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Standards for Clinical Research: Keeping Pace with the Technology of the Future

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Approximately 70 years ago, the concept of randomization of individual participants in clinical trials was first introduced, along with informed consent, the ethics of randomized controlled trials (RCTs), and blinding of treatment assignment.[1] A decade later Kaplan and Meier described a mathematical approach to estimating event-free survival at any time T, allowing comparison of the response to treatments over time. [2] Building on this strong foundation, clinical investigators began performing a rich array of RCTs that attempted to answer the question whether a medical intervention was effective, under the ideal circumstances of a circumscribed population and defined treatment protocol. (Figure 1) Blinded RCTs are useful for evaluating investigational products and are central to the development pathway of new medical products. The efficacy and safety data generated in an RCT provide regulatory authorities with the information they need to judge whether a product can be approved for use in clinical practice.

In 1990, just over four decades after the seminal RCTs, the International Conference on Harmonization of Technical Requirements for Regulation of Pharmaceuticals for Human Use (ICH) was established. [3] The ICH effort began as a collaboration of drug regulatory authorities in the United States, Europe, and Japan along with representatives of pharmaceutical trade associations in those regions. The ICH mission is "… to make recommendations towards achieving greater harmonization in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration, thereby reducing or obviating duplication of testing carried out during the research and development of new human medicines." [3] Notable work products of the ICH group include guidelines documents, standardization of terminology in the Medical Dictionary for Regulatory Activities (MedDRA), and establishing a standard format (Common Technical Document) for assembling the submission dossier for a new pharmaceutical product to regulatory authorities. [4, 5, 6]

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Of particular interest, the ICH Guidelines are divided into topical areas focusing on Quality, Efficacy and Safety. Within the Efficacy category, the document entitled “Good Clinical Practice” (GCP) [7] guideline describes the clinical trial responsibilities of investigators, monitors, sponsors, and Institutional Review Boards. GCP is organized around 13 principles, some of which are core principles of human investigation that are derived from a pivotal document on ethics -- the Declaration of Helsinki. [8] Other principles and sections in ICH focus on areas such as the organization of the investigator’s brochure, instructions on handling of investigational products, adverse event reporting, procedures for monitoring the conduct of the trial at study sites, and requirements for managing essential trial documents.

GCP standards have permeated the contemporary research infrastructure. Investigators participating in clinical trials of FDA-regulated investigational products must undergo training in GCP. Centers receiving a Clinical Translational Science Award must also provide GCP training for study personnel engaged in NIH funded clinical trials. [9] The values and benefits of GCP and ICH standardization to both the pharmaceutical industry [10] and drug regulatory authorities [11] ultimately extend to patients and the clinicians who care for them. A parallel effort for standardization of medical device development has been undertaken by the International Standards Organization (ISO), an independent, non-governmental organization based in Geneva that publishes international standards on a broad range of topics. [12]

As clinicians caring for patients, we recognize that the ideal circumstances surrounding trials evaluating investigational products, while critical from a regulatory perspective, may not adequately inform usual clinical practice that may differ in important ways from the trial environment. (Figure) This distinction between either studies examining investigational agents or small explanatory (mechanistic) clinical trials on the one hand or real-world (pragmatic) trials on the other has been previously described. [13] Practical issues to date have limited the expansion and conduct of pragmatic trials. Busy clinicians in practice lack access to the infrastructure to conduct trials and the training/documentation requirements (e.g. GCP) have been considered barriers to participation in trials. [14] Inflexible standards required for the conduct of clinical trials are part of the problem.

While the explanatory trials in cardiovascular medicine have provided our clinical care system with a dazzling array of options, we lack a well-coordinated pragmatic trial extension to our system of development of medical interventions. Ideally, there should be a smooth transition from approval of new products to establishing their place in clinical practice by trials testing them under conditions of usual care. An explanatory-pragmatic continuum indicator tool has been developed to guide investigators during the planning stage in mapping a proposed trial along nine domains (Figure 1).[15]

That explanatory-pragmatic continuum is within reach. The emergence and dissemination of electronic health records (EHRs) coupled with a dynamic “learning healthcare system” hold great promise for enabling the performance of much needed pragmatic trials. [16] Embedding randomization at the point of care and using the EHR as the case report form of the future have been proposed as a potential platform to implement such trials. [17] Future versions of the EHR should support pragmatic trials, including streamlined adjudication of events,

incorporation of data reported by patients or transmission of data from wearable sensors or implanted medical devices.

While the technology has advanced to the point where it should theoretically be possible to conduct pragmatic trials more easily, several concerns remain. [18] There is a tension between the more stringent regulatory approach that governs explanatory trials (e.g. the many components of GCP) and pragmatic trials. This is the subject of an interesting opinion piece by Mentz et al in this issue of *Circulation*. [19] They emphasize not only the use of EHRs to facilitate performance of pragmatic trials, but their table 2 also offers some practical solutions for harmonizing GCP with pragmatic trials. It should be noted that many of the suggestions in their table 2 could also facilitate the implementation of mechanistic trials. Mentz et al also discuss other issues that need to be solved when using EHRs to perform pragmatic trials—the completeness and veracity of the data (e.g. ascertainment and verification of endpoint events; missing data; loss to followup). These are critical GCP issues for explanatory trials but their relative importance in a pragmatic trial will depend on the focus and scope. [15]

It is useful to break GCP into its component parts, retaining the principles of autonomy, justice, and beneficence but adapting many of the other components to facilitate performance of pragmatic trials. (Figure) For example, once efficacy and safety are assessed under ideal circumstances, the reporting and monitoring requirements can be adjusted to accommodate a pragmatic approach.

