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Commentary

How Well Are We Protecting Human Research Subjects?

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Protecting human research subjects is an ethical mandate for all contemporary research involving human subjects. From 1974 to 1999, we had the institutional review board (IRB) system and the Common Rule, but realized that in addition to IRBs, investigators, institutions, sponsors of research, research participants, and the government all share responsibilities in protecting human research subjects. Starting in 2000, institutions established human research protection programs to ensure the rights and welfare of research participants and to meet human research ethical and regulatory requirements. Some institutions had their human research protection programs further accredited to ensure rigorous standards for quality and protection. In 2018, the Common Rule was extensively revised to modernize the regulations by enhancing protections and reducing the burden for researchers. However, throughout these periods, we did not know how well we were protecting human research subjects because we did not know how to measure human research subject protections. With the publication of human research subject protections performance metrics in 2023, it became possible for the first time to assess quantitatively how well we are protecting human research subjects. Research institutions can now monitor the effectiveness of their human research protection programs and identify areas of vulnerability for quality improvement. We should also be able to determine how well human research protection programs are doing in protecting human research subjects; determine whether external accreditation improves human research subject protections and whether the revised Common Rule in fact leads to enhanced protections; and identify prospectively which procedures or interventions can enhance human research subject protections.

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Protecting human subjects participating in research is an ethical mandate for all contemporary research involving human subjects. However, for nearly 50 years, we have not known how effective our systems of protecting human research subjects are, because we do not know how to measure human research subject protections.

The institutional review board system (1974–1999)

In the U.S., the institutional review board (IRB) system was first established in 1974 under the National Research Act for the primary purpose of protecting human research subjects[1]. The National Research Act also created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral

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Research to recommend ethical principles underlying research involving human subjects. The National Commission published its report, i.e., the Belmont Report, in 1979, defining the ethical principles of respect for persons, beneficence, and justice for human research[2].

Using the Belmont Report as the foundational background, the Department of Health and Human Services and the Food and Drug Administration revised their existing human research regulations in 1981. In 1991, Subpart A of the Department of Health and Human Services' Federal Policy for the Protection of Human Subjects (45 Code of Federal Regulations (CFR) 46 Subpart A) became the Common Rule as it was adopted by 15 U.S. departments and agencies[3]. The Common Rule defined the basic provisions for IRB, informed consent forms, and assurance of compliance. Through the implementation of the Common Rule, IRBs carried out their missions of protecting human subjects participating in research.

Between 1974 and 1999, most institutions conducting research involving human subjects delegated authorities and responsibilities of protecting human research subjects to their IRBs, often with limited financial and administrative support. A Government Accountability Office report in 1996 found that IRBs were overworked and under-supported[4]. A Department of Health and Human Services Office of Inspector General report in 1998 recommended reform of the IRB system due to a number of vulnerabilities, including, but not limited to, failure to systematically evaluate IRB effectiveness in protecting human research subjects[5]. Two events in 1999, i.e., the death of a research volunteer, Jesse Gelsinger, and the suspension of federally funded or supported research programs at 9 major U.S. academic institutions due to serious and persistent noncompliance, led to the reform of our system of protecting human research subjects[6].

Jesse Gelsinger was an 18-year-old young man with a mild form of inborn error of urea synthesis due to partial ornithine transcarbamylase deficiency. He volunteered to participate in a Phase 1 clinical trial entitled, "Recombinant Adenovirus Gene Transfer in Adults with Partial Ornithine Transcarbamylase Deficiency," at the University of Pennsylvania School of Medicine that was funded by the National Institutes of Health and the Genovo Company, in which the principal investigator of the study had a considerable financial stake[7][8].

On September 13, 1999, Jesse was given the highest study dose, i.e., 6 x 10^{11} particles/kg, of the adenovirus-derived vector containing a functional ornithine transcarbamylase gene through direct infusion into his right hepatic artery. Within hours, he developed jaundice and altered mental status and died 4 days later, on September 17, 1999, due to a fulminant immune reaction to the adenoviral vector[7][8][9].

Extensive internal and external reviews of the study revealed that in addition to significant financial conflicts of interest by the investigator and the University of Pennsylvania, there was egregious noncompliance by the investigator[7][8][9]. Jesse Gelsinger should not have died because the results of his liver function test on the day he received the infusion did not meet the inclusion criteria of the study. In addition, the study should have been suspended as required by the protocol because one of the study volunteers who received a smaller dose of the adenoviral vector earlier developed Grade III liver toxicity[7][8][10].

It became clear that in addition to IRBs, investigators, institutions, sponsors of research, research participants, and the government, all shared responsibilities in protecting human subjects participating in research[11][12]. The Institute of Medicine recommended the following reforms:

1. Implementation of a systems approach toward protecting research participants, i.e., human research participant protection programs, and
2. Voluntary accreditation of human research participant protection programs to preserve public trust[11][12].

