Developing a Clinical Trials Infrastructure in the United States

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*Participants in the activities of the IOM Forum on Drug Discovery, Development, and Translation

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INTRODUCTION

Clinical trials in the United States have a rich history of involving academic, industry, and government institutions (e.g. the National Institutes of Health [NIH]) to address important medical questions. Nonetheless, over time, clinical trials in the United States have become too expensive, difficult to enroll, inefficient to implement, and ineffective to support the development of new medical products using modern evidentiary standards. The nation’s capacity for conducting clinical trials is also inadequate to provide the evidence needed for rational clinical practice. For instance, clinical practice guidelines are routinely issued by professional societies but only a small proportion of these guidelines are based on high-quality evidence from randomized trials (Lee and Vielemeyer, 2011; Tricoci et al., 2009). Furthermore, there is a growing recognition that patients and other stakeholders need to be partners in the development, conduct, and interpretation of clinical trials. Importantly, community medical practitioners and other important caregivers (for example, clinical psychologists) provide an avenue for partnering with patients but largely do not participate in clinical trials as investigators or as practitioners willing to refer their patients to trials. This diminishes patient access to trials and decreases the generalizability or “real-world” relevance of trials that are conducted.

Clinical trials have been funded and sponsored by NIH, other government agencies, academic groups, voluntary health organizations, and industry. The infrastructure to support the trials is often developed specifically for a given trial or in a sponsor-specific manner, with the exception of trials performed by cooperative groups or other organized structures, including NIH’s AIDS Clinical Trials Group [ACTG] network at the National Institute of Allergy and Infectious Diseases and the Cancer Therapy Evaluation Program [CTEP] at the National Cancer Institute, as well as networks set up by patient groups (e.g., the Cystic Fibrosis Foundation and others). Investigators and staff may be recruited for the purposes of a specific trial only, and the team is disbanded after trial completion. Efforts to develop a consistent infrastructure for clinical trials have been limited in scope, often considering only issues of investigator or patient recruitment. Although there are examples of more expansive approaches to developing an infrastructure (e.g., adverse event reporting conventions in cancer studies), in general these efforts have not translated into harmonized national or international efforts. As a result, there are few clinical research structures in the United States that combine mature clinical trials infrastructure, experienced staff, and established procedures that also have access to large numbers of patients with a specific disease or disorder.

1 Participants in the activities of the IOM Forum on Drug Discovery, Development, and Translation. This discussion paper was presented in draft form at the Forum’s November 2011 workshop, Envisioning a Transformed Clinical Trials Enterprise in the United States: Establishing an Agenda for 2020, and finalized by the authors following the workshop.
Over the past decade, factors including the increased number and size of clinical trials to support the development of pharmaceutical agents have resulted in a shift to international multicenter trials in which patients are recruited through open enrollment as a global effort. Since the United States constitutes only 5 percent of the world’s population and provides one of the most expensive and least efficient clinical trials enterprises, it is not surprising that many trials have a very small representation of U.S. participants, or none at all. This has raised concern with respect to the applicability of the results to patients in the United States and whether the human-subject protections and overall quality of international multicenter trials is equivalent to trials that are performed in the United States.

Development of an explicit and transparent national clinical trials infrastructure may potentially increase access to clinical trials for multiple stakeholders. For example, training and recruitment of less-experienced investigators who practice in settings that are relevant to the clinical questions being addressed may improve the applicability of the results to the issues being studied. In addition to improving the ultimate applicability and uptake of clinical trial results, these community-based investigators could provide important expertise, in partnership with patients, in developing innovative clinical trial designs that efficiently study outcomes that are of interest to patients and the public. Patient access to clinical trials may also be improved by taking advantage of nontraditional means for awareness and enrollment, such as web-based trials and the use of social media.

An appropriately implemented infrastructure for clinical trials would recognize the value of participation in trials in the continuous improvement of health care. Quality improvement and evidence-based medicine require the discipline of clinical investigation as an integral component of successful implementation. A key objective of health care reform in the United States is to encourage use of the most effective therapies and implementation strategies. This will require multiple types of clinical trials conducted in many different settings. Academic centers that are involved in clinical trials often take advantage of the infrastructure that is created to address clinical questions. In contrast, nonacademic practitioners and institutions may not have the processes and support to use clinical trial methodology in quality improvement. Broader access to clinical trial expertise may be necessary to conduct trials in real-world settings, evaluate special populations, and understand the long-term consequences of interventions.

