

Legal and Ethical Issues Associated with Patient Recruitment in Clinical Trials: The Case of Competitive Enrolment

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Introduction

The demand for patients for clinical trials continues to increase. There are more clinical trials being done (often involving patients with similar conditions), government regulators require an increasing amount of data for the drug approval process, and some within industry have speculated that patients are becoming less willing to participate.

These pressures have led to the development of a variety of strategies to make the recruitment of patients more efficient and effective, such as the creation of research networks, the implementation of software to determine patient eligibility¹ and the use of email and the internet to find new patients.² Indeed, patient recruitment has become an industry.

Competitive enrolment has emerged as one of the most common patient recruitment practices. Despite being ubiquitous, there is surprisingly little literature on the nature and ethical implications of competitive enrolment. This paper briefly considers the issues associated with this recruitment scheme. I will argue that competitive enrolment creates significant ethical challenges that need to be addressed by both REBs and at the level of national research ethics policy.

Competitive Enrolment

From the perspective of industry, patient recruitment is seen as a critical issue. In a paper written by an industry consultant, it is claimed that “only 15% of clinical trials are completed on time, with over 50% of delays attributed to patient recruitment and 30% of investigator sites failing to recruit a single patient.”³ The authors also suggest that the “estimated cost of patient recruitment is \$1.89 billion. These costs are subject to further increases with each day’s delay in bringing the product to market.”⁴ In another industry document it is stated that “drug companies stand to lose between \$600,000 and \$8 million each day clinical trials delay a drug’s development and launch.”⁵

It shouldn’t be forgotten how much the industry has invested in the research and development process. Though estimates vary considerably, one paper suggests that it “takes nearly eight years to develop a drug, almost twice as long as it took 20 years ago” and, quoting from a study by the Tufts Center for the Study of Drug Development, “\$1 billion per drug, from concept to market.”⁶

While such figures often come from industry sources, there is no doubt that increasing access to patients and promoting patient participation in clinical trials has become an indus-



try priority. A lot of money is at stake. For sponsoring companies, encouraging patients to participate and to complete clinical trials has a direct relationship to profit and the success of a new drug product. As such, it is understandable that sponsoring companies would want to devise strategies to optimize recruitment.

One such strategy is competitive enrolment. Indeed, it is frequently viewed as an essential part of the overall patient recruitment plan. As noted by one recruitment consultant: "We strongly recommend the use of competitive enrolment together with the inclusion of backup sites so they can be brought on board should individual sites drop below their agreed target levels."⁷

Competitive enrolment is often part of the clinical trial agreement between the investigators and the sponsor of the trial – usually a pharmaceutical company. The goal, of course, is the advancement of rapid patient recruitment. It works by pitting investigating sites against one another. In return for involvement in the protocol and remuneration (which is often generous),⁸ investigators agree to recruit a specific number of patients (often within a specified period of time). Such arrangements create a significant incentive for investigators to recruit patients as fast as they can. In a sense, they are in a race with other sites. If the clinical site does not meet a specified recruitment target, the sponsoring company may have the option to drop them from the protocol. For the clinical researcher, this may result in lost time and, even, money.

In some ways, competitive enrolment can be considered a modification to traditional recruitment strategies (such as recruitment fees).⁹ However, unless an REB is aware of the practice and look for relevant provisions in the clinical trial agreement, it may not be apparent that a clinical trial involves competitive enrolment. Moreover, because existing research ethics guidelines do not refer, explicitly, to competitive enrolment, it is worth considering the ethical concerns associated with this recruitment strategy and the ways in which existing policies may be implicated.

Ethical Challenges

As with other recruitment strategies, such as generous investigator remuneration and recruitment bonuses,¹⁰ competitive enrolment schemes could create serious ethical challenges. Because rapid enrolment is the goal, these strategies may compromise the consent process or cause investigators (or the investigators research team) to put subtle pressure on patients to participate. Indeed, one industry paper suggests that "patient motivation to become a research study participant is 'perishable'" and that there is a need create "momentum for every [recruitment] campaign."¹¹

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Given the pressures inherent in a competitive enrolment scheme, there seem little doubt that they challenge the clinical investigator's fiduciary obligations to the patient – that is, the obligation to ensure the interests of the patient remain paramount.¹² A competitive enrolment scheme is designed to place other objectives, the

recruitment of patients, high on the investigator's agenda. At a minimum, fiduciary duties heighten the investigator's obligation to conflicting interests, a point that will be addressed further below.

