CLINICAL
INVESTIGATION

Clinical trials: beyond efficiency – why are we flying blind?

"Even with today's technology, no comprehensive analysis of safety data is undertaken until after a trial is actually completed."

This evening, I will board a 747 in Boston to fly to London. This hardly seems like a monumental event, until one considers that on this day alone, more than 100,000 flights will take-off and land safely all over the world, mostly on time, mostly with all of their scheduled passengers in their assigned seats, with their special meals awaiting them as requested, their bags tucked neatly into the hold for what is usually timely and safe delivery to the baggage claim.

Each plane will be in tip-top shape before it ever leaves the gate; checklists and flight plans reviewed and approved; crews trained and drilled in simulators for that rare encounter with a serious event. Each flight will receive clearance from air traffic control before it pushes back from its gate. Movements across the tarmac to the runway will be monitored by ground control as the tower monitors and manages all incoming and outgoing traffic – all communicating in a common language on designated frequencies.

Upon take-off, my plane will ascend to its designated cruising altitude, course and speed under the watchful electronic eye of each air traffic control tower as the flight crosses from one sector to another all the way from Boston to London. And while I enjoy a 'pint' before attempting a too-short night of quasi-sleep while crossing The Pond, I will take some measure of comfort in knowing that every circuit on the plane, every function of the engines and the controls as well as the weather and position, are being sensed and monitored continuously, informing those responsible for the safety of the hundreds of passengers on-board of any irregularities that portend a potential malfunc-

tion, even an incursion into air space during which a possible collision could occur.

And so it goes – for every international commercial flight in the world, every day, every year – as it has for more than half a century.

Our global air transport system is not perfect, of course. Flights are cancelled or delayed for a variety of reasons including crew issues, mechanical problems and weather, bags are sometimes lost and mechanical failures occur and yes, even a rare catastrophic event does happen.

Still, the simple truth is that this complex, highly competitive global air transportation industry has built a remarkable record of safety and performance through the system it has built to serve the industry as a whole, including all of its stakeholders.

This system depends upon the capture, interchangeability and analysis of important operations and safety information at every step of the process – information shared by the many stakeholders for the benefit of the entire industry and the public it serves.

This system itself drives and promotes the adoption of standards that enable interoperability and connectivity worldwide, and promotes safety as well as performance excellence. Other industries have similarly learned the value of systems thinking and the application of systems engineering principles to their endeavors with salutary results. One can hardly begin to imagine the disastrous consequences of not having such a system in place!

In contrast is the fragmented, silo'ed, proprietary 'hodgepodge process' (as it was recently characterized by a highly placed executive of

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a global pharmaceutical giant) upon which we currently depend for the most expensive and risky part of drug, device and other therapeutic product development – clinical trials – the human testing to demonstrate safety and efficacy of new medical products.

> "We need to think beyond efficiency – we need to adopt a system and that requires systems thinking."

Calls for 'disruptive innovation' to enhance the efficiency of the clinical trials endeavor are as loud as the engines on my 747 to London. There is little doubt that with some $20B of waste through delays, redundancy and inefficient, non-standardized processes at stake, those calls are well justified.

But in a more fundamental sense, the real issue is not just about inefficiency.

Simply put, we are flying blind – in this age of technology and communications that empower us to do the things necessary to enhance safety, quality, efficiency and professionalism, things that will benefit all stakeholders of the endeavor – we have been unable to envision the better way.

In clinical research today, there are no well-established competency-based requirements for education and training of professional research personnel. We rely upon what has been characterized as an apprentice system. Most research sites underperform and more than two-thirds never complete more than one clinical trial in their business lifetime. Many sites still rely upon paper records, despite the ready availability of robust electronic data capturing technologies and clinical trials management systems, with human error being commonplace. Despite a decade developing CDISC standards for clinical data interchange [1], their value and application are still suboptimal. Only recently has an electronic Trial Master File become feasible and only even more recently has the development of standards for electronic Trial Master File gained much momentum.

In addition, during the conduct of trials, sponsors and regulatory oversight agencies must depend upon less than reliable safety reporting processes, and costly, time-consuming monitoring practices. Even with today's technology, no comprehensive analysis of safety data is undertaken until after a trial is actually completed. This is like having untrained pilots and flight crews fly planes without routine safety inspections or electronic navigational gear and functional air traffic control systems.

Not to be overlooked are the challenges of another key stakeholder – for air travel, its the passengers; for research, the patients and study volunteers. For biomed-

ical R&D (and healthcare as a whole), the concerns of this critical stakeholder are now collectively referred to as those of 'patient-centricity.' In brief, this means the engagement of the variety of global communities in the development and use of therapeutic products.

Commercial air travel, like clinical research, regularly experiences lack of public approval. But while public opinion surveys – such as those focusing on public trust – still rank it above the clinical research enterprise, we can learn from commercial air travels omissions. Patient-centricity – viewed in a systemic way – can meaningfully address the dissatisfaction of study subjects and encourage public trust by truly engaging them as partners in the endeavor – part of the system, rather than fuel for it.

