifteen other federal departments and agencies engaged in human subject research [3]. The Common Rule is the part of the Code of Federal Regulations (45 CFR 46) that codifies special recognition and protection for certain vulnerable populations, who are discussed below. For over two decades, the Common Rule has remained largely unchanged while the pace and capabilities of scientific research have greatly altered. This year, the Office of Human Research Protections (OHRP) within HHS has begun the legal procedure for changing the content of the Common Rule to better address modern research environments. This article discusses those changes.

The Structure and Content of the Common Rule

The Common Rule for protection of human research subjects is divided into four main subparts. Subpart A establishes the "Basic HHS Policy for Protection of Human Research Subjects" [4], discussing the jurisdictional power of the regulations and defining the types of research controlled by the Common Rule, including "research that is conducted or supported by a federal department or agency" [5], "research that...must be reviewed and approved...by an institutional review board (IRB)" [6], and "research, involving the

collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded...in such a manner that subjects cannot be identified" [7]. This subpart also defines the composition, operation, and oversight of IRBs at research institutions [8]; the requirements for obtaining informed consent [9]; and the documentation requirements of informed consent [10].

The next three subparts provide regulatory guidance for research on populations considered vulnerable within the research setting. Subpart B provides additional protections for pregnant women, fetuses, and newborns [11]. Subpart C pertains to prisoners, whose capacity to participate voluntarily in research can be restricted or undermined because they are incarcerated [12]. Subpart D considers research involving children, with special attention to risks and benefits. Specifically, this section distinguishes two important sets of conditions: (1) when there is more than minimal risk to the child [13] and the possibility of direct benefit to the child [14], and (2) when there is no direct benefit to the child but the research is "likely to yield generalizable knowledge about the subject's disorder or condition" [15] or "present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children" [16].

Changes to the Common Rule

Reasoning. Since the Common Rule was published and codified in 1991, the human subject research landscape has changed dramatically, growing in both scale and diversity [17]. Study designs have changed in their complexity and variety; sophisticated and detailed inquiries are being conducted in biomedical, behavioral, and social sciences; and large quantities of electronic health and behavioral data are being collected, analyzed, and studied in new ways. HHS acknowledges that "these developments have not been accompanied by major change in the human subjects research oversight system" [18]. So, on September 8, 2015, OHRP published a notice in the *Federal Register* outlining proposed changes to the federal Common Rule [17].

Proposed changes in the 2015 notice of proposed rulemaking [17] incorporate public comments submitted in response to a previous (2011) advanced notice of changes to the *Federal Register* [19] and promulgate eight potential changes to the Common Rule, which can be organized into three categories.

Consent. The current Common Rule specifies elements of and documentation requirements for informed consent [3]. The proposed revisions seek to more precisely clarify what information must be given to prospective subjects and to improve the clarity and [usefulness](#) of consent forms as a way to try to more effectively ensure that subjects and their guardians are appropriately informed about the risks and benefits of protocols in which they or their wards are enrolled [20]. Similarly, proposed changes also seek to limit informed consent guidelines regarding [researchers' uses of biospecimens](#),

particularly in secondary research, in which the use of the specimens for research purposes “may be unforeseen at the time in which consent is being sought” [21]. While the Common Rule allows for use of biospecimens without consent from the donor if the specimens are de-identified, the new rule would require broad consent for both the storage and future research use of these materials [20] and make [waivers of consent](#) much rarer [22].

Exemptions. The second category of changes addresses research thought to be exempt from IRB review or not subject to the Common Rule. These changes propose designation of new categories of research that could be exempt from IRB review because they pose no risk [20]. They also propose that activities deemed by IRBs not to constitute research or to pose less than minimal risk to subjects be excluded from the Common Rule [20]. Proposed changes also would eliminate the need for IRBs to renew approval of expedited-review studies, that is, studies involving de-identified data analysis or observational follow-up in the clinical care contexts [22].

Efficiency. Proposed changes to the Common Rule suggest mandating use of a single IRB for review of collaborative, multi-institutional research in the US, rather than relying upon review and approval from multiple institutions’ IRBs [22]. Proposed revisions to the Common Rule also seek to make it more responsive to the needs of researchers conducting cross-national clinical trials at institutions in the US that receive federal funding for non-exempt human subjects research [22].

Conclusion

With the publication of the notice of proposed rulemaking for the Common Rule revisions, HHS has begun an extensive conversation with the American scientific community and the public about how best to make human subject protection guidelines more responsive to changes in research design and conduct. Greater congruence between research activity and research regulations is one goal of these proposed changes.

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ISSN 2376-6980**

American Medical Association Journal of Ethics

December 2015, Volume 17, Number 12: 1152-1159

POLICY FORUM

US Federal Government Efforts to Improve Clinical Trial Transparency with Expanded Trial Registries and Open Data Sharing

Daniel L. Shaw and Joseph S. Ross, MD, MHS

Policy changes proposed by the US Department of Health and Human Services (HHS) and the National Institutes of Health (NIH) are the latest in a longstanding effort to bring transparency and openness to health care research [1, 2]. The proposals are designed to expand clinical trial registration requirements and promote sharing of clinical data generated from research. Health care advocates have long maintained that selective publication and reporting of clinical trials not only diminishes the integrity of medical research, but also might risk patient lives when it prevents safety concerns from being promptly identified [3, 4]. Hence, there are both ethical and pragmatic reasons to enhance research transparency.

