

Comparing Drug Effectiveness at Health Plans:

THE ETHICS OF CLUSTER RANDOMIZED TRIALS

by JAMES E. SABIN, KATHLEEN MAZOR, VANESSA METERKO,
SARAH L. GOFF, AND RICHARD PLATT

“Cluster randomized trials,” in which groups of patients are randomly assigned to different therapeutic interventions, provide a powerful way of evaluating drugs. CRTs have not been widely used, in good part because of concerns about whether patients must give informed consent to participate in them. A better understanding of how CRTs fit into clinical practice resolves the concerns.

In spite of the thousands of articles published every year in medical journals, many questions remain about the best pharmaceutical treatments for common chronic conditions. In the absence of solid evidence about effectiveness, patients and clinicians base treatment decisions on an assortment of other factors—conventional wisdom, personal experience, advertisements, and cost. Partly for this reason, treatment regimens vary substantially from clinician to clinician, practice to practice, and region to region.

To make grounded recommendations about treatment regimens and to make the best use of the money we spend on health care, we need more information about how drugs compare against each

other under the conditions of actual use. New medications, however, are typically tested against placebo rather than against existing therapies, and clinical trials providing direct comparisons of two or more medications are rare. But head-to-head comparisons are crucial. For example, before the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), angiotensin-converting enzyme (ACE) inhibitors and calcium-channel blockers were widely believed to be a more effective initial therapy than thiazides for hypertension. The ALLHAT findings demonstrated that chlorthalidone, an inexpensive thiazide, was as efficacious as amlodipine, a calcium channel blocker, or lisinopril, an ACE inhibitor, for initial therapy of hypertension.¹

The ALLHAT study has had a major impact on the management of hypertension. But it also illustrates that although randomized controlled trials (RCTs) are the gold standard in clinical research, the costs in both time and resources can be prohibitive.

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The study lasted eight years and cost over \$80 million.

Conventional randomized trials often have two additional drawbacks—their results cannot be generalized to the broad population, and they do not provide information about performance under real-life conditions.² Their generalizability to the intended target population is usually not known because the subjects are typically selected from a nonrepresentative subset. Patients with comorbidities, patients taking other medications, children, the elderly, pregnant women, and many others are typically excluded from conventional randomized trials. Also, the process of obtaining informed consent can overload the study population with people to whom the study can be described readily. These individuals may be more adherent to therapy or may differ in other ways from the general population. Finally, researchers tend to locate randomized trials in settings believed to deliver high quality care, and they devote substantial resources to ensuring that the interventions are prescribed as intended and that adherence is good. Because of these factors, conventional randomized trials typically address “efficacy” (performance in subjects most likely to respond favorably under optimal treatment conditions) rather than “effectiveness” (performance under real-life conditions). A prominent clinical epidemiology textbook ends its discussion of randomized controlled trials with this comment: “Because of the high degree of selection in trials, it may require considerable faith to generalize the results of clinical trials to ordinary practice settings.”³

The research methodology of cluster randomized trials (CRTs) offers a cost-effective approach to comparing the effectiveness of commonly used drugs in representative groups of individuals. In CRTs, groups of people rather than individuals are randomized with regard to an intervention. The methodology has been widely used to evaluate the impact of public health interventions, like community

health education, and medical management strategies, like early treatment of sexually transmitted diseases to reduce HIV transmission in Africa.⁴ The size of the clusters that are randomized typically ranges from single practices to entire communities.⁵

Although cluster randomization has been applied to the study of prescription drugs—as in comparing two different forms of potassium supplements by randomizing pharmacies to dispense one or another formulation—the methodology has not been widely used for this purpose.⁶ To our knowledge, the reasons for this have not been addressed systematically. We believe several factors contribute, including the traditional focus of the clinical trial enterprise on efficacy rather than effectiveness, the lack of financial support for comparative effectiveness trials, the small number of organizations with sufficient infrastructure to facilitate such trials, and concerns about the ethics of cluster randomization and the need for individual informed consent.

