THE FUTURE OF CLINICAL RESEARCH: THE CHANGE IN THE AIR.

Some dread it.

Others create it.

Either way, you know it is inevitable.

Change.

The clinical research industry is no exception. Ever since James Lind’s famous scurvy trial in 1747,1 where he demonstrated the affliction could be cured by the consumption of oranges and lemons, the concepts, tenets, and processes of modern clinical research have been evolving. This is no different today, with the global clinical trials market estimated to grow 7.5% annually to approximately $22 billion USD by the year 2021. Of that, medical device clinical trials are expected to contribute about a third, making transformation of the industry unavoidable.

Global politics, shifting regulations, and technological innovations—all big picture drivers of change— influence not only manufacturers of medicines and medical devices, but the consumers of these products as well. Economic factors affect markets, which drive changes to industry directly and indirectly via changes in regulations. Improvements in technology provide an impetus for changes to processes and efficiency.

These are our top predictions of what is in store for the clinical research industry.
Capitalize on efficiencies and improved data quality resulting from Meaningful Use initiatives

Improvements in technology and the development of electronic health records (EHR) combined with growing inefficiencies in healthcare have triggered federal programs designed to promote the acceleration and adoption of health information technology and EHR. Termed Meaningful Use, the Health Information Technology for Economic and Clinical Health (HITECH) Act and the American Recovery and Reinvestment Act (ARRA) in 2009, provided financial incentives for providers to phase in improved EHR adoption over a number of years. These programs have focused on improving patient quality, safety, efficiency, and reducing health disparities; engaging patients and families in their health, improving care coordination, improving population and public health; and ensuring adequate privacy and security protections for personal health information. As such, these provisions have begun to change how health care functions and as a result, how clinical research is conducted. From 2009 through 2015, the focus of meaningful use was to develop systems and achieve adoption of EHR. As of March 2016, over 9 in 10 hospitals eligible for the EHR Incentive program had achieved meaningful use goals for certified health IT. The focus of the later years, 2015-2019 and beyond is to support interoperability and improve patient outcomes to ensure that health IT is a tool for care improvement and not just an end to itself.

An outgrowth from the meaningful use initiative is the growing ability of clinical trials to tap into the EHR for more efficient and accurate collection of data. While complexities with privacy concerns and usage remain, FDA issued draft guidance in May 2016, called Use of Electronic Health Record Data in Clinical Investigations that provides direction on the integration of EHR and electronic data capture (EDC) systems and lays out best practices for the use of EHR data in clinical investigations.

A primary directive of this guidance is that the fundamental elements of data quality, in paper or digital form should be ALCOA, an acronym first coined at the FDA in the 1990’s2 that refers to source data that is attributable, legible, contemporaneous, original, and accurate. It provides recommendations for best practices when using both certified and non-certified EHR systems in clinical trials and presents general considerations for data modification, audit trails, informed consent, data privacy, and security.

Risk-based monitoring as best practice as sponsors move away from 100% source document verification

The drive towards gleaning the most from our blossoming digital data era has induced a convergence with risk-based monitoring (RBM). RBM is an alternative to 100% source data verification (SDV) and a means to ensure trial quality by focusing on areas with higher risk for error, adverse events, or non-compliance, and using EDC systems to trigger detailed monitoring following certain high-risk occurrences. RBM was reportedly first used as early as 2010 as a means to harness electronic data to improve efficiency and has been written about extensively (also here). In 2013, FDA issued a final guidance
document on RBM. Increasingly, data have been published to show the efficacy of RBM, and that the added impact on data quality that can be garnered with 100% SDV does not necessarily justify its cost for all studies.3

Sponsors are indeed moving toward RBM as the evidence supporting it accumulates. Morrison et al. reported that in 2009, only 12% of organizations conducting clinical trials used predominately centralized monitoring, a type of RBM, instead of on-site visits to oversee study site performance.4 However, in a 2016 report by MCC, the use of traditional 100% SDV has decreased from 75% of studies in 2013 to 62% in 2015.

