

Case Report

Human Research Subject Protections – The Crisis at New York State Psychiatry Institute

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1. Independent researcher

From 1974 to 2000, we relied on institutional review boards (IRBs) to protect human subjects participating in research in the U.S. However, due to the tragic deaths of Jesse Gelsinger in 1999 and Ellen Roche in 2001, we implemented human research protection programs in 2001 to improve our system of human research subject protections. However, there has been no evidence in the literature demonstrating that the human research protection program system provides better protections than the IRB system. Here I report a case of death by suicide of an elderly patient with depression who participated in a randomized clinical trial involving the administration of carbidopa/levodopa (L-DOPA) vs. placebo for depression and psychomotor slowing in older adults at the New York State Psychiatry Institute in 2021. A comparison of these three cases revealed similar egregious noncompliance by the institutions, IRBs, and investigators involved. I suggest using human research subject protection performance metrics data in a continuous quality improvement program to prevent similar incidents from happening in the future.

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Introduction

The modern history of human research subject protections in the U.S. is shaped by major incidents of unethical and/or noncompliant research activities. The revelation of the unethical Tuskegee Syphilis Study on black Americans by the U.S. Public Health Service in 1972 led to the passage of the National Research Act of 1974 ^{[1][2]}. The National Research Act mandated the establishment of institutional review boards (IRBs) for the protection of human research subjects and created the National Commission for the

Protection of Human Subjects of Biomedical and Behavioral Research to recommend ethical principles underlying research involving human subjects ^[2]. In 1979, the National Commission published its report, i.e., the Belmont Report, defining the ethical principles of respect for persons, beneficence, and justice for human research ^[3].

Based on the Belmont Report, the Department of Health and Human Services and the Food and Drug Administration revised their existing human research regulations. 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 46) became the Common Rule ^[4]. Through the implementation of the Common Rule, IRBs carried out their missions of protecting human research subjects.

The death of Jesse Gelsinger, an 18-year-old young man who volunteered to participate in a Phase 1 gene transfer clinical trial at the University of Pennsylvania in 1999, and the death of Ellen Roche, a 24-year-old laboratory technician who volunteered to participate in asthma research at the Johns Hopkins University in 2001, shook the confidence of the public and the government in our system of protecting human research subjects ^{[5][6][7][8]}. This led to the reform that included 1) implementation of a systems approach toward protecting human research participants, i.e., a human research protection program, and 2) voluntary accreditation of human research protection programs to preserve public trust ^{[9][10]}. Under the human research protection programs, IRBs remain an important component; however, the institutional official is ultimately responsible for human research subject protections, including providing adequate resources for the institution's human research protection program and establishing ethics education programs for investigators and IRB members ^[9].

Here I report a case of death by suicide of an elderly patient with depression who participated in a randomized clinical trial involving the administration of carbidopa/levodopa (L-DOPA) vs. placebo for depression and psychomotor slowing in older adults at the New York State Psychiatric Institute (NYSPI) in 2021. I will compare this case with those of Jesse Gelsinger and Ellen Roche, and discuss the potential implications of this case in our current system of protecting human research subjects.

Case Report

1. The Research Project

The NYSPI was a premier mental health research facility and teaching hospital, academically affiliated with the Columbia University Department of Psychiatry. The research project entitled, “L-DOPA vs. Placebo for Depression and Psychomotor Slowing in Older Adults,” under the principal investigatorship of Bret Rutherford, M.D., was funded by the National Institute of Mental Health (NIMH).

It was a double-blind, randomized controlled clinical trial testing the hypothesis that administration of carbidopa/levodopa (L-DOPA) would improve depressive symptoms in adults 59 years or older with mild to moderate depression. According to the IRB-approved protocol, subjects could only be enrolled if they were not currently taking any antidepressant medications ^[11].

2. Office for Human Research Protections (OHRP) Investigation

On August 23, 2021, NYSPI submitted a report of an unanticipated problem involving risk to subjects or others to OHRP regarding the death by suicide of one of the study subjects. The name of the subject has not been publicly disclosed due to state and federal health privacy laws. However, after the subject’s death, unblinding by the research pharmacy revealed that the subject had been assigned to the placebo group.