In principle, CRTs could provide information about comparative effectiveness for two commonly used agents—drug A and drug B—if one cluster (which might consist of a practice, a delivery system, a health plan, a payor, a purchaser, or other entity that affects care for a group of patients) gave preference to A, while another cluster gave preference to B. CRTs could be especially advantageous if implemented in the context of health plans that have extensive information on members, treatments, and clinical outcomes, together with an existing research infrastructure.

To investigate the potential for conducting CRTs at health plans, we carried out a multisite study to canvass views about CRTs among patients, providers, purchasers, and health plan leaders. The study was conducted in the context of the HMO Research Network Center for Education and Research in Therapeutics. Eight sites participated. The HMOs associated with these sites

serve geographically and ethnically diverse populations with a broad age range and have a combined population of over six million members. This article draws on (1) research ethics literature, (2) a discussion of CRTs at the Harvard Pilgrim Health Care Ethics Advisory Group,⁷ and (3) interviews with health plan leaders, physicians, and patients. The goal is to discuss the ethical dimensions of CRTs and offer guidance to health plans, institutional review boards, clinicians, and funders who are considering this kind of research.

Here is a brief description of the form of comparative effectiveness CRT whose feasibility we investigated: A and B are widely used treatments for a common condition. While clinicians and patients may have preferences for one or the other, by Freedman’s well-known criteria a state of clinical equipoise exists with regard to A and B—in other words, “there is no consensus within the expert clinical community about the comparative merits of [A versus B].”⁸ In order to gain information about the relative effectiveness of A and B, several health plans agree to participate in a CRT. Some health plans will favor A; the others will favor B. “Favor” means that unless clinicians have specific reasons for choosing the nonpreferred agent, they will use the preferred one. The health plan databases will be used to follow patterns of side effects, medication changes, and clinical outcomes.

This intervention does not require all individuals to receive the treatment to which their group is assigned, only that the fractions treated with A and B in the two groups differ by a substantial amount. Such separation allows estimation of population-level difference in outcomes, which can inform overall treatment strategies (“in general, A and B yield similar outcomes,” or “in general, people treated with A fare better”). This form of cluster randomization does not address the question of whether the overall result is true for subsets, particularly those for whom clinicians

A CRT asks the physician to prescribe the preferred agent unless she wishes to prescribe the alternative. There is nothing in this chain of steps that is inherently different from ordinary practice. There is no “experiment.”

preferentially override the cluster randomization.

Findings from the Research Ethics Literature

In the seminal article, “What Makes Clinical Research Ethical?” Ezekiel Emanuel and colleagues identify seven requirements for ethical research involving human subjects: value, scientific validity, fair subject selection, favorable risk-benefit ratio, independent review, informed consent, and respect for subjects.⁹ The list provides a useful framework for analyzing CRTs; the domains that raise ethical issues distinctive to CRTs are scientific validity, favorable risk-benefit ratio, informed consent, and respect for subjects.

Scientific validity. Research studies that cannot reasonably be expected to produce scientifically valid results are not ethical. Even if participants are put at no risk, a study that lacks validity wastes resources that could be put to better use.

It is important to recognize that CRTs of the kind we envision test two things—the effectiveness of the therapeutic agents being compared and the mechanism used to influence prescribing. The CRT always provides useful information about the techniques used to influence prescribing. To the extent that the CRT results in a substantial difference in the proportion of individuals treated with the agents being studied, it provides information about comparative clinical effectiveness for the population as a whole. However, if many individuals receive an agent other than the one to which their group is assigned, then the CRT will provide correspondingly less information about comparative effectiveness. As long as it is reason-

able to expect that the clusters will achieve adequate differentiation in use of the agents being compared, a proposed study meets the criterion of scientific validity.

Favorable risk-benefit ratio. As described above, the form of CRT whose acceptability we were studying compares two accepted treatments for which a state of clinical equipoise exists. The fact of clinical equipoise in the expert community, combined with a design that allows individual physicians to prescribe treatment B even if their cluster gives preference to A, means that the CRT has a favorable risk-benefit ratio. If A and B are in clinical equipoise, then no general reason exists to prefer either agent over the other, and patients are not harmed by being assigned to one or the other cluster. For a particular patient, one or the other drug might still be preferable, but if prescribing physicians are free to deviate from the cluster’s general preference, then the patient is not put at risk. Assuming the use of valid research techniques, the study is likely to generate useful information. Thus, the risk-benefit ratio looks favorable.

