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Assessing Benefits in Clinical Research: *Why Diversity in Benefit Assessment Can Be Risky*

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There are increasing expectations about the potential of medical research to produce clinically significant benefits. Bipartisan support for major increases in the National Institutes of Health (NIH) budget reflects a view that medical research offers potential benefits to society at large. And the increasing public demand to participate in clinical research reflects expectations that individuals can directly benefit from research participation.[1] At the same time, there is growing concern about the adequacy of the system of institutional review boards (IRBs) to protect the rights and welfare of human subjects.[2] The resulting pressure to enhance access to the most promising clinical research while at the same time ensuring that such trials are safe, invites examination of how IRBs assess the potential benefits of clinical research.

In the wording of the Common Rule, IRBs must determine that "risks are reasonable in relation to anticipated benefits if any, to subjects, and the importance of the knowledge that may reasonably be expected to result."[3] A reasonable risk/benefit balance must be determined before research can be approved, and before subjects are offered the chance to participate. Some research may be considered too risky for subjects—and the promise of benefits too tenuous—to warrant approval even when subjects might choose to participate. Without clear and consistent benchmarks for assessing potential benefits, IRBs cannot judge what an ethically acceptable risk/benefit ratio for any study might be.

Assessment of potential benefits is equally important in the review of consent forms. The Common Rule specifies that participants in research be provided with "a description of any benefits … which may reasonably be expected from the research" (45 CFR 46.116(3)). Without an understanding of what benefits meet this standard and therefore should be described, IRBs cannot approve benefit descriptions in consent forms.

Despite its importance, this topic has received little attention in the bioethics literature. A background paper for the National Bioethics Advisory Commission (NBAC) by Prentice and Gordon illustrates how attention to risks typically overshadows discussion of benefits.[4] The paper provides a detailed discussion of various types of risks—physical, psychological,

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Table 1. The Sample of 43 IRBs

Characteristic	*Mean (Range)*
Number of Review Boards	3 (1-7)
Number of Members on all Boards	31 (10-105)
Annual Number of New Protocols Given Full Review	340 (15-1000)
Number of Board Meetings per Month	2.5 (1-9)

social, economic, and legal—but the analysis of benefits is noticeably less prominent and less detailed. This asymmetry is reflected in consent forms, which typically feature long itemized lists of possible harms and inconveniences, including descriptions of their nature, severity, and likelihood, but pay much less attention to benefits.[5] Often consent forms describe potential benefits in both a cautious tone and in sparse or vague terms, such as "You may or may not benefit," or "We cannot guarantee your condition will improve."[6] While well intended, these phrases may actually imply that benefit is possible or even likely—though not assured—when this is not the case.

A major goal in the evaluation of human subjects research should be to bring consideration of potential benefits to the same level of maturity that consideration of risks of harm has attained. Describing benefits with greater specificity can be challenging, but the lack of specificity can have adverse consequences. For example, vagueness in the description of benefits may contribute to a "therapeutic misconception" in subjects, since the absence of specificity in describing benefits can lead subjects to overestimate the likelihood of benefits, or to conflate personal benefit for themselves with the long-range benefits of a line of research.[7]

Although accurate assessment of potential benefits is critical if IRBs are to discharge their responsibility to protect human subjects, there are few data about how IRBs accomplish this task.[8] Given this lacuna in the literature, we designed an empirical study to explore the kinds of potential benefits IRBs look for when reviewing a study and how they prioritize particular benefits.[9] Our results document the heterogeneity that currently characterizes IRB review of potential benefit in clinical research, and provide clear and compelling support for more systematic and comprehensive attention to this issue.

