

Transnational Standards for Scientific Research Involving Human Subjects *Situating the Role of Good Clinical Practice in Health Research*

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Chairperson Gutmann and Distinguished Members of the Commission,

Thank you for the invitation to testify before you on transnational standards for scientific research, focusing on the role of Good Clinical Practice. I wish to express a deep appreciation for the important work assigned to this Commission by President Obama. The international research community welcomes the investigation of the US Public Health Service supported research into sexually transmitted diseases in Guatemala involving the intentional infection of vulnerable populations in Guatemala between 1946 and 1948. We also value the President's commitment to take this as an opportunity to conduct a thorough review of human subjects protection 'to determine if Federal regulations and international standards adequately guard the health and wellbeing of participants in scientific studies supported by the Federal Government'. Herewith I summarize my testimony and the ensuing discussion. I include as well the full set of slides prepared for the testimony.

The work of Dr. Susan Reverby in uncovering and bringing to the public's attention the Guatemalan studies is to be strongly commended. The continuation of this investigation by the Centers for Disease Control and the Guatemalan government as well as this Commission is of great importance to our collective commitment to improve human subjects protection in scientific research.

My testimony on the role, contribution, and limitations of Good Clinical Practice (GCP) regulations and guidances focused on the contribution of an ethics of responsibility that complements our strong human rights basis. In particular, GCP has helped to establish clear standards for the responsible conduct of research on human subjects. From a transnational perspective, this responsibility now requires a commitment to full transparency in all scientific research involving human subjects, including health research in all its disciplines. Regulation and guidance on values, principles, and operational procedures are critical. Responsible scientific conduct requires more, however, than regulations and guidelines alone. Regulation needs to be supported by transparency based on a commitment to science as a public good. The initiation, design, data, and results of scientific research involving human subjects need to be carried out openly in the public domain.

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GCP, as regulation and guidance, has brought complex challenges to transnational research on human subjects. Seen from a transnational perspective, three pillars for building trust in human subjects protection are already in development within the system of US government supported research. As the US further articulates the national and transnational GCP framework for protecting human subjects, attention should be given to each of these pillars:

1. transparency: ensuring all research on human subjects is done in broad daylight;
2. the Common Rule: revised to be comprehensive and simplified; and
3. education: directed toward empowering (researchers empowering human subjects; research participants empowering science and society).

Experimentation on persons is never a right that may be claimed by an individual, group, organization, or agency. Experimentation on human subjects is a responsibility that can only be engaged in broad daylight alongside a verifiable commitment to, and compliance with, the highest national and transnational principles, standards, and regulations. Education and transparency are needed to complement and support a comprehensive and clear regulatory framework. No amount of rule-making or verification alone, however, can ensure that science involving human subjects is well designed and the participants are respected. Full assurances that science is conducted according to the highest (thus, the only acceptable) standards or that human subjects are fully respected, requires more than regulation. Regulation needs to be supported by full transparency throughout the scientific engagement. Clearly defined requirements for full transparency would provide a valuable complement to the rich set of regulations and guidances already existing, as well as greater public trust in the scientific enterprise across society and societies.

Just over 20 years ago GCP guidance was introduced in the European Community as a way to respond to the trust deficit in human subjects research. GCP brought with it two important contributions to the debate on research ethics:

1. GCP responded to the core principle in the *Declaration of Helsinki* requiring agreement between the highest standards of science and the highest standards of ethics within the exercise of research; and
2. GCP delineated an ethics of responsibility, identifying the roles and responsibilities of each party engaged in the research enterprise.

Through efforts by the World Health Organization (WHO) and the International Conference on Harmonization (ICH), GCP became the established transnational standard for integrating science and ethics in research involving human subjects. At the same time, the acceptance of GCP was neither immediate nor simple. The implementation of GCP suffered, in part, because of misunderstandings regarding its intentions and capacities. Some researchers resisted its requirements for comprehensive reporting and verifications. GCP also suffered in acceptance because of limitations within its own development: a focus on clinical trials for marketing medicinal products; its promulgation by the pharmaceutical industry and government agencies (without sufficient consultation among academics, IRB members, and patient organizations); and the decision by the drafters of the ICH GCP (the 'gold standard') not to more fully articulate ethical principles and commitments within the guideline (as found in other GCP regulations and guidelines).

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During the course of this 20 year history, GCP has been increasingly adopted (and adapted) by countries and regions, largely because its specificity renders it highly useful and verifiable, as well as because of it being embraced by the authority of the regulators in leading research countries and the WHO. While the ICH and WHO GCP's have functioned as reference points for regional and national implementation, countries and regions have found that adapting GCP to their local needs and priorities in health research have provided them with nationally identifiable frameworks for health research. GCP assists in articulating rules clearly that can be verified through a variety of oversight procedures. GCP also provides countries, particularly developing countries, with an instrument to ensure that health research is designed and implemented according to national health priorities and needs for local patient outcomes.

GCP is now a core regulatory standard for research involving human subjects in all 27 European Union Member States as well as in Canada, China, India, Argentina, Brazil, South Africa, Russia, Ukraine, Singapore, Thailand, Malaysia, New Zealand, and Australia. GCP continues to be developed further in other countries and regions because of its national and transnational value. At the same time, GCP has not replaced or substituted for the need for national and transnational guidances on values and principles in research ethics. Increasingly health research authorities, researchers, and patients are appreciating the complementary roles played by regulation supported by a wide array of guidelines. The increasing development of international guidelines brings a certain amount of confusion to researchers and the public. At the same time, researchers and the public transnationally appreciate the legitimacy of these guidelines with their varying backgrounds and aims. These variances contribute to achieving the highest standards in human subjects protection across disparate disease populations and cultures.