Informed consent. Informed consent is by far the paramount concern in the ethical commentary on CRTs. In research that enrolls subjects as individuals, informed consent is seen as a *sine qua non* of ethical practice. Requiring *consent* ensures that individuals control whether they participate in a research study. Requiring that the consent be *informed* gives individuals the information they need to decide whether the research is consistent with their values, interests, and preferences.¹⁰

In what we believe to be the first extended discussion of the ethics of CRTs, Sarah Edwards and colleagues

make a fundamental distinction between consent for entry of a cluster into the CRT and consent for an individual intervention.¹¹ The first question about informed consent for CRTs is, Who can consent for entry of the cluster into the study? Edwards’s answer is:

[T]he decision about whether a particular cluster participates in the trial is taken by an agent, whom we call a guardian and who has the power to “deliver” the cluster. Examples of guardians include the chief executive of a hospital, managing partner of a primary care practice, or head teacher. . . . In deciding to volunteer the cluster for an experiment that is not routine, the guardian, as advocate, must act in the best interests of the cluster. . . . [However,] guardians, like doctors in conventional trials, have some potential conflicts of interest. . . . Consequently, safeguards, like ethics committee approval, are desirable.

Jane Hutton is more reluctant than Edwards to allow “guardians” to provide valid consent for a cluster to participate in a study.¹² After all, “guardians” consented for the Nazi experiments and the Tuskegee study. Hutton acknowledges that there is no feasible way to solicit informed consent from each member of a cluster for the cluster’s participation in a CRT unless one is prepared to allow a single dissent to block entry. Hutton points out that a cluster typically has several potential guardians, which lessens the risk of bias on the part of any one guardian, and he concludes that CRTs should not proceed unless all potential guardians consent.

Who fills the role of guardian, and how guardians function, is plainly a

pivotal issue in assuring that the CRTs do not violate the requirement for informed consent. A 2002 report from the United Kingdom's Medical Research Council provides a useful elaboration. The council concludes that there must be a "cluster representation mechanism" that consists of "an individual, body, or mechanism that can represent the interests of the cluster." Precisely what the CRM is will depend on the cluster and the intervention. "Thus, agreement to fluoridate the water supply might be obtained by plebiscite, while [general practitioners] might agree to the distribution of an information leaflet to people in their waiting rooms."¹³

The council requires that the CRM process be transparent and sensitive to the culture and values of the cluster: "The CRM must produce a formal document for the cluster that certifies and sets out its ability to [act in the interests of the cluster] (sufficient knowledge of the circumstances, beliefs, and values of members of the cluster, any delegated authority from/for the cluster, lack of conflicts of interest)." Finally, the council stresses that the CRM should be thought of in the same way we think of individual research subjects, and therefore "has essentially the same rights as a patient in an individually randomized trial—including the absolute right to withdraw the cluster, without adverse impact on the cluster, if it decided that the study was not now in the interests of the community."

In 2004, Allan Donner and Neil Klar proposed a further procedural support for making the process of consent for cluster participation transparent:

As a first step in developing a well-accepted set of ethical principles and norms for cluster randomization trials, editors could require all articles describing results to report having institutional review board approval *and to indicate how issues of participant consent were addressed.*¹⁴

In the relatively limited literature about the ethics of informed consent for CRTs, the consensus appears to be that some form of representative mechanism can be allowed to consent for entry of the cluster into a study, but the process requires careful safeguards and should be conducted in a transparent manner. With regard to the need for individual informed consent, the literature concludes that insofar as the CRT is studying an experimental agent like a new vaccine, if informed consent at the level of the individual cluster member is feasible, then it should be asked for. The literature does not, however, address CRTs of the kind we envision, in which the agents being compared are standard treatments that stand in clinical equipoise.