Competitive enrolment may also encourage investigators to push the boundaries of a protocol's inclusion and exclusion criteria. This has the potential to impact the scientific value of the protocol and, more importantly, would have implications for the well being of the patient. Frequently, inclusion and exclusion criteria are designed to ensure that inappropriately "at risk" patients are not involved in the testing of a new therapeutic products. Allowing patients at the margins of eligibility, which may be required to satisfy the agreed upon enrolment targets, could create safety issues.

Aggressive enrolment strategies may also encourage inappropriate advertising practices. For example, one recruit-

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ment consultant laments the impact of REB review on effective advertising, thus: "In most countries, advertisements need to be approved by an ethics committee, which can lead to rather bland messages." He then provides strategies, such as directing the patient to a call centre, that will allow investigators to get around the dilemma of the bland message.¹³ Obviously, there are specific reasons REBs recommend more tempered messages. But these "bland" messages run counter to the goal of rapid recruitment.

Finally, competitive enrolment is frequently used in the community setting, where some investigators may not have a tremendous amount of experience and, as a result, may not be sensitive to the ethical challenges created by aggressive recruiting practices.

Discussion and Recommendations

While I sympathize with the difficulties associated with patient recruitment, competitive enrolment and the associated recruitment strategies create profound ethical and regulatory challenges that must be addressed by the research ethics review process. First, REBs need to recognize that competitive enrolment is an emerging ethical concern.¹⁴ It is a practice that creates many of the same ethical issues as inappropriate physician remuneration and recruitment bonuses, practices that are generally prohibited by research ethics policies.¹⁵

REBs and clinical investigators have an obligation to consider how, and if, contractual obligations create inappropriate conflict of interest issues. This means that REBs must compel the submission of agreements between investigators and sponsors. As noted in article 7.2 of the Tri-Council Policy Statement: "The REB must carefully examine each clinical trial to assist researchers in avoiding potential conflicts of interest concerning the selection and recruitment of subjects, and payments by sponsors to the researchers."¹⁶ To fulfil this task, it has been suggested that "boards will have to develop some expertise in evaluating financial arrangements."¹⁷

Second, REBs should seek to sensitize clinical investigators about how competitive enrolment agreements are designed to create incentives that may compromise the investigator's ethical obligations. This is particularly important for inexperienced investigators who may practice in the community.¹⁸

Third, REBs may want to consider compelling the disclosure of competitive enrolment agreements to patients as part of the consent process. Investigators are already often required (as they should be) to disclose information about other conflicts, such as remuneration and the fact that the protocol is being sponsored by a private company. Requiring disclosure of a competitive enrolment scheme is an extension of the same research ethics policy. Moreover, it is certainly arguable that this is part of the investigators consent obligation as it is something that a reasonable person in the patient's position would want to know.¹⁹ And, as noted above, fiduciary principles require physicians to disclose information about factors that may compromise their dedication to the interests of their patients.

Finally, on a broader scale, the issues associated with competitive enrolment need national attention. As with inappropriately generous physician remuneration and non-disclosure agreements, it is difficult for REBs to act on their own without guidance at the level of national policy – this is particularly so when a practice is viewed as a standard approach.

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1. Atul Butte, David Weinstein & Isaac Kohane, "Enrolling Patients Into Clinical Trials Faster Using RealTime Recruiting" in M. Overhage, ed. *Fall Symposium, American Medical Informatics Association*, (Washington, DC: Hanley & Belfus, 2000) 111. Online: Amia <<http://www.amia.org/pubs/symposia/D20044.pdf>>).
2. See, for example, Mindbranch, Inc., "Patient Recruitment Online: Accelerating the Patient Recruitment Process" (June 2004) online: <<http://www.mindbranch.com/products/R313-6893.html>>. On the website they note: "The inability to recruit patients according to plan has caused significant delays in the progress of clinical trials, which ultimately lead to lost potential sales. Online channels can improve recruitment efforts by facilitat-