On October 26, 2021, NIMH alerted OHRP that the NYSPI’s report to OHRP did not mention the fact that the actual conduct of this study included a psychiatric medication tapering procedure that had never been approved by the NYSPI IRB. In addition, the informed consent document did not include the risks of stopping antidepressant medication. OHRP decided to conduct a joint on-site review of NYSPI’s human research protection program with NIMH (November 29–December 3, 2021).

During the on-site interviews of members of the NYSPI IRB, OHRP noted the following concerns:

- IRB members did not ask the principal investigator during the initial IRB review of the protocol how he was going to find patients with mild to moderate depression without taking antidepressants, and how these subjects would be managed, including stopping their participation if necessary, during the study;
- Some IRB members appeared uncertain whether antidepressants could be tapered if it was not approved by the IRB as part of the study procedures;

- The IRB was not aware of the ongoing enrollment of study subjects who were taking antidepressants in noncompliance with IRB-approved inclusion criteria; and
- The IRB was not aware of the ongoing antidepressant taper of the enrolled subjects in noncompliance with the IRB-approved protocol.

OHRP noted the following concerns about the research team:

- The research team was enrolling subjects who were taking antidepressants in noncompliance with the IRB-approved inclusion criteria;
- The research team conducted antidepressant tapering without IRB approval and did not inform subjects of the risks of the procedure; and
- Some members of the research team appeared to lack sufficient experience and qualifications to properly obtain informed consent from the subjects.

In view of the systemic and serious noncompliance with the Department of Health and Human Services' human research regulations and the need for additional resources and expertise to support the NYSPI's human research protection program, OHRP restricted NYSPI's Federalwide Assurance, effective June 23, 2023 ^[11].

3. NYSPI Response to OHRP Investigation

In response to OHRP's investigation and restriction of its Federalwide Assurance, NYSPI took the following measures:

- Paused all its research involving human subjects and transferred oversight of all its studies to an external IRB;
- Hired an external research compliance consulting firm to audit and monitor its human research protection program;
- Developed and revised NYSPI human research protection program's policies and standard operating procedures, including new IRB Guidelines for Medication Discontinuation and a Principal Investigator Self-Audit Program requiring principal investigators to develop and implement a protocol-specific quality assurance, training, and data management plan;
- Provided NYSPI's IRB members and staff with additional training on the Department of Health and Human Services' human research regulations before resuming its oversight activities of NYSPI's human research program;

- Hired a number of subject matter experts for key positions throughout NYSPI's human research protection program, including a new Director of the Human Research Protection Program; and
- Changed the signatory official of its Federalwide Assurance from the Managing Director to the NYS Office of Mental Health's Chief Medical Officer.

OHRP removed its restriction of NYSPI's Federalwide Assurance on January 10, 2025, and closed its investigation on April 17, 2025 ^{[12][13]}.

4. Food and Drug Administration Inspection

The Food and Drug Administration conducted an inspection of Dr. Bret Rutherford's investigational drug research program between December 19, 2021, and January 10, 2022, and found that Dr. Rutherford failed to ensure that the research was conducted according to the investigational plan. Specifically, five subjects were on antidepressant treatment at the time of the screening assessment and did not undergo the protocol-required medication tapering and washout period before randomization. The Food and Drug Administration issued a Warning Letter to Dr. Rutherford on March 21, 2024, requiring Dr. Rutherford to implement corrective actions to prevent similar violations in the future. However, Dr. Rutherford notified the Food and Drug Administration on January 17, 2023, withdrawing his Investigational Drug Application and discontinuing the research ^[14].

5. Office of Research Integrity investigation

Based on the findings of a NYSPI research misconduct investigation report and analysis by the Office of Research Integrity, it was determined that Dr. Bret Rutherford engaged in research misconduct in research supported by U.S. Public Health Service funds, specifically NIMH grants R01 MH102293 and R61/R33 MH110029 ^[15].