Clinical trials are prospective, interventional studies involving at least one human participant that provide evidence about the safety and efficacy of new therapies. Although the ethics of patient treatment in such trials are generally agreed upon [5], the importance of research transparency is growing as it becomes increasingly feasible to share information, collaborate across institutions, and network among investigators. Historically, the imperative for transparency for both the public and the academic community was satisfied by publishing results in peer-reviewed journals [3]. By today's standards, however, the publication process is slow [6], often creating a significant lag in the dissemination of new research findings. Moreover, the majority of clinical trials are never published and those published are more likely to be reporting positive results [7-9]. Even when clinical trials are published, the articles may not be consistent with the raw data or the results reported to clinical trial registries [10, 11]. In the past, this lack of transparency has slowed access to information on investigational therapies (as with HIV drugs in the 1980s [12]), potentially led to inappropriate use of medications (as with drugs like gabapentin [13] and COX-2 inhibitors [14]), and delayed device recalls (as in the case of metal-on-metal hip replacements [15]). From both public health [16, 17] and human rights perspectives [12], the incomplete dissemination of clinical research results is no longer tolerable.

The Evolution of Clinical Trial Registries

The proposed policy changes by HHS and NIH focus on broadening requirements for clinical trial registration to enhance research transparency. [Trial registries](#) are typically web-based platforms that provide a public source of information on existing clinical

trials, ranging from those specific to particular diseases to those that aggregate trials in a given region. Numerous foundations and disease-specific groups have their own trial registries, with the NIH alone listing close to 40 independent trial registries [18]. Registration provides the public and the scientific community with critical information about both active and completed trials, including title, purpose, eligibility, investigator contact information, and relevant dates.

Historically, patient advocates have led the movement to increase research transparency in the US. The first federally supported registry, the AIDS Clinical Trials Information Service (ACTIS, enacted in 1989), was in part a result of patient lobbying [12, 19, 20]. A decade later, advocacy work by the breast cancer community led to expanded federal funding for a “public resource” for clinical trial data through the Food and Drug Administration Modernization Act of 1997 (FDAMA) [12, 21]. That “public resource” became ClinicalTrials.gov, a central repository run by the National Library of Medicine for information on clinical trials throughout the world [22].

The role and scope of ClinicalTrials.gov has gradually expanded over time, and it is now the largest trial registry in the world, with close to 200,000 registered studies [22]. Initially, the registry was primarily limited to NIH-funded clinical trials. However, in 2005, the International Committee of Medical Journal Editors required registration of trials prior to publication, which led to substantial increases in trial registration [23, 24]. The FDA Amendments Act of 2007 (FDAAA) section 801 expanded the types of “applicable clinical trials” subject to reporting requirements [22, 25], a category of studies initially defined by the Food, Drug and Cosmetic Act but amended over the years by legislation and interpreted by executive processes of rulemaking [1]. It also formalized the data elements (including descriptive, recruitment, contact, and administrative data) required for registration and added mandatory reporting of summary results for applicable trials [22, 25], a category of studies initially defined by the Food, Drug and Cosmetic Act but amended over the years by legislation and interpreted by executive processes of rule making. Such results reporting is particularly valuable, increasing public access to study conclusions that can be used to guide clinical decision making. Several thousand trials now report summary results on ClinicalTrials.gov [22].

However, limits to trial transparency remain. NIH does not currently require registration of all sponsored trials, and there are notable exceptions in the existing interpretation and enforcement of FDAAA clinical trial reporting mandates [26]. For example, trials of drugs and devices not yet approved by the FDA and trials of non-FDA-regulated products are not subject to current regulatory policies [27]. Additionally, some results reporting requirements—including detailed definitions of necessary outcomes measures, results summaries, and adverse events—were not fully specified in the FDAAA, nor were the mechanisms to verify compliance [25]. This has led to poor rates of results reporting on ClinicalTrials.gov across trial sponsors [28].

Proposed Changes

The 2014 HHS Notice of Proposed Rulemaking (NPRM) [1] and the NIH proposal for disseminating NIH-funded clinical trial information [2] revise the scope of FDAAA section 801 [25]. Key features of the NPRM and the NIH proposals include: (1) expansion of mandatory applicable trial registration and results reporting on ClinicalTrials.gov to include more trials—including trials of drugs and devices not yet regulated by the FDA and *all* trials receiving funding from the NIH; (2) collection of new data types, such as specifically-defined outcome measures, during trial registration and data submission; (3) a requirement that all applicable studies required to register must report expanded summary data, including additional efficacy outcomes and adverse events; and (4) implementation of procedures for timely and accurate data reporting to speed information dissemination [1, 2, 29, 30].

