Published in final edited form as:

Am J Bioeth. 2014 April ; 14(4): 54–55. doi:10.1080/15265161.2014.889954.

Which Alternatives Should Investigators Disclose to Research Subjects?

John Phillips and
NIH Clinical Center

David Wendler
NIH Clinical Center

The decision whether to disclose to potential research subjects the possibility of obtaining a study agent on an off-label basis in the clinical setting involves two questions: (1) Under existing regulations, are investigators required to disclose this possibility? (2) Ethically, should investigators disclose this possibility?

We are aware of two cases in which the Office for Human Research Protections (n.d.) cited researchers for not disclosing the possibility of off-label use of the study agent. These determinations suggest that off-label use sometimes qualifies as an alternative that must be disclosed, and present the challenge of identifying the conditions under which this is the case. The present attempt to address this challenge is based on the assumption that, in cases of uncertainty, the regulations should be interpreted in ways that respect research subjects, and protect and promote their interests (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979). Because respecting and protecting subjects is central to treating them ethically, this analysis also provides insight into when investigators ethically should disclose the possibility of off-label use as an alternative to research enrollment.

WHY NOT?

The natural first response to whether investigators should disclose the possibility of off-label use is, “Why not?” Disclosure of this information requires essentially no additional resources, and may be of interest to some individuals (Menikoff 2003; Resnik et al. 2008). Yet the same is true for almost any piece of information. Hence, this line of reasoning suggests that investigators should disclose extensive information about essentially every aspect of the study in question.

This approach would involve significant costs, and likely would confuse potential subjects. If investigators disclosed every possible alternative that has a nonzero chance of being of interest to some subjects, the consent form would be virtually endless, and potential subjects likely would end up understanding important aspects of the study, such as the major risks, less well. This result highlights the difficulties that arise if one tries to determine in isolation

This article is not subject to U.S. Copyright Law.

Address correspondence to David Wendler, Building 10, Room 1C118, Bethesda, MD 20892, USA. dwendler@nih.gov.

whether a given piece of information should be disclosed and points to the need for a general analysis. Among all the pieces of information that have a nonzero chance of being of interest to some potential subjects, which should investigators disclose?

MEDICAL INTERESTS

Investigators should be required to disclose a piece of information when there is good reason to believe that it is relevant to protecting or promoting subjects' medical interests. This standard suggests that investigators should be required to disclose an alternative when there is good reason to believe that it is medically better for potential subjects than enrolling in the research. For example, obtaining the study drug on an off-label basis may offer a more favorable risk–benefit ratio than enrolling in a study that provides the same drug but includes several invasive research biopsies.

In contrast, for the purposes of promoting individuals' medical interests, off-label use need not be disclosed when there is good reason to believe, given the nature of the condition and the study agent being tested, that enrolling in the trial offers a more favorable risk–benefit ratio than obtaining the study agent in the clinical setting. For example, when the study intervention is complex or novel, researchers who possess a high level of expertise may employ it more effectively than inexperienced clinicians. In these cases, off-label use in the clinical setting does not represent an appropriate alternative that must be disclosed to potential subjects. Protection and promotion of subjects' medical interests also does not provide a reason to disclose the possibility of off-label use in two further cases: when there is no evidence that off-label use is medically better than research enrollment, and when there is good reason to think that off-label use and research enrollment are medically equivalent.

NONMEDICAL INTERESTS

Reasonable persons have nonmedical values and preferences that can provide a reason to prefer some alternatives to research participation, even when there is no evidence to believe that they are medically better than research participation. For example, some may prefer to receive treatment locally, rather than travel to the study site.

When investigators are aware that a particular alternative is important to an individual or particular group, respect for persons suggests that they should disclose the alternative. At the same time, investigators and institutional review boards (IRBs) typically are not in a position to know which alternatives are relevant to certain individuals. Recognizing this limitation, the alternatives section of research consent forms should include a statement like: “You may want to ask the investigators or your physician about what options you have besides enrolling in the present study.” Investigators also should ask potential subjects if they have any specific concerns that may be relevant to whether they enroll, and encourage them to ask questions.

Finally, disclosure of the possibility of off-label use may provide potential subjects with a better understanding of the study and their options. Whether this possibility provides a strong reason to disclose it depends on the circumstances.

1. Disclosure as a way of increasing potential subjects' understanding makes sense only when it is not likely to detract from their understanding of more important aspects of the study, such as the risks.
2. Whether disclosure makes sense depends on how much evidence exists regarding the safety of the test article, and whether there is good evidence regarding its efficacy for the condition in question (e.g., data from an early phase trial conducted in advance of the current trial). The more favorable data that exist regarding safety and efficacy, the more reason there is to disclose off-label use as an alternative to research enrollment.
3. It is important to consider whether disclosure may lead even reasonable persons to assume that there must be data that the medication is effective for their condition. When that assumption is mistaken and cannot be corrected easily, investigators have a positive reason not to disclose the possibility of off-label use potential subjects.

The relevance and strength of these considerations depend on the context. Recognizing that IRBs are charged with making determinations of what is included in the consent form/consent process based on the individual study, the best approach may be to allow IRBs to decide in these cases whether disclosure of off-label availability should be required and in what form.

CONCLUSION

This analysis suggests that, in all cases, investigators should ask potential subjects whether they have any questions or individual concerns that may be relevant to deciding whether it makes sense for them to enroll in the study. Whether, in addition, the off-label availability of study drugs must, should, or should not be disclosed varies from study to study.

When there is reason to believe that off-label use will be medically better than research participation, this alternative must be disclosed. Evidence that off-label use is important to some individuals provides reason to disclose it to them. At the same time, this consideration must be weighed against the extent to which treatment outside of a research setting will be medically worse for patients and the possibility that the disclosure of off-label availability may mislead even reasonable persons about the drug's effectiveness. Given that these determinations depend on the circumstances, the decision of whether investigators should be required to disclose the possibility of off-label use in these cases should be left up to the investigators and IRBs to decide on a case-by-case basis.

Acknowledgments

FUNDING

This work was supported by intramural funds of the NIH Clinical Center. The opinions expressed are the authors' own. They do not represent the position or policy of the National Institutes of Health, Public Health Service, or Department of Health and Human Services.

References

- Menikoff J. The hidden alternative: Getting investigational treatments off-study. *Lancet*. 2003; 361(9351):63–67. [PubMed: 12517473]
- National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. [accessed October 17, 2013] Belmont report. Ethical principles and guidelines for the protection of human subjects of research. 1979. Available at: <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>
- Office for Human Research Protections. [accessed October 17, 2013] Informed consent guidelines. n.d. Available at: <http://www.hhs.gov/ohrp/policy/consent/index.html>
- Resnik DB, Peddada S, Altilio J, Wang N, Menikoff J. Oncology consent forms: Failure to disclose off-site treatment availability. *IRB*. 2008; 30(6):7–11. [PubMed: 19119758]