The Office of Research Integrity found that Dr. Bret Rutherford recklessly and falsely reported that all human research subjects met the inclusion/exclusion criteria for late-life depression studies in five published papers. Specifically, Dr. Rutherford falsely reported that all subjects met the study inclusion/exclusion criteria by not taking any exclusionary medications at the time of study enrollment in 45 subjects; by reporting eligibility of subjects who had taken exclusionary medications during a 28-day washout period prior to enrollment in 15 subjects; by reporting full 28-day medication washout periods in 8 subjects who actually received less than a 28-day washout; and by omitting the medication taper administered to 40 subjects after study enrollment.

1. Effects of L-DOPA monotherapy on psychomotor speed and [¹¹C]-raclopride binding in high risk older adults with depression. *Biol. Psychiatry* 2019 Aug 1;86(3):221-229. doi: 10.1016/j.biopsych.2019.04.007. (Retraction in: *Biol. Psychiatry* 2023 Feb 15;93(4):382. doi: 10.1016/j.biopsych.2022.12.007).
2. Neuroanatomical predictors of L-DOPA response in older adults with psychomotor slowing and depression: A pilot study. *J. Affect. Disord.* 2020 Mar 15; 265:439-444. doi: 10.1016/j.jad.2020.01.066 (Retraction in: *J. Affect. Disord* 2023 Jun 1;330-369. doi: 10.1016/j.jad.2023.03.021).
3. Association between neuromelanin-sensitive MRI signal and psychomotor slowing in late-life depression. *Neuropsychopharmacology* 2021 Jun;46(7):1233-1239. doi: 10.1038/s41386-020-00860-z. (Retraction in: *Neuropsychopharmacology* 2024 Jun;49(7):1202. doi: 10.1038/s41386-024-01851-0).
4. Slowed processing speed disrupts patient expectancy in late life depression. *Am. J. Geriatr. Psychiatry* 2021 Jul;29(7):619-630. doi: 10.1016/j.jagp.2020.11.001 (Erratum in: *Am. J. Geriatr. Psychiatry* 2023 Jan;31(1):78-79. doi: 10.1016/j.jagp.2022.09.006).
5. Association of white matter integrity with executive function and antidepressant treatment outcome in patients with late-life depression. *Am. J. Geriatr. Psychiatry* 2021 Dec;29(12):1188-1198. doi: 10.1016/j.jagp.2021.01.004 (Erratum in: *Am. J. Geriatr. Psychiatry* 2023 Jan;31(1):76-77. doi: 10.1016/j.jagp.2022.09.007).

Dr. Rutherford entered into a Voluntary Exclusion Agreement: 1) Dr. Rutherford will exclude himself voluntarily for a period of 3 years beginning on September 27, 2024, from any contracting or subcontracting with any agency of the United States Government and from eligibility for or involvement in non-procurement or procurement transactions, and 2) at the conclusion of the Exclusion Period, Dr. Rutherford agrees to have his research supervised for a period of 3 years ^[15].

Discussion

From 1974 to 2000, the U.S. relied on the IRB system in protecting human subjects participating in research. However, with the deaths of Jesse Gelsinger in 1999 and Ellen Roche in 2001, it became clear that in addition to IRBs, investigators, institutions conducting research, sponsors of research, research volunteers, and the government all share responsibilities in protecting human research subjects ^[10]. The IRB system was replaced by the human research protection programs to improve the protection of human research subjects, and voluntary accreditation of human research protection programs was recommended to further preserve public trust in our system of protecting human research subjects ^{[9][10]}.

However, there has been no evidence that human research protection programs provide better human research subject protections than the IRB system ^[16]. Likewise, there is no evidence to support that accreditation of human research protection programs improves human research subject protections and/or the quality of IRB reviews ^[17].

