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Trust as a Principle for Ethical Decision-Making in Research with Human Subjects

By David B. Resnik

Research with human subjects is a highly regulated activity in the U.S. and many other countries. A regulation known as the Common Rule governs research supported by 16 federal agencies (Department of Homeland Security et al. 2017). Regulations adopted by the Food and Drug Administration (FDA) apply to research that supports applications for FDA-regulated products, such as drugs, biologics and medical devices (Food and Drug Administration 2017a, 2017b). Federal agencies, such as the FDA and the Office of Human Research Protections, also provide guidance for applying the FDA regulations and Common Rule, respectively (Resnik 2018). Additionally, some states, such as California, have adopted their own regulations pertaining to research with human subjects (State of California 1978).

Despite this high degree of government oversight, ethical dilemmas continue to arise in research with human subjects, in part because the regulations do not cover every situation and are subject to interpretation (Klitzman 2015, Resnik 2018). For example, while the regulations require additional protections for subjects who are vulnerable to coercion or exploitation, they only include special provisions for certain classes of vulnerable subjects, such as children, pregnant women, and prisoners, and are silent on the protections needed for mentally disabled adults, students and employees (Resnik 2018). Although the regulations require that risks to subjects be minimized and be reasonable in relation to benefits, they do not clearly define "risks" and "benefits," which often leads to controversies concerning the approval of risky studies involving healthy volunteers or children (Wendler 2010, Wertheimer 2011, Resnik 2018).

Many writers argue that ethical principles can supplement regulations to help resolve ethical dilemmas in research with human subjects (Levine 1988, Emanuel et al. 2001, National Bioethics Advisory Commission 2001, Wendler 2010, Resnik 2018). Nearly 40 years ago, the National Commission for the Protection of Human Subjects of Biomedical or Behavioral Research (1979) published a document, known as *The Belmont Report*, which articulated three ethical principles for research with human subjects. *The Belmont Report* provided a conceptual framework for a major revision of the federal regulations in 1981 and has significantly affected ethical and policy debates concerning research with human subjects (Levine 1988, Resnik 2018).

The Belmont principles include: respect for persons (allow individuals with sound decision-making capacity to make their own choices and protect individuals with diminished capacity (e.g. children or intellectually disabled adults) from harm or exploitation); beneficence (maximize the benefits of research and minimize the risks); and justice (distribute the benefits and burdens of research fairly). These three principles imply rules that appear in the federal regulations. For example, respect for persons implies informed consent requirements and additional protections for vulnerable subjects; beneficence implies requirements that risks be minimized and reasonable in relation to benefits; and justice implies additional protections for vulnerable subjects and equitable selection of research subjects (Resnik 2018).

The authors of *The Belmont Report* recognized that these principles sometimes conflict when applied to research with human subjects (Veatch 2005). For example, research on tissue samples left over from surgical procedures often involves a conflict between respect

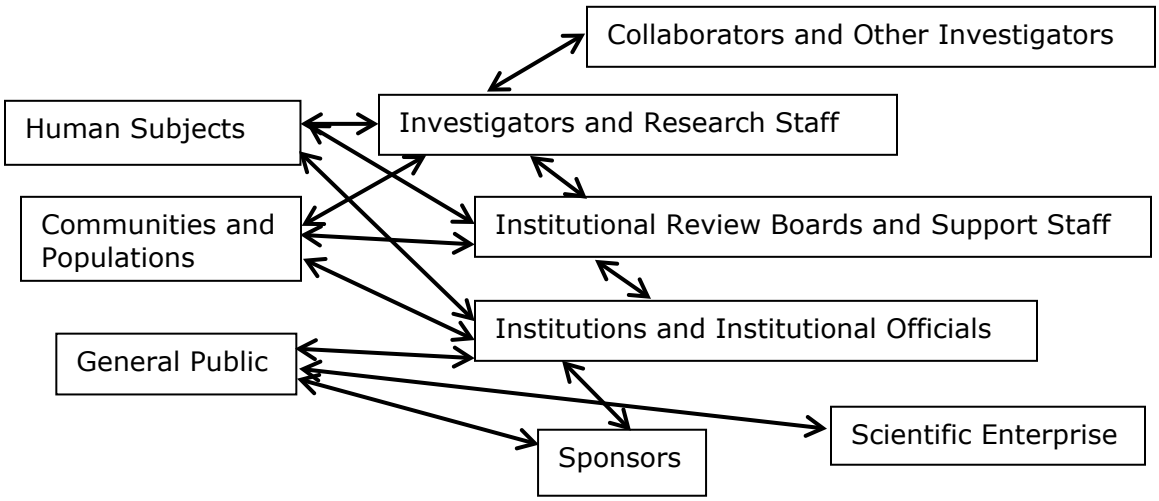
for persons and beneficence, because respect for persons demands that the investigator obtain informed consent but doing so could reduce the benefits of research because it might be difficult to contact people after their procedures to obtain consent and some might refuse to give permission to use their leftover tissues. The authors of *The Belmont Report* asserted that, when conflicts arise, one should balance and prioritize principles in light of the facts and other considerations (Veatch 2005). Since the primary risk of using leftover surgical tissue is loss of confidentiality, one way of resolving the tissue dilemma is to forego consent for use of tissues that have been de-identified (because use of these tissues poses virtually no risk to the donor) but to require consent for tissues that still have personal identifiers (Resnik 2018). This way of solving the dilemma prioritizes beneficence, except when the donor faces the risk of loss of confidentiality.