Image courtesy of www.alinks.com

Increased utilization of adaptive and pragmatic trial designs

FDA’s 2010 draft guidance on Adaptive Design Clinical Trials for Drugs and Biologics and its 2016 guidance on Adaptive Designs for Medical Device Clinical Studies define an adaptive design as one that “allows for prospectively planned modifications based on accumulating study data without undermining the study’s integrity and validity.” The vast majority of these modifications are planned prospectively and described in the clinical study protocol prior to initiation of the study and can include changes to the study design, study conduct, statistical hypotheses, or analysis.

Adaptive study designs can increase efficiency by saving time, money, and resources. They may also improve the chance of success of a study by allowing for an adjustment to the sample size, which could provide additional power to a study that initially is not powered well enough to see a difference in signal, by allowing for a “mid-course” correction. These designs may also facilitate the transition between pre-market evaluation and post-market follow-up studies. Limitations to these designs include the need for more design-stage effort and added complexity, the possibility for operational or statistical bias if the design isn’t done correctly, and the risk that outcomes may change after the modifications, resulting in difficulty with interpretation.

The use of adaptive designs has been increasing. A Tufts senior leadership panel reported in 2013 that approximately 20% of clinical trials used adaptive designs and that this use is expected to increase significantly in the coming years, particularly in exploratory phase trials. In a 2016, systematic review of trials registered with clinicaltrials.gov and the NIMR
registry, Hatfield et al. reported an increase in adaptive trials from one study in 2001 to 25 in 2013.5

Another innovation in study design is the use of pragmatic trial design. This innovation in trial design was borne out of the repeated estimation that it takes an average of 17 years before 14% of research findings are translated into practice.6 Pragmatic research design is designed with input from patients, providers, and healthy systems to produce evidence that accelerates the integration of research, policy, and practice.7 They have also been referred to as partnership-based research or stakeholder-centered research designs and are intended to increase the likelihood of effective dissemination and implementation of study results. Whereas the traditional randomized control trial (RCT) tests a hypothesis under ideal conditions, a pragmatic trial compares treatments under everyday clinical conditions.

According to a presentation on challenges and opportunities for pragmatic trials by Bryan Luce, of PCORI, generally manufacturers have been reluctant to embrace pragmatic trials, partly due to the lack of demand by payers and health plans, and partly to a lack of definition of the requirements of pragmatic trials and a historic lack of guidance from FDA. Notably, FDA has started to acknowledge the utility of practical information in the regulatory pathway. They published draft guidance on July 27, 2016 called, Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices, to clarify how the agency evaluates real-world data to determine whether it is acceptable and robust enough to use in FDA regulatory decision-making. This guidance gives merit to the idea that standard phase III or pivotal clinical trials may be a) insufficient to supply all relevant data for accelerated dissemination of research, and b) not be the only means to obtaining valid and robust data adequate for regulatory approval of a medical product.

**Evolving partnerships with clinical research organizations**

Outsourcing of clinical trial services to clinical research organizations (CROs) is estimated to occur for 20-25% of the total global market for clinical trials. With the global medical device industry expected to reach USD $440 billion by 2018, and with growing pressure on manufacturers to obtain clinical data, staffing the increasing number of medical device clinical trials is estimated to grow substantially. In her June 7, 2016 white paper, Abigail Esposito, posited that the global medical device CRO market was valued at over USD $5 billion in 2015 and is expected to grow to over USD $7 billion by 2018. This market growth combined with cost containment efforts has driven the CRO market and has necessitated the development of more efficient ways to engage CROs.
In a survey by Worldwide Clinical Trials, 29% of respondents said that innovation in trial management would have the greatest impact on clinical development and 26% said that innovations in patient recruitment would have the next biggest impact. CROs and sponsors have responded to the current and expected challenges by starting to change paradigms in how they engage one another. In a traditional model, a sponsor would contract with a CRO to carry out specific functions of a trial like site qualification or initiation visits, source data verification, data management, or data safety monitoring boards. In this model, several CROs may have been used and a sponsor staff member would coordinate and manage the vendors. An alternative traditional model was one in which a sponsor would hire a CRO to conduct the entire trial, but would have very little oversight after that. Both the multiple CRO approach and the “pitch-it-over-the-fence” approach led to scope creep and other inefficiencies due to lack of coordination and collaboration with vendors.

