Hearing on "21st Century Cures: Modernizing Clinical Trials"

Committee on Energy and Commerce
Subcommittee on Health
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Testimony of:

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Introduction

Good afternoon Chairman Pitts, Representative Pallone and distinguished members of the House Energy and Commerce Health Subcommittee. My name is Sundeep Khosla, M.D., and I serve as the Dean for Clinical and Translational Science at Mayo Clinic in Rochester, Minnesota. I also am the principal investigator of the Mayo Clinic Clinical and Translational Science Award (CTSA) from the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH). I salute the 21st Century Cures initiative of this Committee, and in the brief time allocated to me, I would like to summarize Mayo Clinic's perspective on the current status of the conduct of clinical trials in the United States and the tremendous opportunities, as well as significant challenges, we face for bringing new treatments to our patients.

Mayo Clinic Background on Research and Clinical Trials

Mayo Clinic is a not-for-profit health care system dedicated to medical care, research, and education. With more than 3,600 physicians and 60,000 employees, Mayo Clinic demonstrates a relentless and unwavering commitment to excellence, which has spawned a rich history of health care innovation. The Mayo Clinic logo of three interlocking shields symbolizes Mayo's commitment to excellence and interdependence in the three areas of Research, Education and Clinical Practice.

Mayo Clinic, which has facilities in six states, provides care for more than one million people annually from all 50 states and 135 countries around the globe. This year, we are celebrating our 150th anniversary as an institution, and throughout our history, the needs of the patient have always come first. In addition to clinical care, this includes conducting both laboratory-based and clinical research, including clinical trials. Indeed, as stated so eloquently by Dr. William Mayo, "The research we do today will determine the type of medical and surgical practice we carry on at the clinic tomorrow." Perhaps the most dramatic example of this commitment to research is the discovery of cortisone in the 1930s by Dr. Edward Kendall and his subsequent partnership with a clinician who saw patients with arthritis, Dr. Phillip Hench, leading them to test cortisone clinically in a patient in 1948. The rest is history, including the awarding of the Nobel Prize in Physiology and Medicine to Drs. Kendall and Hench in 1950. Since then, Mayo Clinic has played a critical role in pivotal clinical trials in many areas, including the treatment of diabetes, osteoporosis, heart disease and cancer. Mayo Clinic also had identified clinical trials as an extremely high priority for Mayo research.

Future of Clinical Trials

It is safe to say that with the investment in discovery science at academic medical centers throughout the country by the NIH over the past several decades, we are now in an era where there are more possibilities for understanding disease pathways and developing new drugs than ever before. These are truly exhilarating and exciting times to be a scientist involved in biomedical research. Thanks in large part to the NIH-supported human genome project, there are now literally thousands of new potential drug targets, and patients with many serious diseases

have the right to have real hope that cures for their diseases may be achievable in their lifetimes. With these opportunities, however, come significant challenges. Perhaps the biggest of these is what has come to be called by many the translational "Valley of Death." This refers to the fact that the average length of time from target discovery to approval of a new drug currently averages approximately 14 years, the failure rate exceeds 95%, and the cost per successful drug exceeds $2 billion, after adjusting for all of the failures.

To address these challenges, Dr. Francis Collins (NIH Director) created the National Center for Advancing Translational Sciences (NCATS) in December 2011. The mission of NCATS is "To catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of interventions that tangibly improve human health across a wide range of human diseases and conditions." Largely through the Clinical and Translational Science Awards (CTSAs), NCATS is pursuing this goal at multiple levels, including facilitating new drug discovery, providing the tools to better understand human physiology and disease, discovering new biomarkers, and most relevant to the discussion today, enhancing the conduct of clinical trials.

As astutely recognized by this Committee, the clinical trials process in the US, and indeed around the world, needs to be modernized. At a national level, NCATS is doing this by funding CTSAs at 62 sites around the country, thereby essentially creating a network of potential clinical trial sites. Thus, the vision is that high priority clinical trials, funded either by NIH or by industry, could be run very efficiently through all or part of this network. However, this is clearly not as easy as it sounds.

First, each institution currently has its own Institutional Review Board (IRB) that reviews human studies, and there are routinely considerable delays in multi-center clinical trials as each IRB reviews and eventually approves a clinical trial protocol. Additional delays are encountered when modifications are made to a clinical trial, leading each site IRB to review those modifications. A goal that the CTSA network is pursuing is to have IRB reciprocity between as many sites as possible, and potentially all 62 sites, so once the IRB at the primary study site approves the protocol, that approval is accepted by the remaining sites. This "IRB reliance" model is currently being rolled out through multiple CTSA sites and has the potential to significantly accelerate the conduct of multi-site clinical trials.

Second, there needs to be much greater interoperability of the electronic health records. This could facilitate, for example, a study investigator's search across all 62 CTSA sites and beyond for the potential pool of study participants at various centers, which – with appropriate privacy protections – could allow her/him to select the ones where the study could be most rapidly conducted. While not the topic for today, interoperability is also critical for other types of outcomes research, including comparative-effectiveness research in real work clinical practice.