For example, since the promulgation of the European Directive on the Implementation of GCP (Directive 2001/20/EC) in 2001, European Member States have developed a more harmonized approach to health research. GCP has instigated greater information sharing and mutual understanding, more cooperation between academia and industry, highly improved national ethical review (IRB) systems, and increased patient involvement in the initiation and design of health research. Indeed, the European development of GCP over just the last 10 years has had a dramatic impact on human subject participation and protection in scientific research. While not all of this is due to GCP alone, most of this development would not have been possible without a shared European GCP framework. At the same time, every European country has insisted on its own approach to GCP in order to adjust research to its national health care system and ensure its own approach to health economics, health insurance, and public health priorities. Further, not all European GCP developments have been positive. In particular, there has been an increase in bureaucratic requirements, including procedures that may dissuade research and add costs.

The European Union remains committed to a GCP framework for health research. At the same time, Europe is engaged in a continual improvement of that framework. This is not unlike other regions and countries (for example, the ongoing WHO and PAHO initiatives, and developments in South Africa, China, India, Nigeria, Argentina, Thailand, and the United States). The provisions and requirements originally articulated by GCP guidelines in the early 1990's (particularly, WHO and ICH) have been significantly revised and adapted during their implementation into regulation and practice. GCP has provided the fundamental framework for an increasingly larger number of countries that want to take their place in mainstream research.

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A leading example of transnational cooperation in GCP began in August of 2009 with the United States and European Union Bilateral GCP Initiative. Through this initiative, based largely on collaboration and exchanges in GCP inspections, closer cooperation in developing good scientific methodology and cross-lateral human subjects protection has been achieved by sharing knowledge, resources, and practices. Although variances regarding specific GCP regulations and guidances exist between the partners, reference to a common GCP framework for promoting sound research and human subjects' protections has facilitated understanding, cooperation, and trust across the Atlantic. This provides researchers and research participants with improved clarity, insight, and confidence in transnational research.

GCP is increasingly associated and assimilated into US regulations for research involving human subjects. This is evident from the strong contributions made by the US government to the development of the ICH and WHO GCP guidelines. In 2008 the US adopted GCP into its regulation specifically to strengthen human subjects protection in transnational research. More recently, in 2009 the US opened the FDA GCP Office, which also has responsibilities for ethics in the agency. GCP is now the *de facto* international standard for scientific research involving human subjects.

To further promote human subjects protection and trust in US supported research, at home and globally, this Commission should consider the value the Common Rule has had over the last 30 years. From the transnational perspective the Common Rule, not only partially unified US government requirements for human subjects protection, it also strengthened and deepened them. It is now perhaps time to review, extend, update, and simplify this Common Rule within a framework of ethical principles and GCP. The Common Rule should be reinforced by requiring full transparency for all US supported scientific research involving human subjects. In addition, education programs directed toward empowering human subjects, and human subjects empowering science and health outcomes.

In the transnational perception, as well as in reality, US support of human subjects research is not limited to only research directly funded by the US government. The US support of organizations and infrastructure as well as access to markets for scientific (health, medicine) products is equally relevant from the points of view of ethics and society. A Common Rule covering only a certain number of government agencies represents internationally something less than a commitment by the US to the highest standard and may foster the impression that exceptions are ignored, even sanctioned. A thorough revision of the Common Rule would require a systematic review and simplification of current US regulation intended to protect research subjects.

The Common Rule should be directed and articulated according to an ethics of responsibility for those who seek the privilege of using human beings as subjects of experimentation. It needs to be seen transnationally (and nationally) as a rule that governs all research on human subjects. The current US regulatory framework, including the limited Common Rule, regulates largely the funding or products of research. For the greater protection of research subjects, the Common Rule should articulate 'common' requirements that apply to all scientific research on human subjects. Appropriate subparts of the Common Rule could then be more clearly directed at specific areas of research.

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GCP, the *Declaration of Helsinki*, and the *WHO Operational Guidelines for Ethics Committees That Review Biomedical Research* have demonstrated an enormous capacity to drive a transnational discussion that brings about real improvements to human subjects protection. A comprehensive and simplified Common Rule could become a key reference point for international cooperation on achieving common values, principles, and operations to guide transnational research.

GCP demonstrates the value of strong regulation and guidance for protecting human subjects, within countries and across countries. GCP has also shown us that it needs to be supported by full government and stakeholder commitment to transparency. A robust GCP framework not only requires transparency, but also encourages and facilitates it for all scientific research involving human subjects. The GCP framework also needs to be complemented by empowered research subjects who, through their equal participation in the research process, lead to better research designs and better scientific/health outcomes for patients and society. This empowerment requires education.

As with the transnational development of GCP, our commitment to human subjects protection needs to develop and be extended. The abhorrent practices disclosed in the Guatemalan experiments during the late 1940's are perhaps less likely today. Improved regulation, a wider acceptance of GCP, and the international debate on research ethics have made significant contributions. Nonetheless, we still are confronted regularly with human subjects research whose practices are nefarious: the inadequate consideration of vulnerable persons and populations, the neglect of patient populations and communities in designing research, ghost writing and inappropriate authorship claims, failures to report or share health research data. Full transparency, a comprehensive and simplified Common Rule, and empowering education programs would offer greater protections for research subjects and instill more trust in US supported scientific research.