Interviews with IRB Representatives

We contacted 58 IRBs based on criteria related to a larger project on informed consent in gene transfer research.[10] According to the Office of Biotechnology Activities at NIH, the institutions had been sites of at least one gene transfer study between December 1998 and April 2000. We completed telephone interviews with 43 IRB representatives between December 2000 and November 2001, a response rate of 74%.[11] The IRB chair was invited to participate or, if unavailable, to refer us to other experienced personnel including IRB co-chairs, vice chairs, administrators, and board members. The mean number of years of IRB experience of the respondents was 12 years, including an average of 6 years in their current position. The 43 IRBs varied considerably in size and workload, as shown in Table 1, but represent well funded and technologically sophisticated institutions in the United States.

The chief aim of the interviews was to determine how IRBs assess benefits in general, with more specific questions about experiences with benefit assessments in gene transfer trials as compared with other early phase research and with all clinical research. Previous studies have demonstrated that there can be substantial variation in how different IRBs review identical protocols and consent forms, as in review of applications for multi-center trials.[12] But we wanted to focus on the overall framework or approach toward benefit assessment used by a sample of IRBs, and then assess variation in that. We could have selected among several methodologies. One approach is qualitative and observational—taping and analyzing IRB protocol discussions to evaluate benefit assessments and whether benefit is "short changed" in contrast to risk. This would have produced rich ethnographic data but not a suffi-

Table 2. The Benefit Question: "What Kinds of Benefits Does Your IBR Look for When Reviewing a Study?"

Response	*Frequency*
Mentions Benefit to Society and Benefit to Subjects	35 (83%)
Mentions Only Benefit to Subjects	6 (14%)
Mentions Only Benefit to Society	1 (2%)
Total	**42 (100%)**

cient number of cases to approach representativeness. An alternative approach is survey research, relying on standardized questions with fixed response categories. This depends upon well-established, valid categories, which in this case were lacking. After considering the strengths and limitations of these approaches, we opted for a hybrid approach that combined a structured interview with questions that had an open-ended format and no predetermined response categories, to allow maximum flexibility in the response.

The interview began with questions about the respondent's background, experience with IRB work, and characteristics of the IRB, followed by an open-ended question about benefit: "There are several kinds of benefits that might be associated with research. What kinds of benefits does your IRB look for when reviewing a study?" The advantage of this approach is that the respondents' answers are not restricted to choices pre-determined by the investigator. This was particularly important, as we wanted to know what people would say without any prompting. The trade-off is that respondents are not provided a checklist and asked whether they consider a particular category of benefit in their review, and this limits some of our conclusions. The other interview sections included a series of specific questions about the IRBs' experiences reviewing early phase and gene transfer research.

The 40-minute interviews were tape recorded and transcribed, and all identifiers were removed. Themes were identified inductively through close reading of the text by all investigators; response codes were developed, underwent a number of iterations, and were validated by the group. Pairs of investigators coded answers to individual questions and reconciled their answers. Because coders worked with transcribed answers to particular questions, they were blind to both site and respondent characteristics. We used the software program N6[13] to help organize the codes and analyze the text responses.

How IRBs Think About Benefits

The question, "What kinds of benefits does your IRB look for when reviewing a study?" prompted interesting and quite diverse responses. To capture this diversity, we created two sets of thematic codes. The first describes the categories of benefits suggested by respondents; in our analysis we link these to the lexicon of benefits defined by King, as discussed below and reflected in Tables 2 and 3.[14] The second set of thematic codes is more interpretive, and captures the relative priority among these categories. Some respondents also identified specific benefits that were deliberately excluded, either from the IRB's risk/benefit assessment or from the consent form.

■ ***Categories of Benefits.*** The main types of benefit categories offered by respondents were *benefits to subjects* and *benefits to society*. 35 respondents (83%) reported that their IRBs looked for both major categories of benefit during IRB review (Table 2). A typical response was: "We look for direct benefit to the subject, [and] we look for benefit that might be provided by certain kinds of information to society at large, or to a group from which the subject is being recruited." Some of these respondents mentioned both types of benefits but discounted the importance of one of them, or emphasized protection from risk rather than assessment of either type of benefit. Most surprising, in response to this question, seven respondents mentioned only benefits to subjects or benefits to society, but not both.