Third, for a national network of clinical trial sites to truly function efficiently, there needs to be greater harmonization of regulations across federal agencies and across states. Just as an example, an investigator today has to deal with somewhat different regulatory requirements from the Office for Human Research Protections (OHRP) (Common Rule), the Food and Drug Administration (FDA), and the Office for Civil Rights (Health Insurance Portability and

Accountability Act [HIPAA]) privacy rules. Superimposed on this are individual state requirements.

How Congress Can Help

What can Congress do to help facilitate clinical trials at the national level? First, continue to support the efforts of NCATS and the CTSAs through ongoing and, if possible, enhanced funding. As summarized by the June 2013 Institute of Medicine (IOM) report on the CTSA program, "The IOM Committee found that the CTSA program is contributing significantly to advancing clinical and translational research," although they did recommend "a number of revisions to make the program more efficient and effective and to ensure its future success." Second, help develop policies that encourage IRBs to have greater reciprocity with other institutions and thereby avoid duplicating efforts multiple times for a given clinical trial. Third, provide funding and incentives for developing greater interoperability of medical records across the country. Finally, develop policies for greater harmonization of regulations across federal agencies and across states.

The responsibility for modernizing clinical trials falls also, however, to the individual academic medical centers. Each step in the clinical trial process needs to be closely examined and potentially modified. Prior to study activation, the time required for contract negotiation with industry and IRB approval should be made as short as possible. The use of "master agreements" between academic medical centers and companies, as well as greater IRB reciprocity (as noted above), would greatly facilitate relieving this bottleneck. An additional issue that often causes considerable delays is disagreements between the medical center and the industry sponsor

regarding the use of biospecimens; having a more streamlined biospecimens policy that is broadly accepted across sites and companies would be of tremendous value. There also needs to be a greater feasibility assessment for subject recruitment at each site in order to avoid initiating studies that are doomed to fail at that site.

Following activation of the clinical trial, there is a need for better electronic capabilities to enhance recruitment, screening, enrollment and tracking of study participants. There also is a tremendous need to train young clinicians in the conduct of clinical trials in order to have both a robust cadre of clinical trialists as well as a pipeline for future clinical trialists. Finally, many institutions struggle with having sufficient ethnic and racial diversity in a given clinical trial, and ways to enhance the participation of minorities in clinical trials are clearly needed. This also has been a problem in terms of representation of women in trials. While many of these issues are local to each academic medical center, Congress can help by providing incentives to enhance the ability of the medical centers to streamline their clinical trial process. It is only through a concerted national and local effort that the problem of modernizing clinical trials can be adequately addressed.

Industry also must play a role in modernizing clinical trials, in partnership with academia and regulatory agencies. The current clinical trial model of a placebo-controlled, randomized, double-blinded clinical trial may not be the most effective model, particularly for early phase studies. Thus, there is growing interest in alternate clinical trial designs, including "adaptive trials," which aim to use the information generated in the trial as it emerges, not simply when the study has been completed. As an example, by pre-specifying analyses to be conducted during the

trial, subjects could be allocated to drug doses that show the greatest benefit early on, thereby exposing fewer patients to ineffective doses, resulting in more ethical treatment of patients. Importantly, the FDA has published guidance on the appropriate use of adaptive clinical trial designs. However, there needs to be ongoing dialog between pharma, academia and the FDA in developing more creative, and yet scientifically rigorous, methods to conduct clinical trials more efficiently. In short, the science of clinical trial design needs to continue to advance, and this should be facilitated by the FDA and other regulatory agencies.

Conclusion

In summary, the opportunities for bringing new drugs to patients have never been greater, but significant challenges remain. Congress can, and should, help this effort through continuing and enhancing support for discover science, NCATS, and the CTSA system. Legislative policy changes and incentives are necessary to remove specific roadblocks in the clinical trials process. Together, government, the private sector, and academic medical centers must all step up and do all we can to rapidly deliver discoveries to our patients.

About Mayo Clinic:

Mayo Clinic is the first and largest integrated, not-for-profit medical group practice in the world. Doctors from every medical specialty work together to care for patients, joined by common systems and a philosophy that the needs of the patient come first. 4,100 physicians and scientists and 53,600 allied health staff work a Mayo which has campuses in Rochester, Minn.; Jacksonville, Fla.; and Phoenix/Scottsdale, Ariz. Mayo Clinic also serves more than 70 communities in the Upper Midwest and Georgia through Mayo Clinic Health System. Collectively, these locations care for more than 1.1 million people each year. Mayo Clinic is governed by a Board of Trustees composed of public members and Mayo physicians and administrators.

Mayo Clinic's mission is to inspire home and contribute to health and well-being by providing the best care to every patient through integrated clinical practice, education, and research.

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