Respect for subjects. Emanuel suggests that the term "human subjects" "may not fully reflect appropriate respect: human research participant or partner may be more appropriate terminology."¹⁵ This almost offhand comment has tremendous ramifications for the possibility of conducting CRTs at health plans. Individual clinicians, medical groups, and health plans rarely discuss the depth of uncertainty that prevails in medicine about the clinical effectiveness of many common treatments. Conducting comparative effectiveness CRTs of the kind we envision would require explicit acknowledgement of the degree to which important areas of medical practice are not based on solid evidence. Showing respect for "human subjects" by treating them as "research partners" would appear to require that the existence of the CRT and the rationale for conducting it be made explicit within the health plan site. We regard candor about the degree to which routine medical practice is analogous to research as a positive step, but doing this in a respectful manner calls for more than a perfunctory written document.¹⁶

Findings from the Harvard Pilgrim Health Care Ethics Advisory Group

Since 1996, Harvard Pilgrim Health Care, a New England-based not-for-profit health insurance company with more than a million members, has convened a group to advise the organization about the ethical dimensions of the health insurance business. This ethics advisory group includes Harvard Pilgrim staff, consumers (that is, people with Harvard Pilgrim insurance), physicians who practice in the network, employers who offer Harvard Pilgrim insurance to employees, and leaders in health policy and ethics. On July 20, 2005, the group devoted a two-hour discussion to the form of CRT described above.¹⁷ It felt that if CRTs were conducted at the health plan, then that fact should be communicated to members and other stakeholders to inform them about the activities and the health plan's reasons for participating. Allowing research to be conducted within the plan says something about the kind of organization it is. The ethics advisory group felt that research of this kind was ethically admirable, but that individuals will have different reactions to the very idea of research. They need to know about the health plan's activities in order to make informed decisions about joining or remaining members.

With regard to the need for individual informed consent, the ethics advisory group differed sharply from the ethics literature. Several group participants felt that as long as evidence did not show one drug to be superior to the other, then conducting a CRT without seeking consent from potential members of the cluster was, in principle, acceptable. These participants felt that, as long as (a) physicians retained authority to prescribe as they wished and (b) patients were not penalized for using the non-preferred drug, then (c) the potential gain in knowledge justified use of the CRT methodology.

The ethics advisory group felt strongly that patients have a right to know that a CRT is being conducted if giving that information would properly be part of clinical communication. If drug A is the cluster's preferred drug and would have been the physician's recommendation anyway, then discussing the CRT would be unnecessary, as it would not have any bearing on his advice. But if in the absence of a CRT the physician would have been equally likely to prescribe A or B, then informing that patient about the CRT as a factor in the

in which actors portrayed a physician and patient discussing initiating medication for either depression or hypertension in the context of a CRT. After playing the vignette, she posed a series of open-ended questions. Fifty interviews were conducted, recorded, transcribed, coded, and analyzed in a qualitative manner.

Here is the key portion of the vignette from the hypertension example played for the patient-interviewees. The physician has just recommended BPdown, an antihypertensive agent:

the others. So our first choice medication for treating high blood pressure is going to be BPdown. Of course, if BPdown is not appropriate for a particular patient, we'll use an alternative. Several other clinics around the country are also in this study; in some places doctors will recommend BPdown; in others they'll recommend a different drug.

Patient: Are the drug companies behind this? Is that what this is about?

Surprisingly few interviewees appeared to grasp the idea that there might be no evidence-based reason for seeing one agent as more effective than the other. For many patients, the very idea of equipoise was implausible and disturbing.

recommendation would be warranted. The ethics advisory group recognized that in actual clinical practice, many influences are not reported. Physicians rarely say, "My last patient was helped by A," "I am persuaded by the advertising," or "I heard about drug A and am curious to try it." But if a health plan wants to cultivate trust among its stakeholders, then information about a CRT conducted within its network should be readily available to its members.

Findings from Interviews with Health Plan Stakeholders

Patients. Lists of adult health plan members from two of the participating health plans were randomly sampled to create mailing lists of invitees who were sent letters of invitation, describing the purpose of the study, and offering an incentive of twenty dollars. Those who were interested called and scheduled an interview. All interviews were conducted via telephone by a trained interviewer who introduced herself, reiterated the purpose of the interview, and confirmed their consent to participate. She then played a three-minute audio vignette

Patient: Are there any other choices?