In my recent book, *The Ethics of Research with Human Subjects: Protecting People, Advancing Science, Promoting Trust*, I argue that a principle of trust (i.e., "promote trust in research with human subjects") should be adopted as an ethical principle (Resnik 2018). The principle of trust can provide useful guidance for dealing with ethical dilemmas in research and resolving conflicts among principles. Trust supplements but does not supplant the Belmont principles. Indeed, the Belmont principles promote trust. Respect for persons promotes trust, for example, because participants are more likely to trust researchers that treat them respectfully.

I develop several arguments to support my view. First, I show how history indicates that existing regulations and ethical guidelines have been developed, in large part to restore and solidify the public's trust in science in the wake of abuses and scandals involving human subjects, such as Nazi research on concentration camp prisoners, the Tuskegee syphilis study, and Jesse Gelsinger's death in a Phase I gene therapy experiment.

Second, I argue that trust is essential to maintain ethical relationships between various stakeholders in research with human subjects, including participants, investigators, research staff, collaborators, communities, institutional review boards, institutions, regulatory agencies, and the public (Kass et al, 1996, Richardson and Belsky 2004, Kraft et al. 2018). See Figure 1. Trust also facilitates many research activities involving human subjects, such as recruitment, informed consent, data collection, collaboration, community engagement, publication and regulatory compliance.

Figure 1: The Web of Trust in Research with Human Subjects (Resnik 2018)



Third, I argue that the principle of trust can provide useful guidance for dealing with ethical dilemmas and resolving conflicts among principles. In the book, I apply the principle of trust to various topics in research with human subjects, including informed consent, privacy and confidentiality, risk and benefits, vulnerable populations, research integrity, and regulatory reform.

Examples

Genetic Data

For an example of how a principle of trust can help investigators and IRBs deal with ethical dilemmas, consider the ongoing controversy concerning the return of individualized genetic or genomic results to participants (Beskow and Burke 2010). Many argue, based on the principle of beneficence, that participants should receive only clinically useful results, because the harms of returning clinically useless or inconclusive results may not outweigh the benefits (President's Commission for the Study of Bioethical Issues 2013). For example, if a genome-wide association study indicates that a participant has 50 genomic variants collectively associated with a 10% increased lifetime risk of developing a rare form of liver cancer, sharing this result with the participant could do more harm than good because this information may not provide actionable guidance for cancer prevention, diagnosis or treatment, and may cause the participant needless worry. Others argue, based on the principle of respect for persons, that participants should be allowed to receive all individualized results, including those that have no clinical utility, because receiving this information can promote their autonomous decision-making (Schaeffer and Savulescu 2018).

The principle of trust can provide some guidance for addressing this dilemma. Investigators and IRBs can ask, for example, "Which policy best promotes participants' trust in investigators and institutions?" Some studies have found that the vast majority of participants want to receive genetic/genomic results, including those without clinical utility (Bollinger et al. 2012, Christensen et al. 2017). Other studies have found, however, that many participants recognize the potential harm of receiving results that lack clinical utility (Ryan et al. 2017). One could argue, based on the principle of trust, that studies involving genetic/genomic testing should offer to return all results to participants to respect their preferences and interests, but should also inform participants about the benefits and risks of receiving results and offer counseling to those who request it (Resnik 2018).

Financial Compensation

Financial compensation is another example where focusing on trust might help resolve dilemmas related to consent. Although many bioethicists and investigators are concerned that paying subjects too much money for their participation can lead to undue inducement or coercion, underpayment might have more of a negative impact on trust than overpayment because subjects who are not paid enough money might feel they are being exploited or underappreciated (Resnik 2018). Ensuring that subjects are adequately compensated is a way of recognizing the value of their contributions to research and promoting trust.

Discussion of Benefits

Many patients enroll in clinical studies to obtain access to new treatments or to treatments they cannot afford. If a therapeutic misconception (Appelbaum et al. 1987) affects their enrollment decision, it is probably because, in part, their trust in the investigator leads them to make the false assumption that the study is designed to benefit their health. The

investigator should leverage that trust, instead, to communicate to the patient that participating in the study might be a valid decision even if no benefit is expected.

However, if a real health benefit is possible, telling the patient that no health benefit can be expected violates the principles of autonomy and respect for persons. Communicating false or conflicting information, even if it is intended to protect the patient's autonomy, could reduce the patient's level of trust. Investigators should be mindful of their obligations to tell the truth and to promote trust when obtaining consent from patients for enrollment in clinical trials.

Conclusion

Because recommendations implied by the trust principle can depend on empirical data related to which actions and policies best promote trust, additional research is needed on maintaining and promoting trust in research with human subjects. I encourage researchers to interview or survey human subjects or members of the public concerning the factors that affect their trust in investigators, institutions and sponsors. The additional research will help us understand how best to protect the rights and welfare of human participants while advancing scientific knowledge and promoting trust.

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