Six described only benefits to subjects. One respondent cited "the potential for clinical outcome benefit in the individual." Another noted, "Morbidity and mortality reduction, these are all seen as benefits. With many of our psychiatric protocols, benefit is seen typically in terms of better psychological stability of the patient."

On the other end of the spectrum, one respondent mentioned only benefits to society, stating that IRB members "look for benefit to the community, benefit [in] future health treatment options... when [we] talk about benefit [we] are looking at the greater good."

Regardless of which categories of benefits were mentioned spontaneously, when asked later in the interview, "Is the distinction between benefits to subjects and to society very clear, somewhat clear, somewhat unclear, or very unclear to your IRB?" 33 respondents (78%) thought that the distinction was "very clear" to their IRB, and another six (14%) thought it "somewhat clear." Only three respondents stated that their IRB has difficulty distinguishing between the two kinds of benefits.

■ ***Benefits to Subjects.*** Forty-one respondents (98%) reported that when reviewing a study, their IRB looked for benefits to subjects. We attempted to differentiate between responses that were non-specific and those that were more specific with regard to benefits to subjects, employing King's delineation of *direct benefits*—those that directly result from the experimental intervention—and *collateral benefits* (also called "inclusion benefits")—those that result from being included in a study (Table 3). This was possible in some cases, but not in all.

As a consequence of our open-ended interview format, it was sometimes difficult to determine whether respondents were describing direct benefits, collateral benefits, or both types. For example, "benefit to patients," "pretty tangible benefits," "benefit to the individual," "personal benefit," or "benefit

Table 3. Kinds of Benefits to Subjects and Benefits to Society IRBs Look for When Reviewing a Study (N=42)

Coding Category	*Frequency*
Benefits to Subjects	41 (98%)
Described in General Terms*	31
Described in Specific Terms	
As Direct Benefits*	9
As Collateral Benefits*	14
Benefits to Society	36 (87%)
Described in General Terms	36
Described in Both General and Population-Specific Terms	12

*These categories are not mutually exclusive. While a number of respondents used general terms and/or specified direct benefits without mentioning specific collateral benefits, all the respondents who mentioned collateral benefits also used general benefit terms and/or specified direct benefits.

in subjects' condition" could mean one or the other type of benefit to subjects, or both. Because of such ambiguities in how responses were phrased, we did not label responses as discussing either direct or collateral benefits unless respondents offered specific details that enabled us to conclude that they were clearly and explicitly describing such benefits. We call attention to this interpretive challenge posed by our open-ended question methodology because, in our view, vagueness and ambiguity in the words respondents used reflect a lack of standard language to define and discuss these benefits. In fact, we found that the majority of "benefits to subjects" responses were nonspecific, and described in general terms, as indicated in Table 3. Nine respondents did offer specific details that made it clear they were describing direct benefits to subjects, for example, "There are direct benefits and those would include the possibility that someone would actually benefit from the intervention that was being examined in the trial. It might be short-term treatment, or something like that;" and "[We look for] improvement of disease control, improvement of survival, alleviation of pain."

Fourteen of the respondents (33%) offered detailed descriptions of collateral benefits that may accrue to subjects (Table 3). The commonest example was the more intense evaluation, monitoring, attention, and follow-up received "on study"—cited by six respondents. Other kinds of collateral benefits, discussed by a few respondents, included greater access to expertise (e.g., better doctors, prestigious institutions), free treatment, learning more about one's condition, psychosocial benefits from participation, and comfort through helping others (altruism). The fact that only one-third of respondents described collateral benefits, and among them, many different kinds were described, suggests that there is substantial variability in IRBs' consideration of benefits to subjects apart from those derived from the experimental intervention.