Development of a clinical trials infrastructure can only be a component of the solution to the issues highlighted, but the potential of key initiatives to support or catalyze change in the clinical trials capacity and quality in the United States is worth considering and is the topic of this discussion paper. It is also worth considering that while electronic health records, standard nomenclature, and data standards clearly are critical to an efficient and scalable infrastructure, these efforts remain immature with respect to broad implementation in the U.S. health care system. Accordingly, the following discussion topics are proposed:

● What would constitute an optimal clinical trials infrastructure in the United States?
● How would such an infrastructure address the problems stated above? Should infrastructure solutions be universal, tailored to specific research settings, or integrated through common standards?
● What would be required to develop a clinical trials infrastructure? What is achievable in the near- versus long-term?
ELEMENTS OF AN OPTIMAL CLINICAL TRIALS INFRASTRUCTURE IN THE UNITED STATES

Although the sponsor, investigators, and purpose of clinical trials vary considerably, there are common underlying components that can be considered with respect to potential for a clinical trials infrastructure in the United States to enhance quality and reduce the cost of clinical trials. Specifically, the following key common elements are required for most clinical trials, with the exception of non-interventional studies where certain components listed below are not necessary. These components could provide the framework for a sustainable and continuous clinical trials infrastructure:

- Investigator recruitment
- Experienced clinical trial personnel
- Protocol development support
- Regulatory approval to conduct the clinical trial (e.g., Investigational New Drug [IND] applications in the United States)
- Good Clinical Practice (GCP) requirements (primarily for interventional clinical trials), including
  - informed consent,
  - ethical review,
  - human research participant protections,
  - privacy considerations,
  - investigator training and qualifications, and
  - adverse event (AE) reporting
- Contractual agreements between sponsors, institutions, and investigators
- Participant recruitment plan
- Coordination of clinical trial investigators and centers both in the United States and globally
- Quality-control systems to ensure GCP compliance
- Data collection, management, and analysis
- Data standards (e.g., medical concept coding, diagnosis coding, data standards)
- Communication of results (publication)
- Registration of clinical trials and results on ClinicalTrials.gov

POTENTIAL AREAS THAT A NATIONAL CLINICAL TRIALS INFRASTRUCTURE COULD ADDRESS

Investigator Training

- Standardized core content and the availability of Continuing Medical Education (CME) credits for clinical investigator training. Standardized online training and certification would avoid the redundancy of many trial performance sites each developing their own training programs. Also, investigators participating in multiple initi-
atives could satisfy the training requirements periodically for all projects they are working on and physician-investigators could receive CME credit for their participation in clinical research.

- **Centralized certification processes for clinical investigators.** A central online training and certification system as described above would allow sponsors and institutions to centrally verify that participating investigators meet the training and expertise requirements of a given project.

**Investigator Recruitment**

- **Information technology (IT) solutions for matching investigators to sponsors.** If central online information could be available on the expertise, capacity, resources, and patient access of potential trial sites, this would be a good initial step in assisting with site selection. The number of patients with a given condition who are potential trial participants is typically overestimated. To address this, these data could be drawn in a de-identified manner from clinical databases such as electronic medical records (EMRs) or billing records.

- **Development of investigator networks, primary care versus specialty/academic care.** The relationship of the infrastructure with respect to investigator recruitment, training, and support will be important in the development of clinical research networks. For example, investigators in the primary care setting typically are identified by geographical proximity to academic centers. The infrastructure to support investigators in this circumstance would likely be coordinated by the core center. However, a web-based strategy for developing an investigator network is less dependent on geographical concerns or central academic support and would allow investigators to self-organize. However, in both methods for identifying investigators, common approaches to training and certification would facilitate the development of the network.

- **Development of novel approaches to clinical trial development.** For example, clinical questions or concepts could be placed in an online site where potential investigators or sponsors could propose potential trials. This model would allow patients and other stakeholders to propose questions to be answered through clinical trials. Engaging patients in the identification of key research questions that are important to them could also help facilitate their participation and enrollment in clinical trials (Institute of Medicine [IOM], 2012). NIH, industry, academia, professional societies, voluntary health associations, and patient advocacy groups could facilitate this partnership between patients and researchers. An online trial infrastructure would serve many stakeholders. Therefore, this could be done in partnership among private and potentially government organizations.