Under the IRB system of protecting human research subjects from 1974 to 2000, we saw the tragic deaths of Jesse Gelsinger in 1999 and Ellen Roche in 2001 ^{[5][6][7][8]}. We moved on to the human research protection program system and voluntary accreditation of human research protection programs ^{[9][10]}. From 2001 through 2026, we saw another tragic death at NYSPI in 2021. As shown in Table 1, all these three cases showed such egregious noncompliance by the institutions, IRBs, and investigators involved that nobody should doubt that some research participants would get seriously hurt or die, no matter what kinds of human research subject protection systems we have. NYSPI's human research protection program had never been accredited by the Association for Accreditation of Human Research Protection Programs, Incorporated. So, it is impossible to speculate whether accreditation would have made a difference. What we do know is that accreditation is costly ^[17].

Feature	Jesse Gelsinger (UPenn, 1999)	Ellen Roche (Johns Hopkins, 2001)	NYSPI Suicide Case (NYSPI, 2021)
Participant Status	18-year-old, relatively healthy, with partial deficiency of ornithine transcarboxylase	24-year-old, healthy laboratory technician	Vulnerable patient with late-life depression
Intervention Type	Intrahepatic artery injection of recombinant DNA/adenoviral vector	Inhaled chemical agent, hexamethonium	Oral carbidopa/levodopa (L-DOPA) vs. placebo
Direct Cause of Harm	Fulminant systemic immune and inflammatory response	Diffuse alveolar damage and multi-organ failure	Suicide
Institution/IRB/investigator noncompliance	1. Significant financial conflict of interest (both university and investigator) 2. Failed to inform subjects of all relevant potential risks 3. Failed to notify the Food and Drug Administration of animal studies suggesting risks of adenoviral vector to humans 4. Failed to notify the Food and Drug Administration of a grade III liver toxicity	1. Failed to recognize the pulmonary toxicity of hexamethonium, i.e., inadequate literature review 2. Failed to submit an Investigational New Drug application to the Food and Drug Administration 3. IRB failed to require the investigator to submit an Investigational New Drug application to the Food and Drug Administration 4. Failed to report pulmonary adverse	1. IRB approved protocols that were inconsistent with funded research proposals 2. Enrolled subjects who met exclusion criteria into the study 3. Carried out antidepressant medication taper and washout without IRB approval 4. Failed to properly inform subjects of the risks of tapering antidepressant medication 5. Failed to include proper information in reporting an unanticipated event involving risks to subjects, i.e., death by

Feature	Jesse Gelsinger (UPenn, 1999)	Ellen Roche (Johns Hopkins, 2001)	NYSPI Suicide Case (NYSPI, 2021)
	that would necessitate suspension of protocol 5. Made multiple changes to protocol without notifying the Food and Drug Administration 6. Failed to make agreed-upon changes to the protocol	event in the first subject to the IRB promptly 5. Failed to inform subjects that pulmonary administration of hexamethonium was experimental 6. The hexamethonium used was of chemical grade, not for drug use 7. Use of IRB subcommittees, instead of full board IRBs, to review and approve protocols	suicide, to the Office for Human Research Protections

Table 1. A comparison of the three landmark cases

So, where do we go from here? It would not be practical to change the system for protecting human research subjects whenever there is a crisis. I suggest that one potential solution to improve our system of protecting human research subjects is through performance measurements and continuous quality improvement of our current system of human research subject protections ^[18]. This is an approach that has been shown to be effective in many fields, including the health care system ^{[19][20]}.

Under the proposed approach, institutions conducting research involving human subjects should hire one or more qualified research compliance officers, depending on the size of their human research programs, to carry out annual audits and performance measurements of all human research protocols to ensure ongoing compliance and high quality of human research. When program vulnerability is identified through this process, quality improvement activities should be implemented to improve the

program and prevent similar incidents, such as those described in this case report, from happening in the future ^{[18][21]}.

Notes

Running Title: The human research subject protection crisis

Statements and Declarations

Funding

No specific funding was received for this work.

Potential Competing Interests

No potential competing interests to declare.

Data Availability

The manuscript is a case report. No actual data were used in this article.

Author Contributions

The author is the sole author of this manuscript. He conceived the idea, reviewed the literature, and wrote the manuscript.

Acknowledgments

The author thanks Beverly Lii Mei Chang, M.D., for critical review of the manuscript.

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Declarations

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.