- ing communication between sponsors, patients and physicians.”
3. Michael Bowdon & Steve Mackenzie-Lawrie, “Accelerating Patient Recruitment” *Pharmafocus* (undated) online: *Health Decisions* <http://www.healthdec.com/lit_downloads.html>.
 4. *Ibid.*
 5. Cutting Edge Information, “Accelerating Clinical Trials: Budgets, Patient Recruitment and Productivity” (May 2004) online: *Cutting Edge Information* <<http://www.acceleratedclinicaltrials.com>>
 6. Susan Warner, “The Tribulations of Clinical Trials” (2004) 18 *The Scientist* 20 at 21. See also, T. Bodenheimer, “Uneasy Alliance: Clinical Investigators and the Pharmaceutical Industry” (2000) 342 *New England Journal of Medicine* 1539.
 7. Bowden and Machenzie-Lawrie, *supra* note 3 at 1. See also, Michael Bowden, “Accelerating Patient Recruitment with an Integrated Approach” online: *Health Decisions* <http://www.healthdec.com/lit_downloads.html> at 2: “Competitive enrolment is more or less *de rigueur* nowadays, and we expect sites to drop out of the study to allow back-up sites on board, should performance significantly drop below that previously agreed.”
 8. For a discussion of investigator remuneration issues see generally, Timothy Caulfield & Glenn Griener, “Conflicts of Interest in Clinical Research: Addressing the Issue of Physician Remuneration” (2002) 30 *Journal of Law, Medicine and Ethics* 305; Office of Human Research Protection, Draft Interim Guidance, “Financial Relationships in Clinical Trials” (January 10, 2001); US General Accounting Office, Report to Congressional Requesters, *NIH Clinical Trials: Various Factors Affect Patient Participation* (September 1999) (GAO/HEHS - 99 - 182); and E. DeRenzo, “Coercion in the Recruitment and Retention of Human Research Subjects, Pharmaceutical Industry Payments to Physician-Investigators and the Moral Courage of the IRB” (2000) 22 *IRB: A Review of Human Subjects Research* 1.
 9. See *ibid.*
 10. See, Caulfield & Griener, *ibid.*
 11. Frank Kilpatrick, “Rev Up Patient Recruitment” (2002) *Pharmaceutical Executive*, online: <<http://www.pharmexec.com/pharmexec/article/articleDetail.jsp?id=14491>>.
 12. *Norberg v. Wynrib* [1992] 2 S.C.R. 226; *McInerney v. MacDonald* [1992], 2 S.C.R. 138; Moe Litman & Lori Sheremeta, “The Report of the Committee of Inquiry on the Case Involving Dr. Nancy Olivieri: A Fiduciary Law Perspective” (2002) 10 *Health Law Review* 3-13.
 13. Bowden, *supra* note 7 at 3.
 14. Though based entirely anecdotal observations, personal experience on REBs and discussions with colleagues on REBs throughout the country, it is my impression that few REBs recognize and respond to competitive enrolment. Studying the extent of this and other enrolment practices and how REBs respond to them would be a worthwhile research initiative.
 15. Canadian Medical Association, *CMA Policy: Physicians and the Pharmaceutical Industry*, 164 (2001) *Canadian Medical Association Journal* 1339-41.
 16. Tri-Council, *Ethical Conduct for Research Involving Humans (with updates of May 2000 and September 2002)* (Ottawa: Tri-Council, 1998) at 7.3. See also Article 7.3 which states: “REBs shall examine the budgets of clinical trials to assure that ethical duties concerning conflict of interest are respected.”
 17. Jesse Goldner, “Dealing with Conflicts of Interest in Biomedical Research: IRB Oversight as the Next Best Solution to the Abolitionist Approach” (2000) 28 *Journal of Law, Medicine and Ethics* 379 at 398.
 18. For example, the TCPS recognizes the conflict inherent in the recruitment process. Article 2.8 reads as follows: “Researchers should disassociate their role as researcher from other roles, in the recruitment process and throughout the project.” *Supra* note 16.
 19. *Reibl v. Hughes* (1980) [1980] 2 S.C.R. 880.