These changes are a significant step forward, enhancing clinical trial transparency and setting the stage for future improvements. The NPRM will not only require more clinical trials to publicly register and report results, but also improve access to this information by making many of these data elements searchable [26]. These new rules will have a significant effect on academic research centers and NIH-funded research, which have poor records of both registering trials and making data publicly available [31, 32]. Improved procedures and implementation of penalties for delays will ideally ensure widespread trial registration and results reporting across all study sponsors and sites.

Nevertheless, the policy proposals contain numerous loopholes that make it possible to avoid registration and some striking omissions. For example, many “exploratory” and phase 1 research trials will continue to be exempt to maintain commercial competitive advantage [1, 26, 27]. Moreover, the proposed policy changes do little to promote open data.

The Benefits of Open Data

Sharing of raw experimental data among researchers is now the norm in many scientific fields. From genomics and drug development to molecular and structural biology, researchers have made commitments to crowdsource studies, share data, and promote the principles of open science [33]. A recent study surveying researchers who conduct clinical trials revealed that nearly three-quarters of respondents believed that data submission to repositories should be mandatory [34], suggesting there is now broader consensus that data from trials should be made publicly accessible. Registration and reporting of summary data in repositories like ClinicalTrials.gov is a good start, but efforts are needed to make clinical data more widely available for research and public health purposes.

Data sharing has numerous benefits. It honors the altruism of study participants by fully leveraging their data for additional research. It also allows existing data to be used to pursue novel research through meta-analysis by groups such as the Cochrane Collaborative and creates opportunities to advance medical science and clinical research [3, 11]. Access to raw clinical trial data, coupled with crowdsourcing, big data, and advanced analytics, offers the promise of more sophisticated and granular analyses that may both identify ways to improve patient outcomes and recognize rare adverse events [3, 35]. Moreover, access to data allows researchers to reconstruct the scientific conclusions of a study independently, ensuring research integrity through data accountability [36]. For example, the negative health impacts of incomplete data—such as occurred with rofecoxib [13] and oseltamivir [11, 37]—may have been determined more rapidly if researchers had had access to de-identified records.

There are also economic reasons to support increased data sharing, including the creation of efficiencies in research and development that spur innovation [35, 38]. Clinical trial data has been proposed to be a public good [38, 39], meaning that its use by one party does not diminish its value to others. Independent analysis has shown that effectively leveraging data liquidity—or the availability of data to researchers, clinicians, and patients—could create up to \$450 billion of value in the US health care market [40]. Indeed, utilizing existing clinical data should be considered “a boon to drug developers” that would reduce the cost of running clinical trials [41].

Toward A Data-Sharing World

Clinical trial sponsors have begun to respond to requests for research transparency. In 2013, GlaxoSmithKline created a data-sharing platform, ClinicalStudyDataRequest.com, now used by 13 of the largest pharmaceutical companies worldwide to share information on dozens of clinical trials [42]. Third parties, like the Yale University Open Data Access (YODA) Project, have also worked to facilitate data sharing [43]. These platforms are promising, yet they are limited in both their scope and their access to data. The number of available trials represents only a small proportion of those completed to date, and some of the available trials have cumbersome data use agreements. Furthermore, the high cost of data-sharing platforms and insufficient funds hamper these efforts.

The value of shared data lies largely in the ability to analyze the aggregated results of several studies to convey a greater truth [33]; thus efforts are needed to incorporate sharing data and using shared data into the reward structures of academic credit and promotion. ClinicalTrials.gov, which already aggregates registry information and summary results for hundreds of thousands of trials, may be the ideal public data repository. Hosting open data is a role that the government is uniquely positioned to fulfill, given its vast resources and regulatory monopoly [44]. In addition, to leverage any data in such a repository efficiently, common data definitions and infrastructure that

ensures security and privacy will need to be developed. To host, maintain, administer, and analyze the vast amounts of clinical data produced every year will also require significant funding [44].

Conclusions

As access to clinical data becomes the next frontier in clinical research transparency, the burden for action shifts onto scientists, clinicians, and study sponsors. The case for full transparency has been argued from public health, human rights, and economic perspectives. As the risks of withholding study information and research results—and the opportunities inherent in open data sharing—become increasingly evident, the rationale for more comprehensive clinical trial transparency grows stronger and the needed steps forward become clearer. The proposed rule changes from HHS and NIH are a step in the right direction. A culture of open data is not just the most ethical approach; it also offers large potential benefits to science and society. Ultimately, the scientific community must advocate for and establish professional norms of data sharing and collaboration.

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Disclosure

Mr. Shaw is supported by the Yale School of Medicine Office of Student Research and the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under Award Number T35DK104689. The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health.

Dr. Ross reports receiving research support through Yale University from Medtronic and Johnson and Johnson to develop methods of clinical trial data sharing, from the Food and Drug Administration to develop methods for postmarket surveillance of medical devices, and from the Centers for Medicare and Medicaid Services to develop and maintain performance measures that are used for public reporting.

