



## Open Label Extension Studies & the Ethical Design of Clinical Trials

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## Open Label Extension Studies & the Ethical Design of Clinical Trials

BY DAVID CASARETT, JASON KARLAWISH, PAMELA SANKAR, KAREN B. HIRSCHMAN, AND DAVID A. ASCH

Recent interest in the protection of human subjects in research has produced renewed concerns about improper inducements to prospective participants,<sup>1-4</sup> including whether free medications provided to research subjects in open label extension trials may be inappropriate.<sup>5</sup> If the value of the free medication in extension studies—continuations of pharmaceutical clinical trials in which subjects receive free medication and continue to provide data about efficacy and adverse events—is substantial, investigators may create ethical concerns not only for the extension study, but also for the "parent" study to which it is linked. For instance, subjects who would not otherwise enroll in the parent trial might be induced to do so by the promise of free medication during the later extension study.<sup>6</sup> If this is the case, institutional review boards, which are charged with minimizing the potential for coercion of vulnerable subjects (45 CFR 46.111(b)), should carefully examine the ethics of such studies.

Extension studies offer two legitimate benefits against which IRBs could balance these concerns. When an activity is designed to produce generalizable knowledge, subjects who have given their time and accepted the risks of research should benefit from that knowledge.<sup>7</sup> An extension study can ensure that sub-

jects benefit from the parent study's results, by allowing them to continue receiving a therapy that has proven effective. But at the conclusion of a trial, subjects may not have access to the investigational drug if it is too expensive, or if it is not available through their insurance formulary. In addition, if the medication has not yet received approval for clinical use, subjects will not generally have access to it at any price. In all of these situations, then, an extension study can help to ensure that the subjects in the trial benefit from the results of the parent study.

Subjects might also benefit from an extension study if it ameliorates some of the risks of the parent study. This might be the case if a change from the study medication to another medication at the conclusion of the study requires dose adjustment and titration, which leads to sub-optimal treatment for a period of time. If an extension trial provides continued access to a study medication, these risks of adjustment and titration may be substantially reduced. This would suggest not only that extension studies are appropriate, but also that in some situations subjects should be able to enter an extension trial without intervening delays.

But are these risks and benefits significant to research subjects? The answer to this question is important because if subjects view a medication's availability after a trial as a way to benefit from the knowledge to be gained or as a way to reduce the parent trial's risks, IRBs should

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be disposed to look more favorably on trials that offer an extension study. To evaluate these possibilities, we conducted interviews with chronic pain patients as part of a larger study to define potential subjects' perceptions of research risks and benefits.<sup>8</sup> In this paper, we describe the results of these interviews, which suggest that subjects do in fact view a medication's post-study availability in both of these ways. We conclude by identifying ways in which these results might be incorporated into IRBs' review of extension studies.

## Methods

This study was conducted at the anesthesia pain clinic of an urban tertiary care medical center. Patients were identified by hand searching the records of all patients seen at the clinic over one month with the approval of the treating physician. During this period, 86 patients were identified who met four inclusion criteria: (1) were current clinic patients; (2) were taking scheduled opioids; (3) had a current telephone number; and (4) had experienced pain for at least six months.<sup>9</sup> Criteria 2 and 4 ensured that the patients sampled had suffered moderate to severe pain for sufficient time to gain insight about the impact that pain has had on them, and to consider ways in which changes in medication might affect them. All charts were reviewed and patients' average pain over the past week was recorded, along with clinical and demographic data. Patients were contacted by telephone. After each gave verbal consent and agreed to have the interview tape recorded, a research assistant scheduled a telephone interview.

Each patient was presented with four brief (3-4 sentences) fixed information vignettes describing studies in which new medications would be evaluated (figure 1). These studies, which were reviewed by a panel of investigators familiar with clinical pain research, were adapted from published studies and included: (1) an open label study of a long-acting opioid preparation;<sup>10,11</sup> (2) an open label

### Figure 1: Sample vignette describing a placebo-controlled trial

*I'd like you to consider a study designed to test whether a new long-acting drug works for pain. If you enroll in this study, you would stop taking your [opioid]. Instead, you would receive either this new long-acting medication that you would take once a day, or a placebo, which is a sugar pill that will have no direct medical effect. Whichever you received, you would still be able to take all of the "as needed" or "breakthrough" medications that you take now for additional pain.*

study of a nonopioid adjuvant pain medication;<sup>12,13</sup> (3) a crossover trial comparing two opioids in clinical use;<sup>14</sup> and (4) a randomized placebo-controlled trial of a sustained-release opioid preparation.<sup>15</sup> None of these studies was described as having an open label extension. They were chosen because they represent a broad range of clinical studies in which medications are evaluated.