Human Research Protection Programs (2000-2023)

Since 2000, based on the Institute of Medicine's recommendations, institutions conducting research involving human subjects have established operational frameworks, referred to as human research protection programs, to ensure the rights and welfare of research participants and to meet human research ethical and regulatory requirements[6][11][12]. Under this system, IRBs remain an important component of the human research protection programs. However, the institutional official is ultimately responsible for human research subject protections. The institution must ensure the integrity of its human research protection program by providing adequate resources and establishing ethics education programs for investigators and IRB members[12][13]. Some institutions have their human research protection programs further accredited by external human research protection program accrediting organizations to ensure that their human research protection programs meet rigorous standards for quality and protection. As of September 6, 2024, a total of 248 organizations worldwide were accredited by the Association for the Accreditation of Human Research Protection Programs, Incorporated, of which 209 organizations were from the US[14].

While our systems for protecting human research subjects changed from the IRB system to the human research protection program in 2000, the Basic Federal Policy for the Protection of Human Research Subjects, i.e., the Common Rule, remained unchanged until 2018 when it was extensively revised. According to the Office for Human Research Protections, the intended purpose of revising the Common Rule was to modernize the regulations by i) enhancing protections for human research subjects, and ii) reducing unnecessary burden and ambiguity for researchers. The revised Common Rule was adopted by 20 U.S. departments and agencies and was implemented on January 21, 2019[15][16][17].

With all these changes, the obvious questions are: "Have we made any improvement in protecting human research subjects?" Do human research protection programs provide better human research subject protections than the IRB system? Do accredited programs perform better in protecting human research subjects than non-accredited programs? Does the revised Common Rule, in fact, enhance human research subject protections as claimed by the Office for Human Research Protections? Without knowing how to measure human research subject protections quantitatively, we really do not have answers to these important questions. Thus, it is imperative that we develop a set of performance metrics for measuring protections of human subjects participating in research.

Protecting Human Subjects Participating in Research (2024 and beyond)

The need for measuring human research subject protections has long been recognized; however, the quest to answer this question has been elusive[5][10][18][19][20][21]. At the end of 2023, Tsan and Puglisi proposed a set of 5 performance metrics for measuring human research subject protections and published data on these performance metrics collected from 107 Department of Veterans Affairs research facilities from 2010 through 2021[22].

The rationale for the proposed human research subject protections performance metrics was rather straightforward. As the primary purpose of IRBs and human research protection programs is to protect human research subjects from being harmed while participating in research, in order to determine the effectiveness of IRBs or human research protection programs in protecting human research subjects, one needs to measure harms actually experienced by human research participants[22].

The first metric, i.e., unanticipated, serious adverse events related to the research, captures all physical and psychological harms actually experienced by subjects participating in research that are beyond the known risk of adverse events associated with the procedures or interventions involved in the research and the expected natural progression of the subject's underlying diseases[22].

The second and third metrics, i.e., failure to obtain informed consent and failure to obtain Health Insurance Portability and Accountability Act authorization, capture dignitary harms caused by violation of the subject's autonomy and privacy rights actually experienced by human research participants[22].

The fourth and fifth metrics, i.e., failure to obtain required initial IRB review and failure to obtain required continuing IRB review while continuing research activities, place subjects at increased risk of harms in the absence of objective oversight[22].

The availability of the above human research subject protections performance metrics offers opportunities to improve human research subject protections, including, but not limited to, the following:

- Research institutions can start to monitor the effectiveness of their human research protection programs in protecting human research subjects and identify areas of vulnerability for quality improvement purposes.
- Determine how well human research protection programs are protecting human research subjects. Since we no longer use the IRB system alone to protect human research subjects, we will not be able to find out how well the IRB system is protecting human research subjects and whether human research protection programs are better than the IRB system in protecting human research subjects. However, we should be able to determine how well human research protection programs are doing in protecting human research subjects.
- Determine whether accreditation by the Association for the Accreditation of Human Research Protection Programs, incorporated, improves human research subject protections by comparing the effectiveness of human research subject protections before and after accreditation, or by comparing the effectiveness of human research subject protections of accredited and non-accredited institutions. If accreditation fails to improve human research

subject protections, then there is no reason to spend the time and effort on this costly accreditation.

- Determine whether implementation of the revised Common Rule in fact leads to enhanced human research subject protections as claimed by the Office for Human Research Protections[15][16][17]. Prior to the availability of human research subject protections performance metrics, one could not possibly know which procedure or intervention is going to improve human research subject protections. The human subject protection literature is loaded with this kind of non-substantiated claims. Now, with the availability of human research subject protections performance metrics, we can find out the validity of these claims.
- Identify prospectively which procedures or interventions can enhance human research subject protections for future implementation to improve human research subject protections.

Statements and Declarations

Conflict of Interest

The author has no financial or proprietary interest in the subject matter of this article.

Author Contributions

MFT conceived the idea, conducted the literature review, and wrote the manuscript.

Data Availability

This commentary discusses concepts and previously published data. The data underlying the performance metrics discussed are available in Tsan MF, Puglisi JT. Protecting human subjects participating in research. Am J Transl Res. 2023; 15(9): 5707-5714 (Reference [22] in the main text).

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