

Paying Research Subjects: Historical Considerations

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Introduction

Paying research subjects money to participate in medical experimentation is not a recent phenomenon. In the late 1800s, for example, Walter Reed paid volunteers in his yellow fever studies \$100 in gold for their participation. If they contracted yellow fever, he paid them a \$100 bonus.¹ Subjects today continue to be paid, in varying amounts, to participate in research. Despite this practice's lengthy history and ubiquity, no consensus has developed about its ethical propriety. While most regulations and guidelines governing human experimentation permit some sort of monetary remuneration to research subjects, they provide little instruction on evaluating the amount of a payment. The regulations and guidelines reflect the apprehension expressed in the academic literature about the philosophical and practical ramifications of both paying and not paying research subjects.

This paper explores the historical development of the debate about paying research subjects. A review of the debate over the last 30 years reveals that payments have mainly been conceived of as a threat to voluntary consent. Further, the issues discussed in the 1970s are largely the same issues being discussed today. I suggest that a preoccupation with voluntary consent may have slowed the progress of the debate and is part of the reason why consensus remains elusive. The importance of achieving some sort of consensus is that it translates into practical and ethical guidance in evaluating the propriety of a given payment.

In recent years, there has been a slight shift in emphasis in the discussion such that issues that were historically on the periphery of the payments debate are receiving increased attention. This may signal a turning point in the debate which may lead to practical and ethically sound guidance about how to evaluate payments to research subjects.

Prison Experiments

The appropriateness of paying research subjects began to be explored in a meaningful way in the context of prison populations. During World War II, American researchers increasingly used prisoners for medical experimentation. The ability of prisoners to freely consent was challenged both during and after the war,² especially where rewards were offered.³ American researchers, however, insisted that all prisoner-subjects freely chose to participate and prison research flourished in the post-war years.⁴ This emphasis on voluntariness would dominate the debate about payments for the next 50 years, even after prisoners ceased to be used.

After World War II, news of illness and death associated with prison research prompted formal hearings to consider the ethics of certain prison experiments. Rather than focus on the health problems caused by the experiments, excessive reward was often seen as the key ethical concern. In particular, some feared subjects might conceal symptoms rather than risk disqualification from the experiment and the reward. Consequently, the validity of the research results was jeopardized.⁵

In the late 1940s, publicity about the terrible side-effects associated with the wartime malaria research conducted in an Illinois prison prompted the Governor of Illinois to form a committee to investigate the ethics of the research. The committee found the research conformed to ethical rules and focussed its attention on the issue of rewards to prisoners. It found a subject's sole motivation ought to be to contribute to human welfare. If that was the motive, then a reduced sentence was a reward, not an undue inducement. The Commission, however, deliberately and explicitly did not consider when a reward is excessive. Rather, it said this should be reviewed on a case-by-case basis.⁶ This reluctance to iden-

tify when a reward is excessive is a trend which regulatory bodies unfortunately have continued.

By the 1960s, the pharmaceutical industry had well-established drug-testing programs in American prisons. The program in Alabama came under scrutiny in 1969 after the *Montgomery-Advertiser Journal*⁷ published news of epidemics in the prisons and sub-standard medical care of subjects enrolled in the program. The journal raised numerous concerns about the experiments, but money was central: specifically (1) excessive profits made by investigators; and (2) large payments to prisoner-subjects which apparently caused some to give false information about their medical histories and reactions to the drugs being tested.

The committee investigating the epidemics in Alabama prisons found that most prisoners volunteered because of the money and remained in the studies despite serious side-effects simply to collect the pay.⁸ In its report, the committee sent a mixed message about paying subjects. It found the pressure to volunteer because of the need for money was problematic, but at the same time noted that drug-testing programs in prisons served valuable purposes, including providing prisoners with the opportunity “to earn some extra needed money.”⁹

By the 1970s, a variety of scandals had focussed attention on human experimentation in general. Well-publicized cases like the cancer experiments on senile patients in the Brooklyn Jewish Chronic Disease Hospital¹⁰ and the Tuskegee syphilis study,¹¹ along with the publication of Jessica Mitford’s book on prison experiments, *Unkind and Usual Punishment*,¹² all highlighted concerns about the use of vulnerable populations as subjects in research.¹³ Mitford’s book clearly brought the concept of exploitation into the discussion of payments. She highlighted the concern that amounts paid to subjects were high compared to other prison jobs, but a “pittance” when compared to amounts paid to free subjects.¹⁴ As a result of the heightened focus on all human experimentation, research began to move outside of prison gates and by the late 1970s, the United States federal government ended medical research in federal prisons.¹⁵

Guidelines and Regulations

As prison research was falling out of favour in the United States, the National Commission released its 1976 “Report and Recommendations on Research Involving Prisoners.”¹⁶ While the Commission did not make recommendations about payments, it did discuss them. It echoed Mitford’s concern about paying prisoner-subjects more than other

prison jobs but much less than non-prisoners volunteers.¹⁷ Thus, the Commission highlighted the often competing concepts of voluntary consent and exploitation, which had and would continue to frame the payments debate.