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ISSN 2376-6980**

American Medical Association Journal of Ethics

December 2015, Volume 17, Number 12: 1160-1165

POLICY FORUM

Research on Medical Practices and the Patient-Physician Relationship: What Can Regulators Learn from Patients?

Stephanie Alessi Kraft, JD, Kathryn Porter, JD, MPH, Benjamin S. Wilfond, MD, and the Research on Medical Practices Group

The practice of medicine is markedly improving due to increasing availability of health care data. Systems-level efforts to continually evaluate clinical practices [1] and prospective randomized studies that compare the efficacy of different medications and procedures used routinely in clinical practice provide physicians with critical information for making evidence-based treatment decisions. These activities, which we term “research on medical practices” (ROMP) [2], have the potential to improve patient care by determining which standard practices are most effective.

Physicians who engage in ROMP face a professional and ethical challenge, however. This research takes place in the context of ordinary clinical care, blurring the boundary between research and practice. A physician’s primary obligation is to act as a fiduciary toward her patients, whereas a researcher’s duty is to benefit society at large by producing generalizable knowledge. Having physicians serve both roles simultaneously is considered by some to be cause for concern due to potential conflicts of interest [3]. Yet others have argued that these two roles can be aligned, even in clinical trials, when physicians are knowledgeable about their patients’ preferences and the research protocol [4]. Indeed, when research is integrated into clinical practice, physicians might be best situated to discuss the research with their patients and to obtain consent.

One approach for physicians to take in conversations with patients about potential participation in ROMP is the “integrated consent model” [5]. This approach integrates research consent into the same model as consent for treatment: the physician and patient discuss the research, including its rationale, risks, benefits, and alternatives, and the physician documents the conversation and the patient’s decision in the patient’s medical record. The integrated consent model accomplishes two things: first, it allows patients the opportunity to discuss the proposed research and its implications with their physicians, just as they would with any clinical decision. Second, it streamlines the consent process in cases in which waiving documentation or other elements of informed consent is appropriate from both a research design and an ethical viewpoint [6].

From a patient perspective, the integrated consent model can accommodate a patient’s desire to discuss research participation with her physician. A national survey on attitudes

about ROMP [7] (the “ROMP survey”) found that three-quarters of US respondents prefer to have conversations about participating in randomized or retrospective medical record studies with their physicians rather than with researchers. These survey data are supported by findings from focus groups with patients [8], which show that patients desire and expect information about ROMP to come from their physicians. When research takes place in the setting of clinical care, patients prioritize the maintenance of the patient-physician relationship and, in fact, rely on their physicians to advise them and offer recommendations about the research—because they trust that their physicians will only propose that they participate in studies that are safe and worthwhile [8]. This trust highlights the need for physicians to be careful and deliberate about how they present the possibility of research participation to their patients.

Although the integrated consent model has not been studied in practice, these studies on patient preferences suggest that it could be a favorable approach that meets the needs of individual patients and promotes the conduct of valuable research. For example, although many patients would prefer to have their consent documented in the traditional manner of a signed form [7, 9], more than two-thirds of respondents in the ROMP survey were comfortable with using an alternate approach to a written consent form if the research could not otherwise take place [7]. By using the integrated consent model and altering the elements of consent, physicians can focus on the most critical questions that patients need to consider in making decisions [5]. Weiss and Joffe, for example, have recently proposed reframing research oversight to focus on four key topics—the purpose of the study, alternatives to participation, risks and potential benefits of the study agents, and any other risks or discomforts of participation [10]—rather than including all of the elements required for traditional research consent [11] and documentation [12]. Simplified approaches can allow physicians to engage in straightforward consent processes and more clearly convey information to patients. This could also include innovative approaches such as mobile applications and videos.

Yet the Office for Human Research Protections (OHRP) has issued draft regulatory guidance [13] that, if finalized, would prohibit the use of [nontraditional informed consent models](#) and effectively forestall the possibility of pursuing the integrated consent model. The draft guidance, which is intended to help local institutional review boards apply federal research regulations to ROMP, asserts that, if a prospective study is designed with the goal of assessing a risk, for regulatory purposes that risk is categorized as a risk *of the research itself*—even when that same risk also exists in ordinary clinical care. By categorizing the risks of the clinical treatments as research risks, the draft guidance characterizes most randomized ROMP as carrying more than minimal risk to participants; this means it cannot, under federal regulations, qualify for a [waiver](#) of written documentation of consent [12].

