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Connected Trials

Mr. Abi Velurethu, Bayer Pharmaceuticals, Whippany, NJ, U.S.A.

ABSTRACT

The **Digital Transformation** has taken over the technology industry by storm. The evolution of Digital Technologies has never been faster than today – smaller, smarter, safer technologies are released almost daily. Similarly, the disruptive adaptation of these technologies into our everyday lives will never be slower.

The **Digital Adaptation** is more evident in the consumer space – from Smart Homes using existing home networks to support devices, connecting advanced technologies using existing infrastructure to support the increasing demand for reliable, secure, high-performance connectivity. In other words, the digital adaptation is digitizing human life by connecting machines to machines, machines to clouds and clouds to clouds and everyday physical things to the digital world. The Internet of Things (IoT) has given the ability to make our everyday products smarter, things such as lights, gym equipment, refrigerators, coffee makers, door locks, etc.

The Pharmaceutical industry recognizes the tremendous potential and significant disruption that the digital technologies offer in healthcare based on the idea of passive data generation in clinical trials with a distributed patient population. The benefits include:

- Continuous measurement of health status as the patients follow their daily routines in a real world setting enabling to build richer patient health profiles
- Improvement in patient retention by generating actionable alerts, encouraging compliance, facilitating patient-physician communication
- May reduce costs by decreasing the need for facility visits, and due to the ability to collect more data in a short period
- There is a potential to bring a benefit of better clinical research, safety, compliance, and efficacy

DIGITAL TRANSFORMATION

"Digital Transformation" generates an instant energy and reaction across various industries. Media and Technology industries have adopted strategies to meet the digital customer base – the ones that have adapted the strategies are on top, holding majority of the market share.

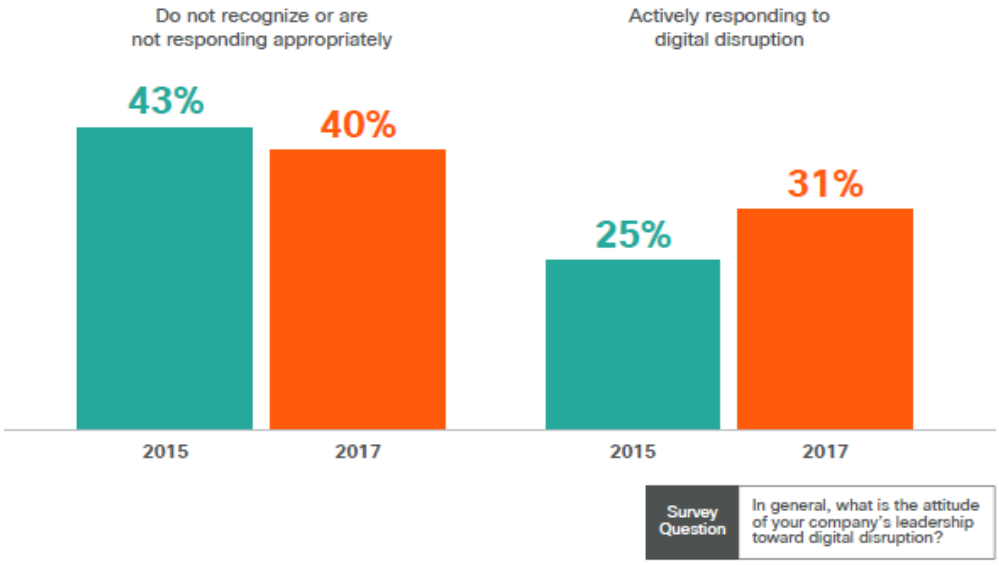
The report "*Life In The Digital Vortex – The State of Digital Disruption: 2017*" (by Global Center of Digital Transformation) discusses the changes since 2015 – based on the research the authors conducted to uncover the state of disruption across industries.