Doctor: There are other medications we could try. But right now we don't know that any of the other drugs are any better. Our clinic is participating in a research study to find out which of the medications is most effective. As part of the study, BPdown will be more affordable. Instead of the forty dollar copayment you'd normally have to pay, it'll only be ten dollars. So it's a substantial discount.

Patient: Wait a minute. Are you saying you're giving me this medication as part of a study?

Doctor: Yes and no. We are involved in a study. But it's not a typical clinical trial. For one thing, we already know that all the medications being studied are effective. They've all been on the market for quite a while, they're all safe, and they're all widely used to treat high blood pressure. We know they're all effective, but we don't know whether one is *more* effective than

Doctor: No, this is not a drug company study. Drug companies don't usually do this type of study because they don't want to find out that their drug is *less* effective than the competition's. But the government—specifically the Agency for Healthcare Research and Quality, which is sponsoring this study—does want to find out which drugs work best. They also want to know if two drugs work equally well—that's especially important if one of them costs a lot less.

Patient: OK. Let me make sure I understand. You think I need to start on medication for my blood pressure. You're recommending BPdown because that's what you're supposed to do as a part of this study.

Doctor: Right—and because I think it's an appropriate choice for you. I don't think there's some other drug that would be better—in terms of effectiveness or side effects. There may be another drug that's as good, but I don't think there's one that's better.

The fact that BPdown and its alternative are in clinical equipoise is the core reason for proposing the hypothetical CRT. Surprisingly few interviewees, however, appeared to grasp the idea that there might be no evidence-based reason for seeing one agent as more effective than the other. For many patients, the very idea of equipoise was implausible and disturbing. To these interviewees, the suggestion that to the best of our knowledge, the alternatives being studied were equivalent and no evidence-based reason existed to recommend one over the other simply did not make sense:

I think that they hopefully would have enough information to tell them what is the most effective drug. If one is just as effective as another, then I would think they would know the side effects. . . . Maybe one might have more troublesome or uncomfortable side effects and they would then prescribe the one that is equally effective but with less side effects.

Even though the doctor tells the patient, “I think it’s an appropriate choice for you. . . . I don’t think there’s some other drug that would be better—in terms of effectiveness or side effects,” the idea of research made many patients wary. One asked, “Why would I give up the opportunity to [take] the best drug?” Another described how the idea of a “study” created insecurity:

When they do studies it is a trial and error and when you say “study” it doesn’t seem like it has been tested before on somebody else and that it’s 100 percent or 99.5 percent safe. “Study” kind of makes me think it’s like well if anything is going to happen it is going to happen to me!

Among the small number of patients who clearly understood equipoise, some agreed with the Harvard Pilgrim ethics advisory group that individual informed consent was not required:

I think companies should test the effectiveness of their product from time to time and however they choose to do that is up to them. . . . I think it would have been perfectly ethical whether they chose to tell the patient or not as long as it is the best choice or one of the best choices. If there are other equally good choices and this was the one that they chose to give you because it was a trial, then that’s fine. I really have had no problems with it at all.

Others responded in accord with Emanuel’s assertion that respect for subjects is a key dimension of ethical research. For these patients, even though the hypothetical CRT described in the vignette did not—in their view—require formal informed consent, respect required that patients in the cluster be told that a study was occurring:

I don’t know why anybody would say no. It’s in their best interest. I’m not sure why they would care, but it is good to know and you should be asked. Just like you asked me to participate in this. You didn’t just call me up one day and start asking questions.

In the same vein, another patient commented, “[Being told about the study] would be a common courtesy, but it [formal informed consent] didn’t seem like a huge issue to me.”

Physicians. We also interviewed nineteen physicians and two physicians’ assistants from the eight participating health plans. (For simplicity, we will refer to this group as “physicians.”) Before the interviews, they listened to the same vignettes that were given to the patients. Unlike the patients, essentially all of the physicians understood the concept of equipoise. Many were enthusiastic about the prospect of head-to-head comparisons:

It’s about time we did studies where we compare two drugs. This has been a problem for a long time

so I love the fact that it is being addressed . . . I think most primary care physicians would understand the need for this kind of work and be a little bit excited about it. . . . Hopefully, if you phrase this right [with patients] you actually increase collaboration in terms of seeking better solutions, better knowledge, better eventual therapeutics. So if you can get them involved they will probably be pretty excited. I think most patients like to think they are in a cutting-edge organization that is actually trying to understand things and get more information for everybody, so I think overall most people would probably think of this as a positive.