This characterization has serious implications for the future of ROMP. First, nearly all randomized ROMP would require documentation of informed consent in a signed, written form, thus precluding patient-friendly alternate proposals such as the integrated consent model. A second undesirable consequence of the OHRP draft guidance is that it could discourage some potential participants by making ROMP sound riskier than ordinary clinical care, which might not be accurate. Specifically, by reframing clinical uncertainty as a research risk, the draft guidance could lead those obtaining consent from patients to misattribute the source of the risk, giving patients the impression that participating in this kind of research is significantly riskier than getting their usual clinical care [2, 14]. As a result, some patients who otherwise would have been interested in participating in research might hesitate to do so. The vast majority of ROMP survey respondents, however, strongly support using ROMP to improve medical practices [7], and many focus group participants view participation in ROMP as a chance to contribute to the medical system in recognition of the medical advances from which they have personally benefited [8]. Thus, respecting patient values might mean not only obtaining patients' informed consent, but also working to ensure that patients have the opportunity to support and participate in valuable research.

The OHRP draft guidance could also reinforce the popular myth that physicians are typically confident in their treatment choices in everyday practice. In reality, there is great clinical uncertainty in many areas of medicine about which treatments are best for patients. This is precisely the reason for the national efforts to support systems-level learning and evidence-based medicine. The OHRP draft guidance, however, implies that the potential for harm associated with clinical uncertainty only exists when patients are randomized by research protocols, not in everyday practice. In the ROMP survey, nearly all respondents said that, in order to maintain their trust, it is at least moderately important that their physicians tell them when they are uncertain about which treatment is best, including more than 80 percent who said that disclosure of uncertainty is very important [7]. So, not only could the OHRP draft guidance result in physicians overstating the risks of research to patients, but it could also foster mistrust between physicians and patients. Trust and transparency in the process of informed consent are critical for the preservation of the ongoing patient-physician relationship [8]; if these two criteria are not fulfilled, there could be implications for the patient's continuing medical care that go far beyond a particular research protocol.

A growing body of literature on patient preferences about ROMP has raised questions about whether the OHRP draft guidance really protects the values that are most important to patients [15]. The studies cited here show that patients value ROMP, are sometimes willing to forgo written documentation of informed consent, and place a high value on their relationships with their physicians. These preferences should be integrated into regulatory oversight in a nuanced way that achieves the goals that are meaningful to patients and allows them a voice as stakeholders in the improvement of

medical care at the systems level. As written, the OHRP draft guidance could preclude opportunities to streamline informed consent processes in ways that fit with patients' values about research and the patient-physician relationship.

As systems-level learning increasingly informs medical practice and as new regulatory guidance goes into effect, physicians will play a critical role in overcoming challenges to the incorporation of ROMP into clinical settings. Physicians can provide a bridge between their patients and the greater medical and research communities, and they are therefore uniquely situated to guide and support their patients throughout their everyday care, in their decisions about research participation, and as potential beneficiaries of the future medical advances that ROMP can help bring about.

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The Research on Medical Practices Group at the University of Washington's Institute of Translational Health Sciences (ITHS) and the Stanford Center for Clinical and Translational Research and Education (Spectrum) were jointly established in October of 2013 to conduct empirical research as a basis for informed policy recommendations on the ethical conduct of research on medical practices and communicating with patients about such research.

Acknowledgement

This work was supported by grants from the National Center for the Advancement of Translational Sciences at the National Institutes of Health: UL1 TR000423-07S1 (University of Washington and Seattle Children's Research Institute) and UL1 TR001085 (Stanford University).

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ISSN 2376-6980**

American Medical Association Journal of Ethics

December 2015, Volume 17, Number 12: 1166-1171

HISTORY OF MEDICINE

Dying for Science: Historical Perspectives on Research Participants' Deaths

Susan E. Lederer, PhD

June 2016 will mark an important anniversary in clinical research ethics. It will be 50 years since the publication of Henry K. Beecher's "Ethics and Clinical Research" in the *New England Journal of Medicine* [1]. Reportedly the single most influential paper "ever written about experimentation involving human subjects" [2], Beecher's seven-page indictment of what one reporter dubbed research on "human guinea pigs" [3] inflamed both public and professional discussions of the ethics of human experimentation in the tumultuous 1960s [2].

Many will recall how Beecher, the Henry Isaiah Dorr Professor of Anesthesia Research at Harvard Medical School, focused in his paper on pressing ethical problems created by the enormous expansion of clinical research after the Second World War. Among the 22 troubling cases of risky experiments performed on patients without their knowledge or consent that Beecher documented was a study involving 408 "charity patients" suffering from typhoid fever. Beecher described how researchers withheld an effective treatment for the disease from 157 of the patients, resulting in 23 additional deaths [1]. In an early manuscript version of his seminal paper, Beecher harshly criticized the researchers' conduct: "These investigators, knowing full well the efficacy of chloramphenicol in the treatment of typhoid fever, evidently believed they had the right to choose martyrs for science, 23 of them" [4]. Although the published version of the paper did not include the characterization of the patients as "martyred," it's clear that Beecher felt impassioned about these unnecessary deaths.

One interesting feature of Beecher's deleted characterization was that "martyrs for science" more generally referred to researchers and physicians who died in the course of medical experimentation than it did to patients whose deaths were associated with research. In the 1920s, for example, *JAMA* published editorials on "martyrs of medicine," and its index included entries for both "heroes" and "martyrs." In the *New York Times*, deaths of researchers could be found under the heading: "science, martyrs to" [5].