The new paradigms in CRO engagement expand strategic partnerships and utilize insourcing. Pfizer provided a good example of this new approach when they reduced their CRO vendors from seventeen to only two in 2011. Their goal was to make each CRO more accountable, with higher productivity, by providing them each with a significant amount of work. In a survey conducted by Booms Research for Parexel, a global CRO, executives for 26 global biopharma companies said that strategic partnerships were enabling them to reduce the amount of oversight needed, lower fixed costs, and give them access to increased capabilities, and these deeper relationships have transformed the clinical research industry. They projected that the next phase of strategic partnerships would need to better align commercial incentives, deepen collaboration, and accelerate cycle times for faster time-to-market in order to continue to improve upon the partnership paradigm.
Insourcing is an alternative model that aligns itself naturally with deep strategic partnerships. In a traditional CRO model, the contracted staff works remotely or at the CRO’s offices. An insourcing model places the CRO’s employees at the sponsor’s offices, embedding them into the culture, process, and direct lines of communication of the sponsor. This approach facilitates idea sharing and problem solving. R&D and manufacturing functions have utilized insourcing, but this approach could be translated just as well into clinical affairs or regulatory functions. Doing so would enable a coordinated effort and deep collaboration between sponsor and CRO. We predict these innovations in partnerships will continue to grow and evolve.

The changing face of the clinical research workforce

Given the innovation and continued growth in this industry is a portent for the workforce that propels it, the roles and skillsets necessary are likely to expand as well. According to the Bureau of Labor Statistics, Clinical Research Associate (CRA) jobs are expected to grow at 36.4% in the period from 2012-2022, which is better than average job growth. A 2016 blog post from the Association of Clinical Research Professionals (ACRP) asserts that the demand for qualified CRAs has already exceeded the supply of workers, with a shortage of at least 10,000 CRAs in the US alone. The shortage has created difficulties with retention as workloads have increased and work-life balance is affected. Some consensus exists that the standard requirement of two years’ worth of direct experience prior to assignment to a trial is the driver of this shortage. ACRP believes that to help address this shortage, standard credentialing should change from time on the job to the ability of a candidate to meet competency requirements successfully. Some believe that the automation of data collection expected to result from the convergence of EHR and clinical trial data will drive the number of jobs for CRAs down, which will alleviate part of the shortage, but others think that the CRA role will evolve and other roles will emerge. RBM may shift CRA responsibility back to a therapeutic area model, in which CRAs are involved with study design and reporting as well as monitoring, versus the travel-budget-saving regional CRA model that was popular in the early 2000’s.
Clinical study operation involves many components other than monitoring or remote data capture that the new technologies will not be able to manage. New roles will also emerge for knowledge professionals to manage algorithms and technical content within electronic data capture and EHR systems. These knowledge roles go beyond the historical role of a data manager, and merge hands-on clinical skills with EHR management skills. With the roughly 6,000 clinical trials operating in the US at any given time, clinical operations roles are likely to evolve, but the need for human involvement in clinical studies is unlikely to disappear anytime in the foreseeable future. In whatever scenario develops, a highly qualified clinical research workforce will remain valuable and in strong demand. See here for more details how CRAs can stand out.

The clinical research industry continues to grow and evolve. We are creating innovative strategies that address the challenges inherent in ensuring accurate, precise, and high quality evidence for the medical products we help bring to patients. Our industry is developing new ways of working more efficiently and more cost-effectively than we have in the past, while continuing to develop a talented and satisfied workforce. In the end, we work to embrace change in the industry, which leads us to having better products and better treatment that ultimately results in the best possible patient care and outcomes.

In the words of Isaac Asimov,

“It is change, continuing change, inevitable change, that is the dominant factor in society today. No sensible decision can be made any longer without taking into account not only the world as it is, but the world as it will be.”