By 1978, the National Commission clearly located payments within the concept of informed consent,¹⁸ particularly undue inducement. As a protective measure, it recommended limiting remuneration to “payment for the time and inconvenience of participation and compensation for any injury resulting from participation.”¹⁹ The elements of “time and inconvenience” factored prominently in the debate over how much subjects may be paid.

“[O]ne of the most influential analyses of ethical issues in human research”²⁰ is the National Commission’s penultimate 1979 report, the Belmont Report.²¹ Although it does not expressly address remuneration, it provides guidance about coercive and unduly influential offers and their potential relationship to fairness in subject selection. These relate to two of three principles enunciated by the Commission: respect for persons, which demands the absence of coercion and undue influence in the consent process; and justice, which requires fairness in subject selection.²² Coercion and undue influence are defined as follows:

Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.²³

The Commission identified the involvement of vulnerable subjects, including the economically disadvantaged, as a “special instance of injustice.” It warned that:

. . . given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their . . . socio-economic condition.²⁴

The principles enunciated in the Belmont Report solidified the debate’s focus on voluntariness and its relationship to the potential exploitation of economically vulnerable peo-

ple. This focus may be seen in both national and international guidelines and regulations regarding human experimentation. Unfortunately, these documents generally do no more than identify concern about paying subjects, but provide little guidance on how to address it.

For example, the Medical Research Council of Canada's 1987 Guidelines on Research Involving Human Subjects warn against "excessive remuneration" but allow for compensation for "losses reasonably assessed ... provided it does not distort freedom of choice."²⁵ Its successor document, the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS)*, instructs research ethics boards to consider the "economic circumstances of those in the pool of prospective subjects."²⁶ It does not, however, provide instruction on how to evaluate a proposed payment except to caution against a payment structure "that might place undue pressure on research subjects either to join or to remain within a research project."²⁷

In the United States, the Code of Federal Regulations calls for "appropriate additional safeguards" to protect subjects that may be vulnerable to coercion or undue inducement,²⁸ but gives no hint as to what those safeguards might include.

Interestingly, one of the foundational international documents concerning research involving human subjects, the *Declaration of Helsinki*,²⁹ did not identify economic vulnerabilities as a consideration until its amendment in the year 2000. The *Declaration* requires researchers to submit information to research ethics boards about incentives offered to subjects.³⁰ Like the *TCPS*, it provides no guidance on how to evaluate those incentives.

Even where lawmakers have taken the rare step of prohibiting payments to subjects, as in Quebec,³¹ compensation for inconvenience is permitted. Thus, it appears the prohibition does little to assist in assessing when a given remuneration is acceptable. The difference between a "payment" and "compensation for inconvenience" is not clear.³²

As one can see, the guidelines and regulations governing human experimentation offer no more than vague guidance to research ethics boards about how to assess payments. The lack of guidance reflects the lack of consensus on evaluating payments and the complexity of the issue, which is evident in the academic literature.

Academic Literature

The question of whether payments above compensation for out-of-pocket expenses are ever acceptable has been raised throughout the history of the payments debate. From the time of the prison experiments³³ to today³⁴, some have argued that altruism should be the subject's sole motivation. The majority of the academic literature over the past 25 years, however, has attempted to flesh out when a payment is ethically acceptable, rather than whether payments are ever acceptable. Even some writers who favour altruism as the basis for participation, accept payments as inevitable and focus on minimizing the dangers associated with them.³⁵

Despite the duration of the debate, little progress has been made towards resolving how to evaluate the amount of a payment. The same issues continue to be debated and the problem is mainly conceived of in terms of voluntariness, and exploitation as it relates to voluntariness. Discussions have centred around different views of autonomy, paternalism and the distribution of the benefits and burdens of research. The following issues have been appearing and re-appearing in the literature over the past 30 years: whether payment is ever acceptable;³⁶ whether payment can be coercive;³⁷ whether healthy subjects and patient subjects should be treated the same;³⁸ whether research subjects are like unskilled workers;³⁹ why we might want to pay subjects (for example, to aid recruitment, or to compensate for time, inconvenience or risk);⁴⁰ and which payment structures minimize the concerns about voluntariness and exploitation.⁴¹ All relate to the threat of undue inducement.