Whereas investigators who sickened or died while conducting research were memorialized as heroes and martyrs, healthy subjects and patients who suffered as a result of their participation received little, if any, attention. One exception was a short-lived effort by a research advocacy group, the National Society for Medical Research (NSMR). In 1951, the NSMR established the Walter Reed Society to honor those

individuals who had risked their welfare and lives in medical research [6]. The NSMR hoped that the Reed Society, like the organization's Research Dog Hero Award created in 1946, would demonstrate both the value of medical research and the need to maintain research free from government oversight. Whereas the Dog Hero Award explicitly called for a healthy-looking specimen, the Walter Reed Society looked for articulate volunteers who exhibited their bravery and selflessness in advancing the cause of science. One of the most important qualifications for membership in the short-lived Walter Reed Society was the ability to describe the nature of individual research experiences (as the application form instructed) "in simple non-technical language." Applicants were also encouraged to "be as colorful, dramatic and specific as possible" [6]. By 1954, the Walter Reed Society boasted some 135 members who were able to attest to the value of human experimentation and the valor of volunteers. One such volunteer was Lloyd T. Koritz. As a University of Illinois medical student, Koritz participated in a variety of experiments, including being hung unconscious from a telephone pole to study the effects of electric shock on linemen and eating a pound of raw liver a day for thirty days in a study of liver metabolism [7]. When he received an award from the Walter Reed Society in 1953 for his efforts, Koritz informed reporters, "I guess it's necessary to prove to the world that research is not all just cutting up dogs as many people seem to think. New drugs may be excellent with animals, but eventually they must be tried on human beings" [7]. As Koritz's award suggests, there was some incentive to recognize enthusiastic volunteers willing to make the case for ongoing research.

What about those healthy subjects and patients who did not survive their research experiences? Before Beecher's bombshell paper, except for a handful of names, they had largely disappeared from the historical record. The few recorded names include Clara Maass, an American army contract nurse who died in 1901 in Havana in tests of yellow fever immunity, and Frank Olson, a scientist from the Army Chemical Corps who fell to his death from a New York City hotel in 1953 after receiving LSD without his knowledge as part of the CIA's MKULTRA project [8].

Other resources for learning more about such deaths include the growing collections of digitized newspapers. In the 1950s, for example, references to deaths of "human guinea pigs" appeared in the American press [9, 10]. Such deaths received very different public responses than they would have in the late twentieth century. In one case, the front pages of the *Chicago Tribune*, the *Washington Post*, and many other papers across the country informed readers that a doctor's error was responsible for the deaths of two "human guinea pigs" at the University of South Dakota Medical School [11-13]. In August of 1951, Dr. Louis F. Michalek was only two months into his residency when he mistakenly administered methadone—instead of meperidine, known under the trade name Demerol—to Jack Clifford, a 30-year-old technician, and Ardys Pearson, a 26-year-old secretary. Both Clifford and Pearson reportedly were paid 60 cents an hour for their participation in this research on sedatives. At a coroner's inquest, Michalek

explained that he had mistakenly injected the two volunteers with 100 milligrams of methadone (10 times the normal amount) in an experiment with the new drug cortisone. At a hearing into the deaths, he testified that he recognized within five minutes that something had gone terribly wrong and that he immediately telephoned his superior, pharmacologist and dean of the medical school Donald Slaughter. The coroner's jury deliberated an hour before clearing the young doctor. Because they found no evidence of "culpable or intentional negligence," he was allowed to return to his position at the hospital but removed from participation in clinical research [14]. The medical school instituted a review of all policies regarding research in the medical school, and in October of 1951, University President I.D. Weeks ordered that no investigational drugs be administered in the future to students or employees of the University [15]. Two months later, Donald Slaughter was jailed as a drug addict and removed from his post [16].

The following year, newspapers reported research deaths in Seattle and Tacoma (the hepatitis studies at McNeil Island Federal Penitentiary) [9]. In March of 1952 James S. Leedom (known as "Stan") was an 18-year-old freshman honors student at Seattle University, and one of 40 volunteers in a University of Washington study of the safety of blood storage [17]. Leedom received a transfusion of blood that had been preserved for more than three weeks and had become inadvertently contaminated with bacteria. He died three days later. In the newspaper reports about Leedom's death, two themes were repeated: the safety of the research and the absence of blame.

First, the investigators expressed their confidence in the research project. Although Robert Williams, chair of the department of medicine, and hematologist Clement Finch could not explain how the student had received contaminated blood, each informed reporters that they "would gladly participate in the same experiment tomorrow" [18]. But the response of Leedom's father was more surprising. When he was interviewed by reporters, Stanley Leedom explained that he held no one at fault in the research. "I don't blame anyone for this," he said. "I just don't want this tragedy to deter in any way from the blood donor program or these experiments" [17]. The elder Leedom was apparently as good as his word. In May of 1952—two months after his son's death—when Seattle University organized the Stan Leedom Memorial Blood Drive, the 400 young men who pledged to donate blood for the Korean conflict were reassured that the blood drive was in no way connected to the blood preservation research and that Leedom's family did not want "the unfortunate incident" of his death to interfere with it [19].