Because the agents being studied were in equipoise and physicians were free to prescribe in accord with their convictions, most physicians did not see a need for individual informed consent. Some, however, felt that the term “research” automatically required individual informed consent:

The rules on these things tend to be so stiff that I would be surprised if [informed consent] weren’t required. . . . Every time I have ever touched anything with research I have had to document out the yin yang. . . . It is a real pain, but that’s just the rules that you have to play with.

To other physicians, the CRT seemed so close to the conditions of ordinary practice that informed consent was not required in ways that were not part of ordinary practice:

If there was a drug that is widely used and the patient agrees, it is almost like you prescribed any other agent. . . . I wouldn’t agree that that would require specific consent.

If you are using a drug that has been FDA approved with testing, that is indicated for the condition . . . I don’t think you would have to

Acknowledging uncertainty can undermine patients' confidence—"why doesn't my doctor know what pill is best?" But hiding the uncertainty—giving a false impression that we know what is best—is paternalistic and disrespectful.

get informed consent . . . because it is a drug that we use anyway.

Health plan leaders. Finally, we interviewed thirty-four leaders (medical directors, pharmacy directors, IRB chairs, and compliance officers) from the eight participating health plans. For these interviews, we used modified versions of the vignettes used for patients and physicians.

With regard to the need to obtain written informed consent, a majority of the health plan leaders, including five of the seven IRB chairs, thought that if the drugs being compared were standard treatments in a state of equipoise and if physicians could deviate from the preferred option, then individual informed consent would not be needed. One commented that informed consent would not be required for a CRT any more than it would be when a clinical guideline was implemented. Another observed:

If there is no evidence-based reason for starting someone on one agent versus another then it comes down to preference or custom. I do not see a call for each person to sign an informed consent because they are not taking experimental medication and the care process isn't being distorted in ways that it is not distorted by ordinarily. I do feel strongly that it would be important that the fact of the study and the rationale behind it and what its components were should be readily available to present to the patients and to the patient group as a whole.

The health plan leaders expressed three major concerns. First, since CRTs would pose significant logistical challenges, the scientific validity (Emanuel's first dimension) must be impeccable to justify the required ef-

fort. The study drugs must be in equipoise, outcome measures must be sound and appropriate, the study must be scientific and objective, there must be a real absence of data, and the study must be able to answer an important clinical question. Second, even though the leaders endorsed the goals of the CRT, the process itself is new. They felt it would be important to educate all stakeholders, including patients, physicians, health plan leaders, IRB committees, and the public. In this spirit, one commented:

We make decisions now in rather odd ways. . . . This approach [could be] the counterbalance for that and so if people can begin to sort of look behind the curtain and see that this is really needed. . . . It's an educational challenge for the community to understand why this approach is warranted or is important.

Finally, in the context of the competitive U.S. health care system, the health plan leaders worried that prospective members might be turned off by the idea that a health plan participates in research and choose not to enroll.

Medical Uncertainty and Patients' Needs

Cluster randomized trials of comparative drug effectiveness could provide valuable information. Since health plans routinely collect information for claims payment and other managerial activities, they offer a promising site for conducting studies of this kind. For CRTs to be acceptable at health plans, multiple logistical challenges would have to be solved. But apart from logistics, the question of ethical acceptability looms large.

We conducted this ethical analysis as part of our exploration of the feasibility of carrying out CRTs at health plans. Our analysis is grounded in three sources. First, we reviewed pertinent articles in the research ethics literature. Second, since one of the participating health plans has an ethics committee, we consulted with that body. Finally, we drew on research interviews conducted with health plan patients, physicians practicing in the health plan networks, and health plan staff. We have organized our analysis and the guidance we offer to health plans, IRBs, and other stakeholders into three categories.