As research moved out of prisons, the concern about voluntariness continued to be discussed in the context of the use of drug company employees in research,⁴² students⁴³ and free (as opposed to institutionalized) volunteers in general.⁴⁴ The continuing emphasis on inducements and their relation to exploitation in the 1980s may have been fuelled by the deaths of two healthy volunteers in phase I drug trials. They died as a result of withholding information which would have disqualified them from the studies. It appeared that their participation and their concealment of information were motivated by the payment offered.⁴⁵

An interesting divergence from the usual conceptualization of payments came in 1989 when the United States Food and Drug Administration (FDA) identified payments as a benefit in the risk-benefit analysis, as well as a potentially undue influence.⁴⁶ Some feared categorizing payment as a benefit was dangerous since a high payment could be used to justify otherwise unacceptably risky research.⁴⁷ By 1995, the FDA

had changed its position, stating that payment should not be viewed as a benefit but as a “recruitment incentive.”⁴⁸ It may or may not be appropriate to view payment as a benefit - I do not intend to argue either side of the issue. It is interesting, however, that the categorization sparked little academic discussion and the debate generally continued to focus on consent. The brief change in policy represented a missed opportunity to approach the issue from a fresh perspective.

I suggest the heavy emphasis on voluntary consent has slowed the progress of reaching some consensus on how to ethically pay research subjects. I do not intend to minimize the importance of informed consent in the payments debate. Nor do I suggest that other ethical issues have not been factors in the discussion. Rather, my concern is that the heavy focus on voluntariness and exploitation as it relates to voluntariness has resulted in other factors, most significantly the impact of commercial realities in human experimentation, not being thoroughly analysed and then integrated with the valuable work done concerning consent.

That said, recently there has been a shift in the tone of the debate to address the commercial nature of much research. Commercial interest has been a factor percolating in the background of the debate for decades. As indicated earlier, the media highlighted the profits that investigators reaped in relation to research in prisons in the 1960s. With the growth of contract research organizations and the media attention in the late 1990s to scandals involving commercial conflicts of interest,⁴⁹ the profit motive of many sponsors has gained increased influence over the tone of the debate about payments.

While Terence Ackerman, in 1989, questioned the ethics of not paying subjects involved in research which was financially lucrative for the sponsor,⁵⁰ the influence of commercialization in the analysis of payments is most evident in the late 1990s. Christine Grady and Neal Dickert sparked discussion in 1999 with their analysis and proposal of a wage-payment model. They argued this model balanced concerns about protecting subjects from undue inducement and justice in subject selection, while also considering the cost of research and the need to recruit subjects.⁵¹ Similarly, Trudo Lemmens and Carl Elliott, in 1999, proposed a labour model for payments, with a heavy analytical emphasis on justice and the power imbalance between subjects and com-

mercial sponsors of research.⁵² Viewing research subjects as workers is not new⁵³ but the implications of treating subjects as workers now are receiving needed scrutiny and are infusing commercial realities into the analysis.

Conclusion

Payments have been and continue to be conceptualized as a problem of voluntariness and exploitation as it relates to voluntariness. Recent years have witnessed a growing acknowledgment of commercialization’s impact on the evaluation of payments in general. Despite the fact that payments to research subjects are common, the issue remains controversial. Ethicists seem to have put renewed efforts into conducting empirical and analytical work to review institutional policies on payments,⁵⁴ the factors motivating individuals to participate in research⁵⁵ and the implications of certain payment schemes.⁵⁶

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There is much work to be done in terms of developing the various ways of conceptualizing payments. The recent literature suggests that the debate is moving forward to include a comprehensive analysis of the many factors operating in the research environment and may move us closer to some sort of consensus as to the best way to protect subjects from the perils of payments in the commercial reality of modern medical research.