As the responses to the deaths of Jack Clifford, Ardys Pearson, and Stan Leedom suggest, there was considerable public support for the research enterprise, including recognition of the need for medical research to continue and the realization that mistakes might happen in the course of research. Just two years later, for example, millions of American parents would sign forms requesting that their children take part in

one of the largest and most publicized clinical trials ever undertaken, the Salk polio vaccine field trials of 1954 [20].

Contrast the responses to these 1950s research deaths with [those](#) that rocked the research establishment in 1999 and 2001. In 1999 Jesse Gelsinger, an 18-year-old man with a rare metabolic disorder, died in a clinical trial of gene therapy at the University of Pennsylvania [21]. Two years later, in 2001, Ellen Roche, a 24-year-old lab technician at Johns Hopkins University, died after inhaling a drug to induce a mild asthma attack in a study of natural defenses against asthma [22]. Gelsinger's death, the first recognized death from gene therapy trials, prompted suspension of similar trials, numerous public inquiries, and a lawsuit that resulted in fines for the University of Pennsylvania and the Children's National Medical Center [23, 24]. After Roche's death, the Office for Human Research Protections stopped all research at Johns Hopkins for several days until the university developed a plan that provided additional resources for institutional review of research.

In a *New England Journal of Medicine* article, the dean of the Johns Hopkins University School of Medicine, Edward D. Miller, offered a more tempered response. He acknowledged that, despite all efforts to ensure safety of research subjects and to minimize risk, the death of a research subject was always a possibility. But the alternative, he suggested, was "not to do any clinical investigation, the status quo, and still have children on ventilators, after polio" [22].

But there are other alternatives as well. One is to acknowledge the importance of human participants in research in more meaningful ways. In the decade following the death of Ellen Roche, Johns Hopkins reeled from the publicity surrounding another high-profile case involving the death of a patient and the harvesting of her cells [25]. Although historians had written about Henrietta Lacks (1920-1951) and the importance of HeLa cells in biomedical research, journalist Rebecca Skloot placed the family of Henrietta Lacks in the spotlight [26]. Skloot's book brought enormous attention to research practices involving the use of human tissues. Although Lacks was not a research participant in the usual sense, the principle of respect for research participants, according to the National Institutes of Health (NIH) director Francis S. Collins and deputy director Kathy L. Hudson, encouraged an unusual agreement with her descendants. After several discussions with the family, the NIH agreed to control access to the full HeLa sequence data and to include two members of the Lacks family on the HeLa Genome Data Access Working Group at NIH [27].

The Lacks case is unique, and such research-related deaths as those of Stan Leedom, Ardys Pearson, Jack Clifford, Ellen Roche, and Jesse Gelsinger—among others—are rare. Nonetheless, it behooves us to offer more robust public recognition of research participants whose time, experience, and potential injury are essential to biomedicine.

We don't need a Walter Reed Society to do this, nor should we wait for another tragic circumstance to make meaningful changes in how we value research participants.

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ISSN 2376-6980**

American Medical Association Journal of Ethics

December 2015, Volume 17, Number 12: 1172-1175

SECOND THOUGHTS

How Publish or Perish Promotes Inaccuracy in Science—and Journalism

Ivan Oransky, MD

The brilliant website *Kill or Cure?* is a catalog of “the *Daily Mail*’s ongoing effort to classify every inanimate object into those that cause cancer and those that prevent it” [1]. Berries prevent cancer, biscuits cause it, and beer—well, beer causes it as well as prevents it, a conclusion that may drive some to drink. And those are just the kills or cures that start with “B.”

What the hilarious website is, of course, is a sendup of what has been referred to as “single study syndrome” [2], journalists’ penchant for overstating findings from medical studies. The [weaknesses of this approach](#) can range from applying conclusions from small populations to the world at large, to bestowing cause-effect status on observed correlations, to omitting the fact that a scientific “breakthrough” happened in mice, not humans. This all adds up to what Gary Schwitzer—founder of *HealthNewsReview.org*, which has rated the content of medical reporting for nearly a decade—has called “an unhealthy steady diet of news stories” [3]. And it happens in most news outlets, not just the *Daily Mail*.

That syndrome, however, is the natural sequela of academia’s “publish or perish” reward system, aided and abetted by journals’ use of embargoes to control the flow of scientific information. Researchers love to blame journalists for this mess, but journalists often turn the tables and blame scientists for being boosterish (or opaque). And there’s some evidence that medical journal press releases aren’t helping [4]. But to really understand how we arrived at the news environment we inhabit today, it’s necessary to look more deeply at how these problems began.