■ ***Benefits to Society.*** Thirty-six respondents (86%) mentioned that benefits to society were considered by the IRB. Twenty-four respondents used only general terms to describe benefits to society, including "generalizable knowledge," "scientific benefit," and "benefits for the future." Twelve respondents went further and also framed their descriptions of benefits to society in terms of specific populations of current or future patients, such as "a group from which the subject is being recruited," "future participants," "[the] class of people with that condition," or "for the illness involved, especially with respect to children."

■ ***Priorities Among Categories of Benefits.*** Most respondents believed that their IRBs clearly distinguished between benefits to subjects and benefits to society, but their discussions revealed that they sometimes assigned different weight to them. Though we did not ask specifically about the relative importance of benefits to subjects and benefits to society, in their responses to the benefits question some respondents told us that they considered one category of benefits to be primary. Thirteen respondents volunteered that they believed that benefits to subjects are primary. For example, one remarked, "[T]he major thing that we're concerned about is benefit to the patient—not benefit to science or the universe." Another respondent said, "We are looking for primarily benefit to the patient, and secondarily also benefit to basic knowledge and to increase medical information, but the primary benefit is actually to patients." One respondent was especially emphatic on the primacy of benefits to subjects:

> Many protocols contain an appeal to the patient's altruism—that participation in the protocol may contribute to general knowledge—we have come to be increasingly intolerant of that claim over the past

several months, and usually will not even allow it in the consent or will allow it in the consent only if there is a reasonable claim of individual benefit also.

By contrast, eight respondents stated that benefits to society are primary. For example, "[G]eneralizable benefit or benefit for the future . . . that's obviously closely tied to scientific value and so the IRB pays a lot of attention to that package of things." Another respondent said, "So little benefit ever really accrues to the individual...we're interested in the social impact of the research, whether the new drug that we're studying or the new procedure we're studying really will benefit a population of need."

Those who viewed benefits to subjects as primary seemed to equate research with providing the best patient care. Conversely, those who viewed benefits to society as primary seemed to want to distance their analysis from any consideration that research could improve the health of current subjects. We were impressed by how deeply these perspectives diverged.

Responses to our benefits question included not only comments on the kinds of benefits IRBs look for when reviewing a study, but also what they proscribe. For example, when discussing collateral benefits, four respondents said their IRBs prohibited a consideration of any collateral benefits. One said, "I do not think that free office visits or free medication for six months or a year is a benefit. We won't even allow that to be considered." Another stated that "often an investigator will say 'well the benefits are that they'll get much better monitoring than they would if they were just getting clinical care,' and again … the investigator has no basis in fact for making that claim, so we do not allow that as a benefit either." Some respondents also reported a reluctance to allow specific discussion of direct benefits in consent forms: "We have argued over the adjective to include, such as 'remote' chance of benefit, and we basically have over time recognized that it's impossible to quantitate these levels of benefit." Such proscriptions reflect views about benefit assessment that merit further attention and analysis.

Finally, and perhaps not surprisingly, we found that even when asked about review of benefits, some respondents were apt to focus on risk. According to one respondent, risks are often easy to see, and his committee "struggles to come to terms with what sort of benefits might be expected, given the obvious risks." Other respondents stated that their weighing of risks and benefits differs significantly according to the types of benefits anticipated, distinguishing, in particular, between benefits to subjects and benefits to society: "we accept a higher degree of risk if the benefit is to the individual than we would if the benefit were only to society." In fact, a few respondents thought that benefit assessment was tangential to their chief task, stating, for example,

"Our principal interest is more a question of minimizing risks as opposed to defining the benefits."

"As far as benefit to the individual, frankly, given the limited benefit offered by most of these things … I think the IRB takes more of a 'do no harm' approach than looking for active benefit, because to look for active benefit you'd be hard put to find any."

"Our IRB usually doesn't look at benefit because you can't assume a benefit, what you have to assume is that it's safe, that it's not going to hurt the patient. And if you get a benefit out of it, well that's a plus."