Who can consent for entry of a cluster into a study? We agree with the Medical Research Council that a cluster representation mechanism can legitimately provide consent for entry of a cluster into a CRT, and with Hutton that a CRM should include multiple perspectives. A robust CRM process would require consideration of the views of patients and physicians who are part of the cluster, the employers and public agencies that purchase insurance for health plan members, and the health plan itself. The IRB would have responsibility for assessing whether there is a true state of equipoise for the drugs whose effectiveness is being compared, whether the study is structured in a way that will produce useful, scientifically valid findings, and whether the CRM has adequately considered the best interests of the cluster.

CRTs of the kind we envision can supply evidence about comparative effectiveness that we currently lack. This kind of evidence is crucial for wise allocation of health care resources. Because comparative effectiveness is often unknown, cost-effectiveness judgments frequently boil down to cost alone. For resource allo-

cation decisions to be fair and legitimate, they must be open and publicly available, with a clearly articulated rationale, input from all stakeholders, and the opportunity to revise policies as new experience emerges.¹⁸ Health plans and other organizations participating in CRTs should be held to these same expectations with regard to the decision to participate in CRTs.

Is individual informed consent required from patients in the cluster?

We believe that individual informed consent with regard to the medications whose effectiveness is being compared is not required. In the studies we envision, agents A and B are widely used standard treatments in a state of equipoise. If a physician believes that the nonpreferred agent is indicated, she can prescribe it, and if a patient wants the nonpreferred agent, she can receive it. Practicing physicians are familiar with the state of “internal equipoise,” in which they would be equally comfortable recommending one agent or another. A CRT simply asks the physician to prescribe the preferred agent unless she wishes to prescribe the alternative. There is nothing in this chain of steps that is inherently different from ordinary practice. With regard to the prescribing of A or B, there is no “experiment” being done and nothing requiring informed consent beyond what is ordinarily required in clinical practice.

For some physicians and health plan leaders, the word “research” elicited a reflexive reaction that individual informed consent must be sought. Insofar as this reaction is a reflex and not based on deliberation, it reflects the double standard with regard to research and clinical practice that Iain Chalmers and William A. Silverman described twenty years ago, when they delineated the ways in which much ordinary medical practice should be seen as nonsystematic research. When physicians prescribe treatments whose effectiveness is not known they are, in effect, doing an experiment. Chalmers and

Silverman quote Claude Bernard, who wrote in 1865 that “physicians make therapeutic experiments daily on their patients . . . [M]edicine by its nature is an experimental science, but it must apply the experimental method systematically.”¹⁹ Comparative effectiveness CRTs place the “daily experiments” of medical practice into a framework that can, over time, provide systematic knowledge.

We do not believe these CRTs’ influence on physicians’ prescriptions requires patients’ individual informed consent any more than if the physician chose a drug because a colleague had just spoken enthusiastically about it or because her last patient had benefited from it. We do, however, see the fact that a cluster is participating in a CRT as creating a higher-level choice for patients to make. Teaching hospitals publicize the fact that patients will be seen by students and house staff. They quite reasonably argue that teaching can contribute to overall improvements in quality of care. But some patients may not want to be seen by students, and by publicizing the fact of teaching, the teaching hospital makes it possible for those patients to choose to receive their care elsewhere.

Similarly, we believe that health plans that participate in CRTs should make that fact known to those who belong to the plan, or might join, and to the employers and public agencies that purchase insurance for health plan members. This would allow a prospective or current member of a health plan or practice to decide either “this isn’t for me—I don’t like the idea of research” or “that is a plan I want to be part of.” (Although employees often have no choice with regard to health plans, plans are sensitive to public criticism, and dissatisfaction about participation in CRTs would likely have an impact.) We think that providing the opportunity to make this choice, however, comes under the heading of “respect,” not “informed consent.” Once patients enter a teaching hospital, they are not asked for informed consent to allow

students or house staff to examine them. Similarly, patients insured through a health plan that allows CRTs of the kind we envision to be done would be asked for informed consent only with regard to clinical interventions, not with regard to participation in research.