For each vignette, subjects were asked to describe the risks that such studies might pose, and the ways in which they might benefit from participating. All responses were transcribed verbatim and read by the two primary coders (DC and KH). Next, codes were developed by the investigators to describe the risks and benefits that patients reported. NUDIST software was used for all qualitative data analysis. Codes to describe each risk or benefit were worded as broadly as possible while still retaining their intended meaning.<sup>16,17</sup> When all interviews were complete, the transcripts were reviewed and coded independently by the two primary coders. Disagreements between the coders were resolved by consensus among the investigators.

## Subject Characteristics

Of 86 patients identified, interviews were completed with 40 (46%). For three patients, the interview was interrupted and could not be rescheduled. The remaining patients either could not be reached by telephone (n=25) or declined to participate (n=18). Most patients did not give a reason for refusal, but of those who did, the commonest were

time commitments (n=4) or pain severity (n=3). The subjects who were interviewed were similar to patients who were not in terms of age (mean 47 vs. 49), gender (male: 40% vs. 50%), and average pain during the preceding week (mean 6.5 vs. 6.4 on a 0-10 numeric rating scale). Subjects represent a diverse mix that is typical of the population of patients followed in this pain clinic. (Demographic and clinical characteristics are summarized in Table 1.)

## Results

Of the subjects interviewed, 32 (80%) spontaneously reported that the availability of the study medication after the trial was over would be an important factor in deciding to enroll in any of the studies described. In discussing the importance of post-study availability, subjects cited two factors: the benefits of the knowledge generated by the parent study, and the risks of changing medications at the study's conclusion.

**Benefits of Knowledge.** Most subjects said that they would want the option of continuing to take the study medication if it proved to be effective (n=22, 55%). For instance, one subject said "Hypothetically, if the medication did work . . . after the study is over, I would like to have access to it." Another subject said, "[I]f it decreases the pain, of course I would continue to take it, if it was available."

These subjects were concerned that they might have trouble gaining access to the medication after the trial was over. One asked: "Are you able to have a prescription written for this

**Table 1: Characteristics of subjects**

Age (mean; range)	47	30-86
	N	%
<b>Sex:</b>		
Male	16	40.0
<b>Marital Status:</b>		
Married	22	55.0
Single/Divorced/Separated	18	45.0
<b>Ethnicity:</b>		
White	34	85.0
Black/Other	6	15.0
<b>Annual Household Income:</b>		
< \$15,000	18	45
\$15,001 - \$30,000	4	10
\$30,001 - \$50,000	6	15
> \$50,000	12	30
<b>Education Level:</b>		
< 12 years	3	8
12 years	6	15
12 - 15 years	15	38
16 years	9	22
> 16 years	7	18
<b>Employment:</b>		
Unemployed	31	78
Full-time	3	8
Part-time	6	15
<b>Cause of Pain:</b>		
Degenerative Joint Disease	19	48
Fibromyalgia/Myofascial	7	18
Visceral/Abdominal	3	8
Neuropathic/Nerve damage	11	28
Current pain	6.3 (2.0)	0 - 10
Average pain	6.5 (1.7)	3 - 10

medication if it ends up working better than the other medication going into the study?" Another asked, "Would my medical coverage cover it, this medication? If I'm prescribed that [medication] . . . would my medical coverage cover it so that I can get it?" Another said, "I think I'd like to know if I feel benefits from it, is there a possibility I could continue that treatment?" In all of these statements, subjects referred not to the direct benefits of the medication during the par-

ent trial, but rather to the potential benefits of continuing to receive a medication that proved to be effective.

**Reducing Risks.** These subjects also volunteered that changes of medication, including changes at the conclusion of a study, created a significant risk (n=25, 62%). Specifically, they were concerned that any change of medication might result in increased pain or new side effects. As one subject said, "You're taking a chance by changing medicines."