Why Diversity in Benefit Assessment Can be Risky

Our findings suggest that there is a great deal of heterogeneity in how IRBs consider benefits in research. When asked an open-ended question—"What kinds of benefits does your IRB look for when reviewing a study?"—respondents answered in ways that were varied and, at times, vague and challenging to interpret. Most respondents mentioned both benefits to subjects and benefits to society, but a few mentioned only one or the other. Although almost all respondents indicated that their IRBs give consideration to benefits to subjects, very few indicated the specific dimensions of such medical benefits that they might consider, for example, their nature, likelihood, magnitude, or duration. These dimensions have become a routine part of assessing risks of harm. Moreover, respondents were far more specific about the kinds of collateral benefits that their IRBs considered than about the dimensions of direct medical benefits, or how those dimensions could be weighed and assessed.

When discussing nonspecific descriptions of direct benefit in consent forms some respondents cited a desire not to mislead potential subjects with unwarranted optimism. Yet it is also reasonable to argue that increased specificity in the description of direct benefit, including not only its anticipated nature but also its magnitude, likelihood, and duration, could promote realism rather than optimism by describing very limited expectations. Such a description could inform potential subjects not only more fully but more accurately than can general and nonspecific references to potential benefit from the experimental intervention. Thus it is possible that less generic language to describe reasonably expectable direct benefits may be morally preferable—and may also help to distinguish even more clearly between benefits to subjects and benefits to society in clinical research.

Interestingly, respondents often used quite specific language when discussing societal benefits, identifying disease populations or individual

patients who would be the ultimate beneficiaries of a line of research. This tendency to personalize societal benefit may be appropriate, but it also can be morally hazardous if incorporated into consent forms. The emotional appeal of "identified lives" over "statistical lives" is well known.[15] The practice of identifying specific populations as beneficiaries should be tempered by recognition that the path leading from a research project to the ultimate beneficiaries may be long and difficult. Making the path seem short or unproblematic may also engender unwarranted optimism and thus mislead potential subjects.[16] While investigators are naturally enthusiastic about the potential for benefit to subject populations, IRBs must be vigilant in moderating this enthusiasm about future beneficiaries, just as they should be about the potential for direct medical benefits to research participants. The use of impersonal and more generic language to describe intended societal benefits is sometimes both more accurate and ethically more tenable.

It would be wrong to conclude that because many of our respondents did not volunteer the types and dimensions of benefits in response to our open-ended questions, their IRBs never consider them. Nevertheless, it was clear from the diversity and lack of specificity in responses that many IRBs do not have well-formulated, standard language for benefit assessment, at least nothing like the careful delineation that typically guides risk assessment.

Similarly, our results document diverse approaches to prioritization between benefits to subjects and benefits to society. We were especially surprised to find that some IRBs do not consider benefits to society an important component in their risk/benefit calculations about clinical research. Given the emphasis on local review established in the federal regulations, as well as dissimilarities in the kinds of studies reviewed by different IRBs, some differences are to be expected. Yet some of the heterogeneity we found seems lodged not in IRBs' experiences with different types of protocols but in differences in the basic understanding of their mission. Each research project will necessarily require its own particular benefit determination, but our study was concerned with the general approach to benefit issues undertaken by IRBs. If there were a strong normative consensus across IRBs about how to categorize and assess benefits, it would have been readily apparent in a relatively homogeneous set of responses. Instead we found wide variation and a lack of consensus on very basic questions. This finding invites the interpretation that benefit assessment is not well conceptualized and is often ad hoc, rather than standardized and systematic.

Why is this finding important? One concern might be that when benefits are unevenly assessed or poorly defined by IRBs, especially if potential benefits are overestimated, subjects may be exposed unnecessarily to risks, or exposed to greater risks than warranted. Yet given the careful attention devoted to risk assessment by IRBs, this outcome, though possible, seems unlikely.