(Figure 1) **Digital Vortex 2017: Industry Ranking**

Source: Global Center for Digital Business Transformation, 2017

According to this article, "the industries closest to the center of the Vortex face most substantial disruption, while those around the edges feel less immediate impact. As a group, all industries have moved closer to the center, where the velocity and magnitude of change are the highest; no industry has retreated in the Vortex (i.e., experienced less disruption)." The Healthcare and Pharmaceuticals industry, although in the Digital Vortex, is placed 13th out of 14 industries. (Figure 1) However, pharma attitude towards the digital transformation has improved over the last two years, evident by the increased number of clinical trials involving mobile and sensor devices. Bayer, for example, has kicked off a company-wide Digital Transformation initiative with sponsorship and encouragement from its top management.

(Figure 2) **Attitudes Toward Digital Disruption**



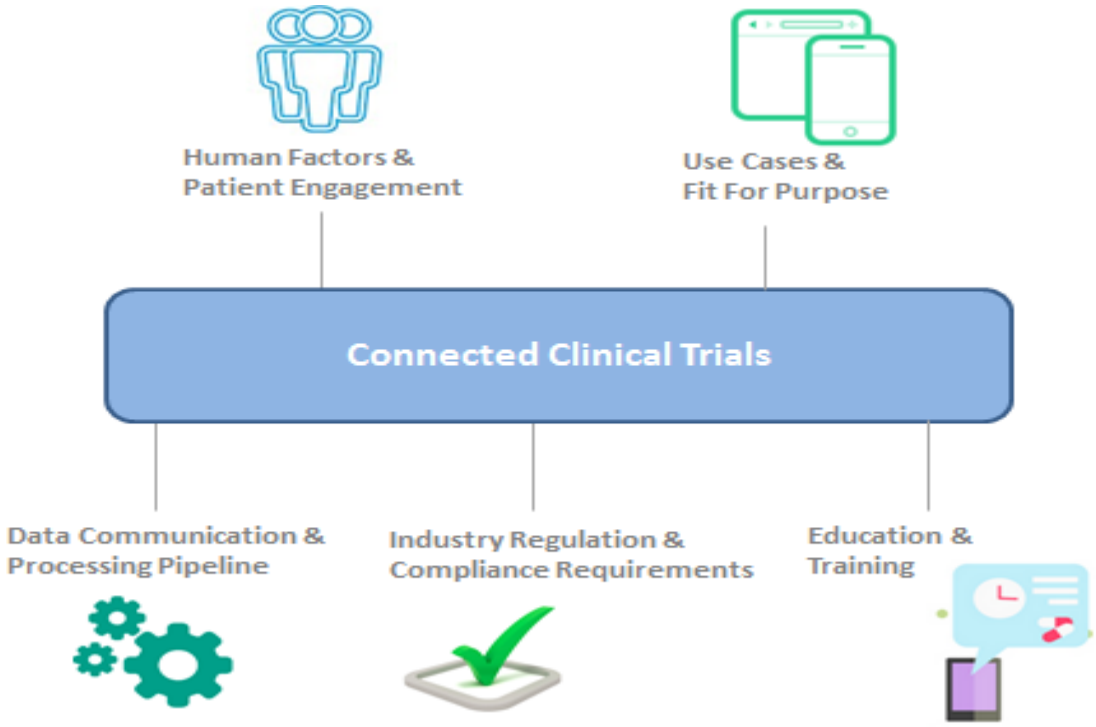
Source: Global Center for Digital Business Transformation, 2017

According to the Life in Digital Vortex, "Organizations, willingness to respond to digital disruption is improving. In 2015, only 25 percent of the executives claimed their organizations were actively responding to digital disruption. This number jumped to 31 percent in 2017." (Figure 2)

Although the transformation is underway, the digital adaptation in the Healthcare and Pharmaceutical industry takes place at a slower pace in comparison to other sectors. Particularly in the Pharmaceutical R&D space, the adaptation is slow due to tight industry regulations, extensive compliance requirements, pharmaceutical development tradition, very long development lifecycle incompatible with the fast changes in systems' landscape, sensing and computing technologies. Most importantly, pharma leaders and medical experts struggle with consumer-grade technology fit for purpose, overwhelming data analysis requirements, and perceived loosening of controls over data security, privacy, and integrity in distributed computing environments.

In order to adapt digital technologies to Clinical Trials, pharma should focus on the following five areas, and understand the challenges, benefits and use cases for a true enablement of Connected Trials.