**Investigator/Clinical Trial Staff Support**

Lack of coordinators/administrative support is one of the barriers to engaging physicians outside of academic centers to participate as investigators in clinical trials. Expansion of the in-
vestigator network for clinical trials should consider approaches to supporting these activities. A flexible infrastructure to provide clinical research coordination and administrative support for clinical trials should be considered along with many of the similar training and certification elements for investigators. Some of the areas in which support is needed for the various components of a clinical trial include the following:

- **Standardized contracts** are key to accelerating the contracting and subcontracting in clinical trials, as contracting typically causes the greatest delays in start-up. Posting trial agreements transparently online and pre-negotiating master trial agreements between potential sponsors and networks can accelerate the start-up of trials as only the few project-specific issues would then have to be negotiated.

- **Standardized approach to reimbursable medical expenses.** It would be helpful if a standard fee schedule for clinical research tasks was available, adjusted for regional and local differences in cost, for example, adjusted in relationship to Medicare or Medicaid payments.

- **Management of privacy issues to facilitate observational trials.**

  **Regulatory Approval**

- Development of a [globally harmonized regulatory database, nomenclature, and identification of clinical trials](http://ClinicalTrials.gov) involving investigational molecules or devices and encouraging regulatory authorities to use this database in facilitating regulatory approval.

- **Centralized institutional review board (IRB) review** for multicenter projects enhances human subjects’ protection. The often serial and circular review of one protocol at multiple sites typically does not add value to the ethics review. Multicenter trials should designate an IRB of record to provide a review. After passing the initial review at the central IRB, the near-final protocol should be sent to the participating institutions for comments within 2 weeks. These comments should be provided by a designated institutional official, but not a full IRB. This allows for the exceptional modification of the consent or protocol to adjust to local context, but will avoid the delays that arise from multiple IRB reviews.

  **Recruiting Clinical Trial Participants**

- **Patient education** is very important to successful trial recruitment. This includes education of the general public as to the need for clinical trials to bring better treatments to people. There are already several online and print resources on clinical trials in general.

- **Disease-specific and consumer friendly solutions for aggregating clinical trial reporting may improve the understanding of the value of participating in clinical trials.** As an example, an individual or health care professional could opt-in to get disease-specific clinical trial information that aggregates ClinicalTrials.gov data and literature
reports and provides links to trials and investigators that are recruiting patients. The service could be paid for by the trial sponsors that are recruiting. However, regulatory implications for sponsors and the assurance that accurate information is provided to the public would need to be addressed.

- **Pre-identification of individuals interested in clinical trials.** If people could indicate their interest in trial participation, trial recruitment could be facilitated. Ways to indicate an interest could include carrying a document similar to an advanced directive or patients being asked at hospital admission or at check-in at an outpatient office if they would like information on trial opportunities. It could also include carrying a card, similar to an organ donor card, identifying an interest in participating in research.

- **Integration of electronic health records with clinical trial databases** would be another means of improving clinical trial recruitment and also developing realistic estimates of potential patients available for specific trials. Patients could be offered an opt-in approach to be made aware of clinical trials for which they might be eligible as part of a health care system interaction. Physicians could also be provided with alerts when patients meet criteria for enrollment in a clinical trial. Examples of the latter have been successfully implemented by some investigators based on laboratory data or other electronic medical information.

- **Developing a patient-friendly interface with ClinicalTrials.gov.** Online information on the availability of trials would be helpful so that patients, their families, and their physicians could more easily find information on trial opportunities. ClinicalTrials.gov is an excellent and complete resource of trial information. However, it was not designed to help find trial opportunities. If a patient-friendly “front porch” to ClinicalTrials.gov could be created that would use the high-quality and up-to-date information on ClinicalTrials.gov but make it searchable—for example, by disease, geographic location, and basic entry criteria for the trial—this could become a very useful tool for patient education and clinical trial recruitment efforts. Other approaches could include use of social media or “opt-in” for clinical trial information triggered by health care or pharmacy interactions. Transparent communication of clinical trials results should be automated and reliable in order to increase visibility into the clinical trials enterprise. ClinicalTrials.gov has increased transparency in the clinical trials enterprise with regards to the registration of trials along with their key characteristics (including population, sample size, entry criteria, and primary outcomes). More recently, the reporting of results has been added to the registry. These results are transparently communicated, but provided at a level that is not aimed at patients and the public. A lay abstract describing the results could be provided through a “patient portal.” An IT system to provide specific information on trial opportunities could be created in partnership with industry, the public sector, and patient groups.