However, the lack of specificity in language and diversity in approaches in assessing benefits may confound IRBs' capacity to balance risks of harm accurately and realistically with potential benefits. When assessments of risks and benefits are asymmetrical—with one assessment undertaken thoroughly, reliably, and specifically, and the other undertaken vaguely and incompletely—IRBs cannot accurately gauge a "reasonable balance" for their own research review. Nor can they determine whether the consent process is adequate, or whether consent forms contain the appropriate information subjects need for informed choices. Thus although variable and incomplete benefits assessments might in some cases increase the potential for physical harms to subjects, our sense is that the greater jeopardy is to IRBs' appropriate fulfillment of the full range of their duties, including promotion of subjects' autonomy through a thorough consent process.

As one of the first attempts to document and describe how IRBs understand benefit, this study is necessarily exploratory and inductive. Nevertheless, we believe that the diversity of responses to the benefits question is significant. Our small sample precludes us from drawing conclusions about the prevalence of different approaches, but it does not affect our findings about the variety of approaches. Even with a larger sample of IRBs, it would not be possible to find less diversity than we found. Thus the diversity of approaches we have documented should be considered a minimum. Furthermore, our sample of IRBs, drawn from those that oversee gene transfer research, is representative of the most experienced scientific institutions in the United States, operating at the cutting edge. If these IRBs exhibit such a wide range of language and approaches to the review of benefit in clinical research, then it is unlikely that a wider pool of IRBs would reflect either greater specificity or clearer consensus.

Conclusion

Over the past 50 years enormous strides have been made in protecting the rights and welfare of human subjects in clinical research. This historical trajectory is especially reflected in the careful and sophisticated discussions of risks of harm from research that now characterize IRB reviews and appear in consent forms.

Assessment and discussion of potential benefits in clinical research is, however, underdeveloped.

Addressing benefit issues and providing reliable standards and common tools for assessment is particularly timely; it will be increasingly important in the future as greater numbers of patients are enrolled in clinical trials. The tasks ahead are both descriptive and normative. The descriptive task is additional empirical studies to provide a more comprehensive picture of how IRBs deal with potential benefits. The conceptual task is one of defining and clarifying the critical elements that should be included in every benefits assessment.

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1. The late 1980s and early 1990s mark a major shift in public and scientific attitudes, aptly described by Mastroianni and Kahn as a move "from protection to access." See Mastroianni A, Kahn J. Swinging on the Pendulum: Shifting views of justice in human subjects research. *Hastings Center Report*. 2001;31(3): 25. For an account of the role played by AIDS activists in this transition see Epstein S. *Impure Science: AIDs, Activism and the Politics of Knowledge,* Berkeley: University of California Press, 1996. For an analysis of the ways this concern for access complicates gene transfer research see Churchill L, Collins M, King N, Pemberton S, Wailoo K. Gene Research as Therapy: Implications of 'Gene Therapy' for informed consent. *Journal of Law, Medicine and Ethics.* 1998;26: 38-47.

2. See General Accounting Office. *Scientific Research: Continued Vigilance Critical to Protecting Human Subjects,* Washington, D.C.: General Accounting Office, GAO/HEHS-96-72, 8 March 1996. See also Office of Inspector General, DHHS. *Institutional Review Boards: A Time for Reform,* Washington, D.C.: Office of Inspector General, OEI-01-97-00193, June, 1998.

3. The Common Rule is the name for the set of federal regulations for 17 federal departments and agencies governing federally funded human subjects research. The harmonization of the separate rules and regulations of these various agencies occurred in 1991. The version most familiar to IRBs and researchers is the DHHS regulations, 45 CFR 46. The requirement that risks be reasonable in relation to anticipated benefits is found at 45 CFR 46.111a(2).

4. Prentice E, Gordon B. Institutional Review Board Assessment of Risks and Benefits Associated with Research. In: *Ethical and Policy Issues in Research Involving Human Participants*, Vol. II (Bethesda, MD., August 2001).