What does respect for participants in the CRT entail? What does it mean for a health plan—the focus of our study—to treat members who participate in a CRT with respect? At the very least, respect will involve truthfulness and disclosure of activities that could be important to a “reasonable person.” Participation in research is not a typical health plan activity. Just as teaching hospitals are expected to make clear that they are replete with students and to explain why this is so and what it might mean to patients, we believe that health plans should do the same with regard to participation in research.

In a deeper sense, a health plan manifests respect for participants in a CRT by seeking to understand and respond to their values and concerns. Recall that few of the patients we interviewed understood the concept of equipoise even after listening to the vignette. We believe their difficulty reflects an emotional need, not an intellectual deficit, that the late Franz Ingelfinger, editor of the *New England Journal of Medicine* from 1967 to 1977, discussed almost thirty years ago after reflecting on his own experience as a patient. Ingelfinger, a world expert on cancer of the esophagus, contracted the disease himself. Colleagues, recognizing his expertise, offered data about alternatives and demonstrated, by their differing opinions about what to do, the lack of certainty in the field and the fact of equipoise within the expert community. Ingelfinger and his family “became increasingly confused and emotionally distraught” until a “wise physician friend said, ‘what you need is a doctor.’” Here is how Ingelfinger explicated the “doctor” function he felt he needed:

[I]f we assume that physicians do make patients feel better most of the time, it is chiefly because the physician can reassure the patient or give medication that is mildly palliative. . . . If the physician is to be effective in alleviating the patient's complaints by such intangible means, it follows that the patient has to believe in the physician, that he has confidence in his advice and reassurance, and in his selection of a pill that is helpful. . . . [I]ntrinsic to such a belief is the patient's conviction that his physician not only can be trusted but also has some special knowledge that the patient does not possess. . . . a physician whom he invests with authoritative experience and competence.²⁰

nalistic and disrespectful. We believe that physicians can learn to acknowledge uncertainty and at the same time engender the confidence and security in their relationships with patients that Ingelfinger called for. Similarly, we believe that health plans can learn to explain the purpose of CRTs to members in ways that will increase trust. But this will involve new learning for physicians, patients, and health plans. Acknowledging the fact of uncertainty in medical science and inviting health plan members to join with physicians and researchers in allowing everyday practice to create new knowledge shows respect for their capacity to understand basic truths and for their willingness to use routine treatment to contribute to long-term extension of medical

however, respect for patients who would be part of a cluster requires educative discussion. CRTs do not change the dynamics of physician prescribing in ways that require individual informed consent, but the fact of the CRT and the rationale for participating in it should be shared. This change in medical culture will not be easy to achieve, but the potential payoff—for patients, physicians, and the public—warrants the effort.

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CRTs' influence on prescriptions does not require patients' informed consent any more than if the physician chose a drug because a colleague had just spoken enthusiastically about it or because her last patient had benefited from it.

On the surface, CRTs of the kind we envision fly in the face of the idealized view that Ingelfinger describes and that many—perhaps most—patients want to have of their physicians. As Chalmers and Silverman comment, “traditionally, doctors have felt obliged to give the impression that they know what is best for those who come asking for relief and cures.” Acknowledging equipoise means acknowledging lack of certainty. This has the potential to undermine patients' confidence in their physicians—“Why doesn't my doctor know what pill is best?” Or perhaps more likely, the idea of a CRT could be interpreted as a ruse on the part of the health plan to cut costs—“They must have something up their sleeve because all health plans care about is saving money!”

But hiding the fact of uncertainty and giving a false impression that we *know* what is best when, in fact, the alternatives are in equipoise is pater-

knowledge. For patients, physicians, and health plans to collaborate in this way would reflect a commitment to the collective good of improving quality and value in our health care system.

On the basis of research ethics literature, consultation with a health plan ethics committee, interviews with patients, physicians, and health plan leaders, and our own ethical deliberation, we conclude that CRTs of comparative drug effectiveness of the kind we envision could be conducted at health plans without requiring individual informed consent. Participating in a CRT, however, involves open recognition of medical uncertainty in ways that are often not acknowledged by physicians or understood by patients. We believe that using everyday medical practice as a source of systematic information on treatment effectiveness would be a salutary change in the culture of medical care. Because it is a change,

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