**Conducting Clinical Trials**
- **Clinical trial identifier standards for identification of patients/trials in EMRs.** EMRs should include codes for clinical research. When possible, harmonized data standards for use in clinical research should be mapped to electronic health records to facilitate screening.

- **Development of a centralized electronic tool for notifying investigators, regulators, and IRBs of AEs, “Dear Investigator” letters, and clinical trial amendments.**

- **Online protocol-authoring tools and templates** can help create more uniform protocol formats and thus facilitate the correct implementation of research protocols by research staff who are often involved in several protocols at a given site. Online protocol systems can also facilitate the central management of amendments and communication.

- **Global harmonization of regulatory requirements for AE reporting to agencies, investigators, and IRBs to reduce clinical trial complexity and cost.** Adoption of the Development Safety Update Report will also facilitate a uniform approach to assessment and reporting of safety issues.

- **Continued development of guidance documents relating to clinical trial design, end-points, and other key considerations is critical.** In addition, revision of guidance documents to update recommendations should be done in a timely fashion and include external stakeholder input. Cross-stakeholder forums should be developed to review clinical trial metrics (e.g., the utility of various clinical trial designs) with a focus on improving the efficiency of the clinical trials enterprise.

- **Advance fit-for-purpose AE reporting.** Alignment of global AE reporting to regulators vs. investigators could increase the efficiency and effectiveness of clinical trials, especially trials conducted at multiple international sites. The burden of AE reporting to investigators and IRBs could be reduced by focusing on significant new safety information and periodic aggregate summary reports.

- **Online management of informed consent and informed consent updates.** Similarly, informed consent templates could be managed and shared online. Overall, consent forms would benefit from simpler, shorter language.

**WHAT WOULD BE REQUIRED?**

One model for a clinical trials infrastructure involves organizing disease-specific networks that include medical practitioners in the community. These networks would not be designed to evaluate a single agent, but rather to evaluate a series of interventions, including investigational therapies or preventives. Standardized data collection and protocols to reduce costs would be essential. Inclusion of community practitioners with the appropriate support and this infrastructure could increase patient access to trials, trial accrual, and engagement of the medical community in evidence-based medicine. Increasingly, practitioners are aligned with local or re-
gional health care systems—both public and privately run. Ideally, such systems would participate in and support clinical trials on problems important to their community as part of quality improvement.

When the creation of disease-specific networks does not make sense because of the resource requirements—which may be challenging in the current environment for less common diseases or for indications in which few trials take place—other alternatives may be more feasible. For example, the Clinical and Translational Science Awards (CTSA) consortium of 60 medical research institutions across the nation could organize clinical trial networks across a broad range of diseases. Alternatively, these networks could focus on a group of diseases or a particular population (e.g., children). In all cases, community practitioners should be supported to participate by provision of training and logistical and administrative support. A “virtual coordinator” could remotely support several community practice sites in a clinical trial network. Another approach is a “hub and spoke” system in which a larger medical center would partner with community health care providers on designing and implementing clinical trials.

How could such networks be supported? Funding such an enterprise in the face of current budgetary constraints is the primary issue. Ongoing costs could be mitigated by the use of consortia, contribution of disease groups, and fee-for-service arrangements for evaluation of new technologies. However, existing structures, including CTSA, health care systems, and academic medicine, do not have sufficient resources to dedicate to creation of a trials network, nor is this seen as part of their core mission. Despite these problems, the question remains: how can the United States afford not to have a clinical trials infrastructure? As the cost of health care continues to rise, advances in basic biomedical science envision new interventions, and the costs of medical product development soar, an effective, efficient, and reliable mechanism for generating evidence on the value of health care must be seen as a necessity, not an option. We cannot afford to continue without the means to generate a solid evidence base for medical practice.

REFERENCES