5. See the detailed treatment of this problem and suggestions for remedying it in King N. Defining and describing benefit appropriately in clinical trials. *Journal of Law, Medicine and Ethics.* 2000;28: 332-343. King also presents a detailed lexicon of benefits, and we use the general categories of her categorization for analyzing data from our study.

6. See ref. 5, King 2000. See also Moreno J, et al. Updating protections for human subjects involved in research. *JAMA.* 1998;280: 1954 ff.

7. Appelbaum P, Roth L, Lidz C. The Therapeutic Misconception: Informed consent in psychiatric research. *International Journal of Law and Psychiatry.* 1982;5: 319-329; Appelbaum PS, et al. False Hopes and Best Data: Consent to research and the therapeutic misconception. *Hastings Center Report*. 1987;17(2): 20-24. More recent confirmation of the therapeutic misconception can be found in the Subject Interview Study (SIS) done in conjunction with the work of the Advisory Committee on the Human Radiation Experiments. SIS indicates that patients are often confused about the difference between being a patient and being a research subject, and that patients routinely enroll in clinical trials with the expectation of personal medical benefits. See *Final Report of the Advisory Committee on the Human Radiation Experiments,* New York: Oxford University Press, 1996: 468 ff.

8. A 1992 study of IRBs and investigators that concerned benefit in oncology research is Kodish E, Stocking C, Ratain M, Seigler M. Ethical Issues in Phase I Oncology Research: A comparison of investigators and institutional review board chairpersons. *Journal of Clinical Oncology.* 1992;10(11): 1810-1816. A more recent study from the Netherlands that documented diverse review of the same protocol by different IRBs is van Luijn H, Musschenga A, Keus R, Robinson W, Aaronson N. Assessment of the risk/benefit ratio of phase II cancer clinical trails by Institutional Review Board (IRB) members. *Annuals of Oncology* 2002;13: 1307-1313.

9. This study was briefly described in Henderson G, King NMP. Studying benefit in gene transfer research, *IRB: Ethics & Human Research.* 2001;23(2): 13-15.

10. The larger project examines conceptions of benefit in gene transfer research among IRBs, principal investigators (and their protocol and consent forms), study coordinators, and research subjects (RO1#HG02087-01). The study was approved by IRBs at the University of North Carolina at Chapel Hill and the National Human Genome Research Institute.

11. Ten were too busy or not interested; five did not respond to multiple requests. In the case of one interview, a taping error prevented coding answers to the open-ended questions, so some of the data presented here include 42 instead of 43 respondents.

12. See ref. 8, van Luijn et al. 2002.

13. Melbourne, Australia; QSR International Pty Ldt. Versions 6.0, 2002.

14. See ref. 5, King 2000. Although we use the lexicon of benefits King describes, there are other ways to talk about "societal benefit." One example is provided by Casarett, Karlawish and Moreno, who refer to societal benefit as the "value" of research projects and suggest a taxonomy that includes "future value to patients," "value for the study population," and "value for research subjects." The last of the categories might seem to overlap with our category "benefit to subjects," but does not, since they restrict their term "value to research subjects" to those benefits that would be made available *following* a

trial, not during it, or directly resulting from participation. Their conceptual analysis calls for a more precise delineation and clarification of the "value" or "importance" of research in a similar way that our research findings indicate a need for greater clarification and standardization in the terms used to describe benefits. See Casarett D, Karlawish J, Moreno J. A Taxonomy of Value in Clinical Research. *IRB: Ethics & Human Research*. 2002;24(6): 1-6. In general we think the terms "benefit to subjects" and "benefit to society," or "societal benefit" are preferable as broad categorizations. These are the terms used in the OHRP's *IRB Guidebook* (http://ohrp.osophs.dhhs.gov/irb/irb_chapter3.htm).