(Figure 3) **Five Areas of Adaptation - Connected Clinical Trials**



HUMAN FACTORS AND PATIENT ENGAGEMENT

The introduction of digital technologies, such as electronic data capture, wearable devices, sensors, and mobile apps broadens the patient population in clinical trials, improves patient connection and engagement with the clinical teams and enables a more comprehensive understanding of the disease and new interaction models to improve the clinical trial experience.

A recent example of this would be the large-scale Multiple Sclerosis (MS) studies launched by Novartis. The study uses a mobile app designed with input from patients, neurologists and disease advocates built on the Apple Research Kit platform. This allows study participants to contribute using their smartphones, regardless of their

location. The trial will collect sensor-based data on participants' performance of physical tasks and their symptoms to improve understanding of the daily challenges the MS patients face.

Another significant value such tools would add to clinical trials is the access to the expanded patient population. Especially in disease areas where the patient is unable to visit the clinics due to their condition or due to their proximity to the clinics. In the Novartis example, the new MS study format eliminates the need for clinical visits, effectively broadening the patient population for the clinical trial.

For the patient, they can participate in the trials from the comfort of their own home, work, or even while on vacation. Apps4Patients, a Bayer proof of concept program, using wearable sensors and a smartphone mobile app, enables the engagement of the patients by keeping track of their tasks, activities and visit schedules. A concept not too long ago is now a reality for pharma and patients.

USE CASES AND FIT FOR PURPOSE

When it comes to digital device use in clinical trials, the fit for purpose and a good understanding of use cases by the patients, healthcare providers and pharma is critical. To achieve the full benefit of leveraging digital technologies in clinical trials, pharma companies should consider the following:

- Identify the unique need for the clinical trial:
  - What data should be collected?
  - What are the needs of the sponsors, the sites, and, particularly, the patients?
  - How will the data be used?
  - How will the data be incorporated into standard event reporting practices?
- Learn the disease conditions:
  - What are patients' daily routines?
  - Would the device help them cope with disease or would it be burdensome?
  - Is there a possibility that the trial outcome might be influenced by the use of devices?
- Engage patient advocacy groups:
  - What are the patients concerns with using the device in the trial?
  - Would one device (e.g. touch, feel, color) be better over another?
- Understand the technology involved in the trial:
  - What are the use indications that the device is cleared for?
  - How are the measurement artifacts dealt with?
  - What are the device failure modes?
  - Is there enough information in the system to ensure data integration?

Digital Health technologists and consultants recommend considering pilot trials, using the devices being considered, before applying it in a clinical study. This would enable the clinical research teams to identify data quality, fit for purpose use and the reliability of the device prior to the technology being utilized in the trial. Accenture Life Sciences recommends the following:

- Determine the unique needs of all clinical trial stakeholders (e.g., sponsors, sites, patients) to inform a digital clinical trial strategy. Consider prioritization of a key therapeutic area or selecting a pilot product.
- Define and implement a digital clinical trial strategy and plan aligned to a broader R&D digital strategy which considers your organization's unique appetite for risk and desire to be viewed - leading or following.
- Evaluate and incorporate the ongoing and planned digital pilots into the digital clinical trial strategy, weighing prior successes and failures, and considering the distinctive needs of each therapeutic area.
- Embed and test the selected digital initiatives and document the success and failures to continue scaling the right tools, at the right time, to new products or therapeutic areas.

DATA COMMUNICAITON AND PROCESSING PIPLELINE

Information processing infrastructure went through a tremendous transformation in the last few years. The idea to convert traditional hardware resources into software services proved to be both disruptive and enabling. As a result, the industry is seeing new trends in software development when old paradigms of monolithically integrated systems are being replaced by loosely connected distributed software applications, capable of processing much larger volumes of data coming with much higher velocity. As a parallel trend, the success of mobile communication led to significant enhancements of mobile computing power, which triggered an explosion in mobile application development.

Since software services are rapidly replacing the traditional hardware infrastructure, the approach to designing data communication and processing pipelines is evolving, too. Instead of focusing on functionality and capabilities of systems' components, the focus now is on data modeling, inter-service interfaces (a.k.a. APIs), scalability and standardization. Software infrastructures can be built and disassembled in minutes, can operate in centralized Clouds, on premises, and on edge (hybrid clouds and mobile computing).