Other approaches to clinical research include case:control and cohort studies, epidemiologic and population-based observations. These do not involve randomization of subjects to medical interventions and may not even involve informed consent. Such observational studies are likely to evolve into Big Data analytic approaches in the future. Big Data analysis integrates multiple inputs from previously acquired data (e.g. genomics from a tissue specimen, epidemiologic data, wearable sensors, medical devices, EHR). A predictive analytic system is used to generate recommendations for more precise care of individuals and populations. [20] Important sociopolitical issues will need to be addressed including privacy and data sharing prior to widespread utilization.

We can be proud of our progress in clinical trials and the seemingly limitless opportunities offered by the technology of the digital age. While standards are needed along the continuum of clinical research, they vary depending on the objectives, risks, and complexity of the type of investigation. It is imperative that we discuss how to utilize emerging technologies to support a range of clinical trials and Big Data analyses in an ethical fashion, while also guarding against the generation of inaccurate or misleading data that could misdirect clinical care. Any standards for the conduct of clinical trials must protect the safety of and respect for research participants, maintain scientific integrity and objectivity, and serve to promote public health. Standards for the conduct of all trials, whether small exploratory trials, trials informing the safety and efficacy of investigational agents prior to approval, pragmatic trials that define appropriate use in the clinical context, or post-approval Big Data analytics of population data, must evolve to keep pace with and benefit from current technologies.

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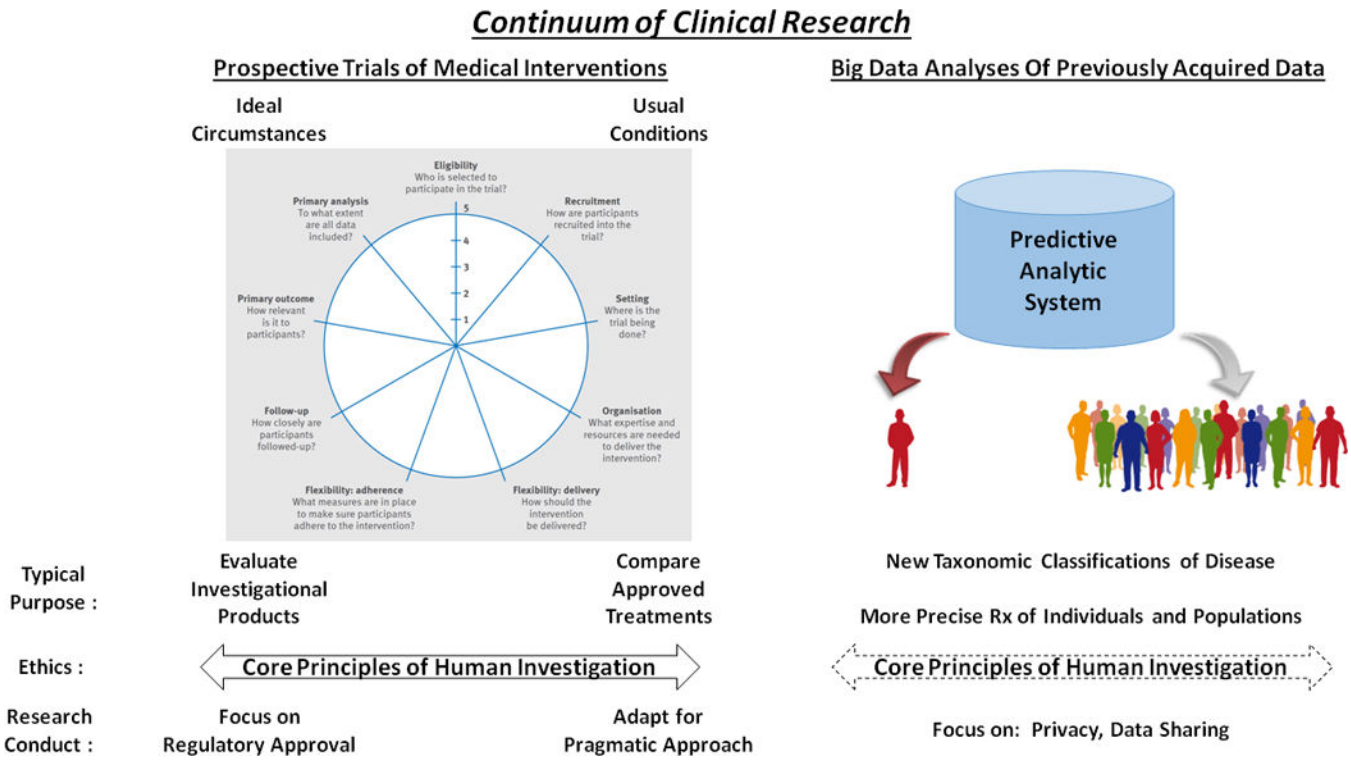

Figure 1.

Interface of the Continuum of Clinical Research and Research Standards. On the left is shown the spectrum of trials where research subjects are randomized to medical interventions and followed prospectively. These range from those conducted under ideal circumstances to those conducted under usual conditions of clinical care. A mapping tool is shown where investigators use a Likert scale to score a trial design along nine domains as to whether it is predominantly explanatory (score=1) or pragmatic (score=5). The typical purpose of the trial type and the ethics and focus of research standards are shown at the bottom left. The core principles of human investigation apply across the spectrum, but the focus of the research standards varies. Big Data analyses incorporate inputs (not shown) of previously acquired data into a predictive analytic system and generate recommendations for more precise care of individuals and populations. Depending on the type of information, it is important to be certain that the data are acquired in accordance with the core principles of human investigation (shown with dashed lines, since this may not be applicable in all circumstances). Here the research standards need to focus on privacy and data sharing. See text for further discussion. The diagram on the left is reproduced with permission from Ref 15: Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: Designing trials that are fit for purpose. *BMJ*. 2015;350:h2147.