Even when they would be returning to a medication that they had used in the past, subjects were concerned that the process of adjustment and dose titration would result in increased pain. One subject explained, "When you are switched onto another medication or off it, it does take a while for your body to adjust to it, and you do have a bad time of it." Another said, "When you adjust doses, that sometimes can be time consuming, and in the meantime you don't want to be left in pain."

Another subject explained, "Some people don't seem to have many problems with changing medication, but I personally do, physically. My system gets very easily traumatized." All of these individuals expressed concerns about changes in medication at the conclusion of a trial that would be ameliorated by continued availability of the study medication.

## Enhancing Research Design

Open label extension studies offer patients in clinical trials the opportunity to obtain medications free of charge in exchange for participating in the parent trial, to which the extension study is linked. Although some ethicists are concerned that these trials may create an inappropriate inducement to participate in the parent study,<sup>18</sup> our data suggest that there are reasons to look more favorably on, and perhaps to require, open label extension studies. Put somewhat differently, these data expand the range of normative judgments about open label studies. Whereas the discussion to date has considered these studies to be either improper or neutral, our data suggest that they may also be desirable, and occasionally essential.

We are not suggesting that judgments about the ethical acceptability of open label extension studies can be derived directly from the subjects' preferences that we report here. Investigators are not required to provide an open label extension study simply because it would reduce risks, or provide benefits, that are important to subjects. Although subjects' preferences should be taken seriously, and do produce normative judgments about trial designs, they do so by following a less direct route.

Accepted guides for ethical research require that investigators and IRBs balance a study's risks and benefits (45 CFR 46.111(a)(2)),<sup>19</sup> and minimize a study's risks, whenever possible (45 CFR 46.111(a)(1)).<sup>20</sup> These obligations are based in turn on more fundamental principles of beneficence and nonmaleficence.<sup>21</sup> With these obligations and the principles that underlie them as a starting point, data that illuminate subjects' preferences can help investigators and IRBs to further define and evaluate research risks and benefits. The data from our study are valuable because they provide a patient-centered specification of these general obligations and principles. In our study, patient-generated judgments offer a fuller understanding of issues in trial design that could lead both to better designed trials and to

greater patient enrollment.

**Minimizing Risk.** These data about subjects' perceptions of risks and benefits suggest that extension studies may be justified if they minimize risks and maximize benefits in either of two ways. First, extension studies may be appropriate when changes in medication pose a risk to patients. This risk may be clearest in studies of therapies for pain and symptom management, in which alterations in medication and dose are often immediately apparent to subjects and may be a significant concern. For studies involving illnesses or conditions in which this is the case, IRBs and investigators should consider whether an extension study would reduce these risks.

In this respect, an open label study would be particularly important for parent studies in which all subjects receive the investigational medication. In that case, all subjects face the risks of increased symptoms or the chance of disease relapse during the post-study titration, and an open label study would reduce these risks for all participants. In a trial with a control arm that includes either a placebo or active therapy, an extension study would reduce these post-study titration risks only for those subjects who were assigned to the investigational medication arm. Nevertheless, if these risks are significant, an extension study that ameliorates these risks for some subjects may be justified.

**Maximizing Benefits.** Second, extension studies may be appropriate if they contribute to the likelihood that the subjects in the parent trial will benefit from the knowledge to be gained. This kind of benefit is distinct from the potential benefits offered by the medication itself in the parent trial. Instead, it refers to the likelihood that the knowledge gained in the study would improve subjects' care at some point in the future. Whether subjects can expect to benefit from a study's results has been proposed as a critical ethical test of any activity designed to produce generalizable knowledge and as a test that may be used to determine the level of regulatory review that is required.<sup>22</sup> Our

data suggest that patients may share this expectation. An extension study might be appropriate if a medication has proven to be effective in the parent trial, but has not yet received approval from the Food and Drug Administration. In this case, subjects in the parent trial will benefit from the parent study's results in the near future only if they have access to the medication that is being evaluated. Ideally, from the subject's perspective, the extension study should continue until the medication becomes clinically available, or until alternative arrangements can be made to receive the drug, such as through a compassionate use protocol.

Of course, the results of the parent trial are generally not available when a subject completes the trial. Thus it is important that the aggregate results of the parent trial be made available to subjects within a reasonable period of time. When a study's design (e.g., a crossover study of two or more therapies) permits subjects and investigators to assess a therapy's efficacy for each subject much more quickly, these individual results, at least, should be made available to enable subjects to make a more informed choice about continuing to take the medication in an extension study.