15. See Schelling T. The Life You Save May Be Your Own. In: *Problems in Public Expenditure Analysis*, edited by S.B. Chase, Jr. Washington, D.C.: Brookings Institute, 1966.

16. See, for example, Stolberg S. The biotech death of Jesse Gelsinger. *New York Times* 1999; Nov. 28. Eighteen year old Jesse Gelsinger died in a gene transfer trial at the University of Pennsylvania in September, 1999. Whether Gelsinger thought he might directly benefit from the trial is uncertain, but it is clear that he believed infants with the disease being studied—ornithine transcarbamylase deficiency (OTC)—would benefit. In a tragically prescient statement, Gelsinger is reported to have said before he left home in Arizona to enroll in the trial in Philadelphia, "What's the worst that can happen to me? I die and it's for the babies."

ANNOTATIONS

Amoroso, Paul J. and John P. Middaugh. "Research vs. public health practice: when does a study require IRB review?" *Preventative Medicine* 36 (2002): 250-253. • The authors argue that the creation of a new set of guidelines that clearly differentiates public health practice from research would clarify and explicitly identify what manner of activities require IRB review. This would both avoid confusion and conflict, as well as strengthen oversight systems such as the Code of Federal Regulations, Title 45 Part 46 which regulate when IRB review of research projects involving human subjects is necessary.

Jubb, AM. "Palliative care research: Trading ethics for an evidence base." *Journal of Medical Ethics* 28 (2002): 342-346. • Given that good medical practice with dying patients requires evidence of effective palliation, the author concludes that focused, palliative care research should be conducted. The arguments against research in the palliative setting are reviewed and rejected. The author contends that patient heterogeneity, the dynamic nature of dying, and the relative risks and benefits of different modes of research investigation demands a more nuanced approach to research with dying patients than the traditional one that conceptualizes palliative care research as a conflict between needs and values. The ethical principles of research should be applied to the palliative setting so that evidence based research can improve care for dying patients.

Miller, Franklin G., David Wendler, and Benjamin Wilfond. "When do the federal regulations allow placebo-controlled trials in children?" *Journal of Pediatrics* 142 (2003): 102-107. • The authors review federal regulations pertaining to research with children to determine whether the regulations permit researchers to conduct placebo-controlled trials with pediatric subjects and under what conditions. After analyzing the regulatory risk-benefit categories and the potential risks and benefits of placebo interventions, the authors conclude that a trial may include a placebo control when the placebo intervention (1) poses minimal risk to subjects, (2) poses greater than minimal risk while offering subjects the prospect of direct benefit from its use that justifies the risk, and is at least as favorable as alternative interventions, or (3) poses no greater than a minor increase over minimal risk with no prospect of direct benefit, if it is likely the study will produce knowledge that is of vital importance to the condition or disease of child subjects.

Sharav, Vera Hassner. "Children in Clinical Research: A conflict of moral values." *American Journal of Bioethics* 3 (2003): InFocus. • The author provides several case studies of research with children as a lens through which to examine the cultural and financial dynamics that shape the pediatric research enterprise. The evolution of federal regulatory policy governing research with children is examined, as are various codes of research ethics. The author concludes that children have increasingly been exposed to experimental risk without deriving benefit from research participation while research benefit more often accrues to commercial sponsors, researchers, and institutions. Recommendations are offered for federal legislation, ethical standards, and IRB policies that will enhance protection to child subjects and foster greater transparency and oversight of research with this population.

Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries. "Fair benefits for research in developing countries." *Science* 298 (2002): 2133-2134. • The authors argue that a framework of Fair Benefits is a preferable alternative to the more accepted theory of Reasonable Availability to avoid the research exploitation of developing countries. A system of fair benefits would include (1) benefits to the participants during the research, (2) benefits to the population during the research, (3) benefits of the population after the research, (4) collaborative partnership with the population, and (5) transparency of benefits agreements and community consultations.