Active involvement of patients in research is more than recruiting and retaining subjects in clinical trials. Thinking of subjects in the context of the life-cycle of research and the variety of processes involved in biomedical R&D engages communities in a range of decision-making that can include protocol development, risk:benefit assessment, privacy concerns, regulatory approval and ethical oversight – in short, the interaction of the patient with the other key components and stakeholders of the research endeavor.

> "...systems thinking is not an event but an ongoing process..."

The clinical trials process we rely upon today is not a system – we are, in fact, at this point in the 21st century talking about re-inventing an approach to clinical research that was largely 'invented' by Claude Bernard in the 19th century with his landmark work laying out the need for doing research on potential medications for human use. We are relying upon a process that emerged half a century ago when the Kefauver-Harris amendments to the US FDA regulations first required safety and efficacy of drugs to be proven before marketing approval [2].

We have seen important innovation, even re-envisioning the basic methodologies of clinical trials. For example, adaptive trial design and risk-based monitoring are among the 'low-hanging fruit' being picked today, but such innovation is being undertaken and applied in a piecemeal fashion, rather than broadly thinking about integration of multiple components into a comprehensive interoperable system.

In many respects, it is remarkable that our hodgepodge approach to clinical research and biomedical research and development has worked as well as it has for so long. That it has is a tribute to the dedication of the many stakeholders who have always tried to do the best they can with what they have to work with, even while knowing that it could be better.

Even dysfunctional systems can continue to perform at a reasonable level, but not at an optimal level and the realities of today's environment call for optimization for many reasons, only some part of which are economic. Calls for reducing the cost and time required for getting a new medical product to market through improved efficiency are certainly justified, but insufficient. We need to think beyond efficiency – we need to adopt a system and that requires systems thinking [3].

Much innovation in the clinical trials endeavor today, particularly that focusing on quality risk management and errors is meaningful, if reactive, as an entry-point to systems challenges. So too are efficiency, ethics, economics and effectiveness. But all must be conjoined in any serious analysis, planning and implementation of a thoroughly integrated systems approach. Calls for disruption have been in response to a crisis and that is all too often the sole reason for change. But in a true systems analysis, we must be more proactive and comprehensive.

Organizational science, human factors and systems engineering all provide insights into re-inventing clinical research as they have been applied in other sectors of the global marketplace. And they are all part of what it takes to truly deal with the elements of 'new science' (from proteomics through clinical trials of single individuals) as well as innovation in regulatory science that is needed to keep up with changes in 'new science.'

In essence, systems approaches require interdisciplinary thinking, including the emerging knowledge disciplines already mentioned and benefit from seemingly unrelated marketplace experience.

Systems thinking alone is not enough to bring about meaningful change or to ensure the development of a workable system.

Cross-sector collaborations are essential. By these sectors, I mean government, industry, academic, nonprofit and multilateral entities. No less critical and pragmatic for progress purposes are two of the most significant dimensions of nation state-building: economic development and healthcare provision.

To achieve a workable system, all stakeholders must be willing to engage and move toward a new paradigm of partnership in which there is greater willingness to work together toward common goals and to build a shared system from which all can benefit. Importantly, a system necessarily drives the standardization, interconnectivity, professionalism and quality – as well as the efficiency and economic rewards called for by the 'disruptors' – but in a comprehensive, integrated way that has to date been so elusive.

Importantly, systems thinking is not an event but an ongoing process, one embodying a feedback cycle of constant analysis, solutions development and implementation, assessment and revision. Even today, the stakeholders of the global air transportation system are engaged in discussions of what will be needed in the future – next-generation thinking.

Central to this way of thinking must be a focus on medical product safety. This is underscored in the report from the National Patient Safety Foundation [4] and recommendations of The Institute of Medicine of the National Academies of Sciences in the United States [5]. The airlines, in cooperation with global civil aviation authorities, have employed a potentially valuable model that the clinical research enterprise could probably learn and benefit from – the creation of an entity comparable to the National Transportation Safety Board. In this global age, a neutral, independent, international multisector Medical Product Safety Board empowered to analyze and address systemic issues of safety and quality in terms of errors management could be extremely valuable to the endeavor as a whole. Apart from a focus on safety, such a body could meaningfully conduct crisis and root-cause analysis on an ongoing basis, an approach, when done properly, that is driven by systems thinking, systems biology and systems engineering.

No doubt, creation of a shared global system for clinical research, one that can be used by and provide benefits to all stakeholders, including patients, is a large and complex undertaking, but its scope and complexity are no greater than that faced by other industries with similar challenges.

With the growing awareness of the solutions such a system provides and the emerging willingness of the stakeholders to work together toward realizing their shared goals, we have an unprecedented opportunity to take meaningful action to make this a reality.

Flying blind will not get us safely and efficiently to our desired destination – thoughtful determination will.

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