

Foreword

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It has been almost thirty years since federal regulations governing research with human subjects were first developed. Since that time, the world of biomedical research has changed dramatically. Not only has the amount of research increased exponentially,¹ but the context in which research is conducted also has changed. Twenty years ago, medical research was virtually the exclusive province of academic medical centers, which designed, conducted, and reported on studies financed primarily by the National Institutes of Health. Today, research occurs in a broad range of nonacademic settings, including for-profit contract research organizations, community hospitals, and private physicians' offices. In addition, an increasingly large portion of research funding comes from private sources. This shift away from an academic model of scientific research to a system more closely aligned with private commercial interests has complicated the process of research oversight, by both reducing the transparency of the research enterprise and increasing the prevalence of conflicts of interest.

In November 2001, Seton Hall Law School, Seton Hall University Graduate School of Medical Education, and the American Society of Law, Medicine & Ethics sponsored a day-long symposium to explore the legal, ethical, and public policy implications of the shift in research away from academic medical centers. Supported by a generous grant from the law firm of Gibbons Del Deo Dolan Griffinger & Vecchione, the symposium brought together leaders in the fields of law, medicine, and bioethics, many of whom have contributed papers to this issue of the *Seton Hall Law Review*.

The paper by Bernard Lo and Michelle Groman of the University of California at San Francisco Medical Center, which

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¹ See 1 NATIONAL BIOETHICS ADVISORY COMMISSION, ETHICAL AND POLICY ISSUES IN RESEARCH INVOLVING HUMAN PARTICIPANTS 4 (2001) (noting that federal research funding almost doubled between 1986 and 1995, from \$6.9 billion to \$13.4 billion, and that private research funding tripled, from \$6.2 billion to \$18.6 billion).

expands on Dr. Lo's keynote address at the beginning of the symposium, highlights one of the most significant deficiencies in the current regulatory regime—the limited applicability of federal human subject protections to research that is not funded by the federal government.² While some privately-funded research is subject to federal regulatory oversight, either because it involves products regulated by the Food and Drug Administration or because it takes place in institutions that have signed multiple project assurances with the federal government, a significant proportion of privately-funded research fits into neither of these categories.³ One of the most important recommendations of the National Bioethics Advisory Commission (NBAC), therefore, was its call for a uniform system of federal regulation for all human subject research, regardless of source of funding.⁴ In addition to discussing NBAC's rationale for expanding federal jurisdiction over research, Lo and Groman's paper also addresses several other important NBAC recommendations, including those designed to reduce unnecessary regulation of low-risk activities; to increase the proportion of outside members of institutional review boards (IRBs), the committees that review and approve research protocols under the federal regulations; to reform the requirements for waiving informed consent to research; and to provide greater guidance for IRBs' process of assessing research risks.

One of the challenges of overseeing research conducted in nonacademic settings is identifying an appropriate body to review and approve research protocols. As research increasingly moves away from academic medical centers, many of the settings in which research is conducted do not have IRBs. David Forster's paper examines a type of organization that has emerged to fill this void—the independent institutional review board.⁵ These organizations, which include the company for which Mr. Forster serves as general counsel, Western Institutional Review Board, operate separate from and unaffiliated with institutions that conduct research activities. Mr. Forster identifies several concerns that have been raised about independent IRBs and offers suggestions for addressing these concerns, including procedures for minimizing the influence of conflicts of interest. In addition, he argues that independent IRBs offer important advantages over traditional IRBs in several respects.

² Bernard Lo & Michelle Groman, *NBAC Recommendations on Oversight of Human Subject Research*, 32 SETON HALL L. REV. 493 (2002).

³ See *id.* at 496

⁴ See *id.*

⁵ David G. Forster, *Independent Institutional Review Boards*, 32 SETON HALL L. REV. 513 (2002).

The issue of conflicts of interest is the subject of an extensive analysis by Mark Barnes and Patrik S. Florencio, both lawyers with the law firm of Ropes & Gray in New York.⁶ Financial conflicts of interest “lie at the core of ethical issues surrounding clinical trials,” Barnes and Florencio argue, “and the anecdotal evidence is that these conflicts are widespread.”⁷ The potential for commercial interests to influence the integrity of research is the result of more than simply private sponsorship of particular studies. Researchers may have financial investments in the drugs or devices under investigation, or they may own stakes in the companies that are sponsoring their studies. In addition, researchers may receive stipends, speaking and consulting fees, and other gifts from research sponsors. The potential influence of financial considerations is most apparent in for-profit organizations involved in research, such as contract research organizations and site management organizations, which “are beholden to their shareholders and less encumbered by academic ideals.”⁸ Barnes and Florencio provide a careful analysis of the current federal regulations’ application to conflicts of interest, identify their gaps, and describe several proposed approaches to reforming the system.

Nancy Dubler’s commentary offers a broad perspective on the ethical challenges raised by the changing research environment.⁹ Of particular concern to Dubler is the process of obtaining the informed consent of individuals who enroll in research protocols. Criticizing the lengthy, legalistic, and often incomprehensible consent forms currently in use, she argues that the informed consent process must “engage[] the subject on an escalating plane of complexity and abstraction.”¹⁰ Real reform, she argues, will require a significant investment of time and money, and those who profit from research must be willing to foot the bill.

While the focus of most of the papers in this issue is research outside of academic medical centers, Nancy King’s examination of clinical innovation reminds us that the use of untested medical interventions within academic settings also may evade effective

⁶ Mark Barnes & Patrik S. Florencio, *Investigator, IRB, and Institutional Financial Conflicts of Interest in Human Subject Research: Past, Present, and Future*, 32 SETON HALL L. REV. 525 (2002).

⁷ *Id.* at 525.

⁸ *Id.* at 527.

⁹ Nancy N. Dubler, *Remaining Faithful to the Promises Given, Maintaining Standards in Changing Times*, 32 SETON HALL L. REV. 563 (2002).

¹⁰ *Id.* at 566.

oversight.¹¹ The reason stems from the definition of research under the federal regulations, which applies only to “systematic investigation[s] . . . designed to develop or contribute to generalizable knowledge.”¹² Because the use of untested medical interventions in the treatment of individual patients generally lacks “the theoretical and empirical preclinical groundwork that characterizes the search for knowledge generalizable beyond an individual patient,”¹³ King explains, it is not considered research, and therefore need not be submitted for IRB review. King argues that, despite this definitional problem, clinical innovation and research share important similarities, including “lack of data, lack of experience, and often, significant imbalances between benefits and burdens.”¹⁴ Indeed, she argues that innovative treatments may actually involve greater uncertainty than research, as research must be supported by preclinical data, while the basis for innovation might simply be “reasoning and intuition alone.”¹⁵ Accordingly, she argues that for most, if not all, innovations, the type of prior review and standardized informed consent processes that govern research would be appropriate.

The papers in this issue highlight both the promises and perils of the new direction in which biomedical research is heading. On the one hand, new sources of funding and incentives, greater access to potential subjects, and innovative collaborations between government, industry, and academia have created enormous opportunities for scientific advances. On the other hand, because our regulatory system has failed to keep pace with many of these changes, much of this new research occurs with only minimal oversight, creating risks for both individual subjects and the integrity of the research enterprise itself. Closing these gaps presents an important challenge to policy makers in the years ahead.

¹¹ Nancy M.P. King, *The Line Between Clinical Innovation and Human Experimentation*, 32 SETON HALL L. REV. 573 (2002).

¹² 42 C.F.R. § 46.102(d).

¹³ King, *supra* note 11, at 572.

¹⁴ *Id.* at 577.

¹⁵ *Id.*