**IRB Review.** An extension study may enhance the ethical appropriateness of a parent trial by decreasing the parent trial's risks, by increasing the likelihood that subjects will benefit from the parent study's results, or both. IRBs should weigh these factors against the danger that an extension study may create an improper inducement for prospective subjects who are considering enrolling in the parent trial. To assess the ability of an extension study to ameliorate parent study risks, IRBs should consider subjects' access to the study medication after the parent trial. They should also consider the time that would be required to titrate to an effective dose of a new medication if the study medication is not available, and the harm that might be incurred during titration.

And IRBs should consider whether an open label study will provide subjects in the parent trial with access to

a medication that has been demonstrated to be effective. Specifically, IRBs should determine whether subjects will benefit from the results of the parent study, and whether an open label study will increase the likelihood that subjects in the parent study will benefit from that study's results. Finally, IRBs should review an extension study on its own merits. That is, IRBs should determine that an extension study's risks are reasonable in relation to its potential benefits, and to the importance of the knowledge to be gained (45 CFR 46.111(a)(2)). In some situations, the addition of an extension trial may significantly change the ethical assessment of a parent trial, and may make a valuable contribution to the ethical design of clinical research.

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## ANNOTATIONS

**Moreno, Jonathan.** "Goodbye to All That: The End of Moderate Protectionism in Human Subjects Research." *Hastings Center Report* 31, no. 3 (2001): 9-17. • Moreno argues that we are entering a new era of "strong protectionism" in human research. Among the elements of this new protectionism are third-party monitoring of the consent process and study procedures, required disclosure of conflicts of interest, independent review of subjects' decisionmaking capacity, and new requirements for educating investigators about research ethics and regulation. He traces the history of modern measures to protect subjects from its beginnings in the "weak protectionism" of the early 20th century, through the revelations of the Nuremberg trial and the Willowbrook and Jewish Chronic Disease Hospital studies, to debates in the 1960s arguing that investigator discretion best protected subjects. The rise of bioethics in the late 1960s and the disclosure of the Tuskegee Syphilis Study, he argues, "demolished" public confidence in allowing scientists to take sole responsibility for protecting subjects, and ushered in "moderate protectionism," with explicit federal regulation and mandated IRB review of protocols. He concludes on a cautionary note: in rejecting investigator

discretion strong protectionism might, in the end, undermine clinical researchers' sense of personal moral responsibility in conducting trials. And what we do not want is a clinical research enterprise that focuses narrowly on science and leaves the task of protecting subjects to others.

**Weijer, Charles, and James A.**

**Anderson.** "The Ethics Wars: Disputes over International Research." *Hastings Center Report* 31, no. 3 (2001): 18-20. • Weijer and Anderson address debates over the use of placebo-controlled trial designs and adopted or proposed changes in standards governing international research. They note that the Declaration of Helsinki adopted in October 2000 resolves many of the conceptual confusions of its predecessors, but still leaves important questions open to interpretation. Notably, Principle 29, which mandates that new therapies be tested against the "best current prophylactic, diagnostic, and therapeutic methods," in itself does not tell us what should count as the "best current" method—the standard of care in the developed world, or the care actually otherwise available to prospective subjects in developing countries? On their view, proposed revisions to the Council of International Organizations of Medical

Sciences's International Ethical Guidelines for Biomedical Research Involving Human Subjects do little to enlighten. The CIOMS guidelines, designed as commentary on the Declaration of Helsinki, in fact seem to conflict with it on the question of placebo control. The proposed language of Guideline 7, they argue, explicitly rejects the requirement of clinical equipoise written into the new Declaration of Helsinki.

**Mastroianni, Anna, and Jeffrey Kahn.** "Swinging on the Pendulum: Shifting Views of Justice in Human Subjects Research." *Hastings Center Report* 31, no. 3 (2001): 21-28. • Mastroianni and Kahn argue that over the past decade the application of the principle of justice in research ethics has undergone a radical shift, with important implications for subject protection. In the wake of the Belmont Report, they contend, justice was seen to require preventing the exploitation of vulnerable subjects, and was implemented in the form of additional regulatory protections for identified groups. With growing public belief that clinical research offered real benefits to subjects themselves, justice has come to be understood in terms of access to research, notably by the HIV/AIDS

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