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2. See, letter from Frank Jewett, President of the National Academy of Sciences, to Ross G. Harrison, Chairman of the National Research Council (16 February 1943), NAS-NRC Central File: DIV NRC: Medical Sciences: Committee on Medicine, Subcommittee on Venereal Diseases: 1943, NAS, cited in Harry M. Marks, *The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900-1990* (Cambridge: Cambridge University Press,

- 1997) at 104-105; Nuremberg Code, Principle I, Germany Military Tribunals, *Trials of War Criminals Before the Nuremberg Military Tribunals: The Medical Cases*, vols. I and II (Washington D.C.: U.S. Government Printing Office, 1948).
3. See the final plea for Defendant Karl Brandt by Dr. Robert Servatius, *Trials of War Criminals Before the Nuremberg Military Tribunals: The Medical Cases*, reprinted in part in Jay Katz, *Experimentation with Human Beings* (New York: Russell Sage Foundation, 1972) at 303; A.C. Ivy, Chairman, *Committee Appointed by Governor Dwight H. Green of Illinois, Ethics Governing the Service of Prisoners as Subjects in Medical Experiments* (1948) 136 J. Am. Med. Assn. 447, reprinted in part in Jay Katz, *Experimentation with Human Beings* (New York: Russell Sage Foundation, 1972) at 1030.
 4. Jessica Mitford, *Unkind and Usual Punishment: The Prison Business* (New York: Alfred A. Knopf, 1973) c. 9.
 5. *Ibid.* at 149-150.
 6. Ivy, reprinted in Katz, *supra* note 3 at 1030. Note that the requirement that a subject be motivated by a desire to contribute was not confined to the prison setting. See, for example, the *Harvard Medical School Rules Governing the Participation of Medical Students as Experimental Subjects*, reprinted in Katz, *supra* note 3 at 1036.
 7. Tinsley R. Harrison, Chairman, *Drug Investigation Committee of the Medical Association of the State of Alabama, The Use of Prisoners for Drug Trials In Alabama*, reprinted in part in Katz, *supra* note 3 at 1042.
 8. *Ibid.* at 1043.
 9. *Ibid.* at 1044.
 10. See Katz, *supra* note 3 at 9-65.
 11. See James H. Jones, *Bad Blood: The Tuskegee Syphilis Experiment* (New York: Free Press, 1981).
 12. *Supra* note 4.
 13. Allen M. Hornblum, "They were cheap and available: prisoners as research subjects in twentieth century America" (1997) 315 Brit. Med. J. 1437 at 1441.
 14. *Supra* note 4 at 144.
 15. *Supra* note 13.
 16. U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Report & Recommendations: Research Involving Prisoners* (Washington: Government Printing Office, 1976).
 17. *Ibid.* at 10-11.
 18. U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Report & Recommendations: Institutional Review Boards* (Washington: Government Printing Office, 1978) Recommendation 4E at 20.
 19. *Ibid.* at 25.
 20. Trudo Lemmens & Carl Elliott, "Guinea Pigs on the Payroll: The Ethics of Paying Research Subjects" (1999) 7 Accountability in Research 3 at 8.
 21. U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report* (Washington: Government Printing Office, 1979).
 22. The third principle is beneficence.
 23. *Supra* note 21 at 6.
 24. *Supra* note 21 at 8.
 25. Medical Research Council of Canada, *Guidelines on Research Involving Human Subjects* (Ottawa: Minister of Supply and Service Canada, 1987). Note that this document is superseded by the *Tri-Council Policy Statement, infra.* note 26.
 26. Medical Research Council of Canada, Natural Sciences and Engineering Research Council of Canada & Social Sciences and Humanities Research Council of Canada, *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (Ottawa: Public Works and Government Services Canada, 1998) at 2.8.
 27. *Ibid.*
 28. 45 C.F.R. 46.111(b) (1991).
 29. World Medical Association, *Declaration of Helsinki* (Adopted by the 18th WMA General Assembly, Helsinki, Finland, 1964. Amended at the 29th WMA General Assembly, Tokyo, Japan, 1975; the 35th WMA General Assembly, Venice, Italy, 1983; the 41st WMA General Assembly, Hong Kong, 1989; the 48th WMA General Assembly, Somerset West, Republic of South Africa, 1996; the 52nd WMA General Assembly, Edinburgh, Scotland, 2000); Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002, online: The World Medical Association <<http://www.wma.net/e/policy/b3.htm>> (date accessed: 15 June 2003).
 30. *Ibid.*, s.13.
 31. *Civil Code of Quebec*, S.Q. 1991, c.64, s.25.
 32. *Supra* note 20 at 9.
 33. For example Ivy, reprinted in Katz, *supra* note 3.
 34. For example Tod Chambers, "Participation as Commodity, Participation as Gift" (2001) 1:2 Am. J. Bioethics 48.
 35. Jeanne M. Sears, "Payment of Research Subjects: A Broader Perspective" (2001) 1:2 Am. J. Bioethics 66.
 36. See, Marx W. Wartofsky, "On doing it for money" in National Commission, *supra* note 16; Paul McNeill,