You’ve Been Ingelfingered

Newspapers have long covered science, but it wasn’t until the 1920s that scientific institutions began trying to nurture more interest in the subject by using embargoes. Journalists were given access to studies and announcements before they appeared in print, so that they could digest the material, report on it, and publish simultaneously on an agreed-upon date. The *Journal of the American Medical Association (JAMA)* may have been the first medical journal to embrace this embargo system in the middle of the last century, when then-editor Morris Fishbein, MD, let Associated Press reporter Howard Blakeslee read page proofs of upcoming issues at AMA headquarters. (For more on this history, see Vincent Kiernan’s *Embargoed Science* [5].)

As the media's interest in science grew, alongside medical advances and the race to explore outer space in the 1960s, the editor of the *New England Journal of Medicine* (*NEJM*), Franz Ingelfinger, MD, became concerned that some researchers were sharing their data with the press before it had been peer-reviewed [6]. This was an understandable concern, since unringing the bell of a public frenzy for the latest professed cancer cure was nigh impossible.

So, in 1969, Ingelfinger wrote an editorial that contained what would eventually be called the Ingelfinger Rule. "The understanding is that material submitted to the *Journal* has not been offered to any book, journal or newspaper," he wrote. "If an author willingly and actively has contributed the same material to any other publication—whether as text to a standard medical journal, or as a 'letter to the editor,' or as a feature in a lay magazine—that understanding has been disregarded" [7]. Although the rule has changed somewhat over time, the Ingelfinger Rule has been reaffirmed by editors at *NEJM* and other major medical journals [8].

An unintended consequence of the Ingelfinger Rule, however, has been to make some scientists afraid of speaking with reporters lest they risk losing the opportunity to publish in top journals [9]. Even journals' attempts to clarify the Ingelfinger Rule—by explaining that typical scientific communication of unpublished findings (for example, at conferences) does not violate the rule, so long as researchers do not actively seek press attention [9]—do not completely mitigate this chilling effect. I've heard many stories about scientists presenting data in posters or talks at meetings—sometimes with immediate implications for public health or safety—only to beg reporters not to publish a story out of fear that no journals will accept their future submissions.

The fact is that publishing papers in peer-reviewed journals is about the only thing that matters to grant reviewers and tenure and promotion committees. And "publish or perish" is essentially true for journalists: when you have an editor breathing down your neck for the day's—or in this day and age, the hour's—story, you need to produce something quickly to earn those page views. [It'd be helpful](#) to pull together trends from meetings on emerging topics like new pandemics, or to pick the brains of researchers working in those areas to write a thoughtful, thoroughly reported piece that covers many aspects of a hot area, but too many scientists tend to clam up. So, instead, journalists wait for each study to be published and promoted in dozens of press releases, scan those that flood their email inboxes daily and find a nugget; then they might quickly write and publish something of suboptimal quality just to try to beat their competition. The concepts of "publish or perish," "least publishable unit," and "salami slicing" data are as real in journalism as they are in scientific publishing [10, 11].

In a nutshell, numerous incentives contribute to the dysfunctional medical science news reporting system we have today. We're left with stories and television segments that strip scientific findings of their nuance and distort the public's understanding of how science actually works.

Never Mind Ethics, Serve Your Readers

Of course, if ethical arguments don't sway researchers, journal editors, public relations staffers, and reporters, perhaps evidence that readers and viewers may not want short, simplistic news reports will. In one recent study of how readers in Taiwan view news stories about contradictory health findings, a researcher concluded that "overrepresenting findings with dramatized characteristics has negative implications not only for the target news but also for the scientific community in general" like "loss of interest or trust in science" [12]. And the authors of another study, who found that frank discussions of uncertainty in stories about research didn't undermine public trust in science, said that if their findings held up, they would "suggest that science communication should incorporate scientific uncertainties in media reports whenever it is required by the current state of research" [13].

In other words, there is no inanimate object that, purely speaking, definitely causes or prevents cancer, despite what we learn from the *Daily Mail*. (And don't dismiss the *Daily Mail* as a caricature that no one reads; it has the largest audience of any English-language newspaper website in the world [14].) Sure, I can blame fellow journalists for rushing to print—or pixel. But just as most biological phenomena aren't explained by a single factor, this is a nuanced problem. Scientists, publishers, and granting agencies need to take some responsibility, too, for creating incentives for researchers and their employers to exaggerate the significance of preliminary and isolated results. [Fixing misleading journalism](#) will, as the saying goes, take a village.

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Acknowledgment

I would like to acknowledge Alison McCook's helpful edits and the assistance of Alison Abris in preparing this manuscript.

Related in the *AMA Journal of Ethics*

[HealthNewsReview.org: Criteria for Excellence in Health and Medical Journalism](#), March 2007

[The Media Miss Key Points in Scientific Reporting](#), March 2007

[Quality Medical Reporting Depends on Media-Physician Cooperation](#), March 2007

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ISSN 2376-6980**

American Medical Association Journal of Ethics

December 2015, Volume 17, Number 12: 1176-1191

Suggested Readings and Resources

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ISSN 2376-6980**

American Medical Association Journal of Ethics

December 2015, Volume 17, Number 12: 1192-1196

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