In the context of Connected Clinical Trial, the following trends are especially important:

HARDWARE VIRTUALIZATION

Practically all hardware capabilities are now available as services. Software Defined Networks (SDN) replaced traditional routing and firewalling. As a result, very complex network topologies can be built and secured, without the need to install and maintain network equipment. When necessary, SDNs can be expanded, extended, and morphed in a matter of seconds.

Computing power can also be provisioned on demand, both vertically (more powerful virtual CPUs and larger memory) and horizontally (more virtual servers). Because of such flexibility, an entirely different generation of information processing algorithms took the stage. Large data structures can be handled, and parallel computing is now built into many steps in the data processing pipeline.

Finally, the storage and databases come now in many different forms. On the basic level, the traditional block storage can be provisioned as a service and made fault-tolerant and extendable. Object storage fulfills a need to store software objects (such as multimedia files or web objects) rather than blocks of data. SQL databases can be provisioned and clustered to cover traditional Relational Data Base Management Systems with well-defined, structured relational data models use cases. NoSQL databases include a variety of other use cases ranging from massively scalable (petabyte size) data lakes to storing searchable data objects and graphs.

The practical implications of infrastructure as software for connected clinical trials are significant. First, it allows creating, experimenting, sharing and evolving systems as teams see fit without inquiring capital expense. Second, it allows infrastructures to be managed as software with the software development practices being applied in place of hardware (design controls, pipelining, verification, continuous integration, and validation). Third, the infrastructures can be built considering data jurisdiction, local cybersecurity, and privacy regulations.

IOT PLATFORMS

Machine to Machine (M2M) communication was always important for industrial systems, but the development of wide area wireless communication and democratization of mobile computing led to the realization that everything can be inexpensively connected into what is nowadays known as the Internet-of-Things. Correspondingly, patients and their wearable devices can be connected too.

After a decade or so of development, there are many IoT platforms available including systems in the healthcare domain. Unfortunately, IoT is not yet fully standardized, - there are many legacy and closed proprietary protocols, which do not integrate well with other systems.

Development of IoT platforms is also related to the development of sensing technologies and the overall

ecosystem domains. When the economic effect is apparent, the development happens quickly. One example is Amazon button, a simple case of convenient ordering process which led to the growth of the AWS IoT ecosystem.