- “Paying people to participate in research: why not?” (1997) 11 *Bioethics* 390.
37. See, Christine Grady, “Money for Research Participation: Does It Jeopardize Informed Consent?” (2001) 1:2 *Am. J. Bioethics* 40; Caroline Todd, “Research Participation and Financial Inducements” (2001) 1:2 *Am. J. Bioethics* 60.
 38. See, Neal Dickert & Christine Grady, “What’s the Price of a Research Subject? Approaches to Payment for Research Participation” (1999) 341:3 *New Engl. J. Med.* 198; Trudo Lemmens & Carl Elliott, “Justice for the Professional Guinea Pig” (2001) 1:2 *Am. J. Bioethics* 51; Ruth Macklin, “‘Due’ and ‘Undue’ Inducements: On Paying Money to Research Subjects” (1981) 3:5 *IRB: A Review of Human Research* 1.
 39. Robert J. Levine, *Ethics and Regulation of Clinical Research*, 2d ed. (Baltimore: Urban & Schwarzenberg, 1986) at 83; Lemmens & Elliott, *supra* note 20.
 40. Macklin, *supra* note 38; Dickert & Grady, *supra* note 38; Carl L. Tishler & Suzanne Bartholomae, “The Recruitment of Normal Healthy Volunteers: A Review of The Literature on the Use of Financial Incentives” (2002) 42 *J. Clin. Pharmacol.* 363.
 41. Macklin, *supra* note 38; Terence F. Ackerman, “An Ethical Framework for the Practice of Paying Research Subjects” (1989) 11:4 *IRB* 1; Dickert & Grady, *supra* note 38.
 42. Karin Meyers, “Drug Company Employees as Research Subjects: Programs, Problems, and Ethics” (1979) 1:8 *IRB* 5.
 43. See, the *Harvard Medical School Rules*, *supra* note 6.
 44. Macklin, *supra* note 38.
 45. See G.B. Kolata, “The death of a research subject” (1980) 10 *Hastings Cent Rep* 5; and A. Darragh *et al.*, “Sudden death of a volunteer” (1985) 1 *Lancet* 93.
 46. U.S. Food and Drug Administration, *Information Sheets for IRBs and Clinical Investigators* (February 1989), cited in Ruth Macklin, “The Paradoxical Case of Payment as Benefit to Research Subjects” (1989) 11:6 *IRB* 1.
 47. Macklin, *ibid.*
 48. U.S. Food and Drug Administration, *Information Sheets for IRBs and Clinical Investigators*, Office of Health Affairs (October 1995).
 49. For example, publication of the *zine* Guinea Pig Zero in 1996; the death of Jesse Gelsinger in 1999, a subject undergoing experimental gene therapy in which the principal researcher, sponsor and research institute all had significant financial interest in the therapy being tested (see J.A. Goldner, “Dealing with Conflicts of Interest in Biomedical Research: IRB Oversight as the Next Best Solution to the Abolitionist Approach” (2000) 28:4 *J.L. Med. & Ethics* 379); and the scandal arising out of Dr. Nancy Olivieri’s public expression of concern about the effects of an experimental drug she was testing for Apotex (see R. A. Phillips & J. J. Hoey, “Constraints of Interest: Lessons at the Hospital for Sick Children” (1998) 159 *Can. Med. Assoc. J.* 955).
 50. Ackerman, *supra* note 41.
 51. Dickert & Grady, *supra* note 38.
 52. *Supra* note 20.
 53. Levine, *supra* note 39; Macklin, *supra* note 38.
 54. Neal Dickert, Ezekiel Emanuel & Christine Grady, “Paying Research Subjects: An Analysis of Current Policies” (2002) 136 *Ann. Intern. Med.* 368.
 55. Tishler & Bartholomae, *supra* note 40; Margaret L. Russell, Donna G. Moralejo & Ellen D. Burgess, “Paying research subjects: Participants’ perspectives” (2000) 26:2 *J. Med. Ethics* 126; Kathryn L. Weise *et al.*, “National Practices Regarding Payment to Research Subjects for Participating in Pediatric Research” (2002) 110:3 *Pediatrics* 577.
 56. James A. Anderson & Charles Weijer, “The Research Subject as Wage Earner” (2002) 23 *Theoretical Medicine* 359; Ackerman, *supra* note 41; Sears, *supra* note 35.