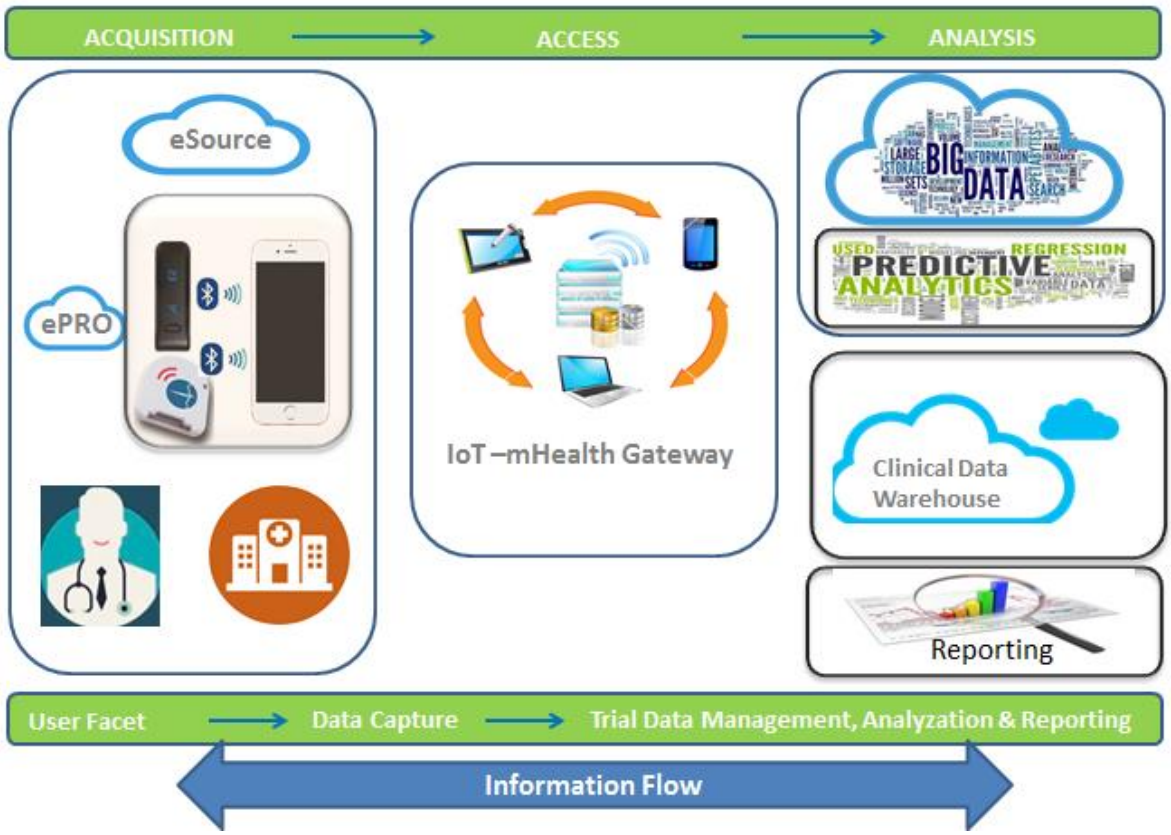
ANALYTICS

As was mentioned above, virtualization of hardware infrastructure helped to implement a different approach to data processing. This new age of analytics deals with both amounts of data available for processing, and speed of computations. Modern machine learning algorithms (such as Deep Belief neural networks) became not only feasible, but practical.

When we discuss “analytics” in the context of information processing systems, we focus on the capabilities of taking the data from multiple sources (including high velocity data), streaming, fusing, normalizing, denormalizing, and cleaning the data, storing the data in structured and unstructured forms and providing interfaces for the post-processing.

Data visualization also plays a significant role in human-computer interfacing. Data visualization in the context of analytics means a research tool allowing specialists to gain access to patterns and shape hypotheses.

(Figure 4) **A Sample Device Data Capture Ecosystem - Mobile Devices, IoT, Analytics**



INDUSTRY REGULATIONS & COMPLIANCE REQUIREMENTS

The pharmaceutical industry is one of the most regulated industries in the world due to the potential risks to human health and well-being, public health, environment, business and societal impact. It is critical for pharma to follow the appropriate guidelines that are established by the relevant regulatory bodies such as the US Food and Drug Administration (USFDA), European Medicines Agency (EMEA) and Pharmaceuticals and Medical Devices Agency (PMDA). The ongoing changes in regulations have increased the significance of regulatory compliance management for drug manufacturers. The addition of mobile devices, sensors, and apps significantly increases the compliance complexity for the regulatory bodies and pharma.

A recent publication, "*Digital Health Innovation Action Plan"* (by Food and Drug Administration), the FDA acknowledges the innovative disruption digital technologies have on clinical trials. "Digital Health technologies can empower consumers to make better-informed decisions about their health and provide new options for facilitation prevention, early diagnosis of life-threatening diseases, and management of chronic conditions outside of traditional care settings. Software and technologies that assist in diagnosis, treatment options, storing and sharing health records and managing workflow can enable more efficient clinical practice."

The regulatory authorities have recognized that the introduction of digital health technologies has brought new vendors and startups to the medical device space. The benefits of new innovative technologies and suppliers are accompanied by challenges of cybersecurity, interoperability, data privacy and data governance. New players need to demonstrate compliance with good development practices (GxP) including verification and validation requirements. Furthermore, continuous validation and monitoring of complaints are necessary to detect and timely correct potential problems during the conduct of the clinical trial.

Per the FDA publication, "FDA recognizes that an efficient, risk-based approach to regulating digital health technology will foster innovation of digital health products. FDA's traditional approach to moderate and higher risk hardware-based medical devices is not well suited for the faster iterative design, development, and type of validation used for software-based medical technologies. The traditional implementation of the premarket requirements may impede or delay patient access to critical evolutions of software technology, particularly those presenting a lower risk to patients."

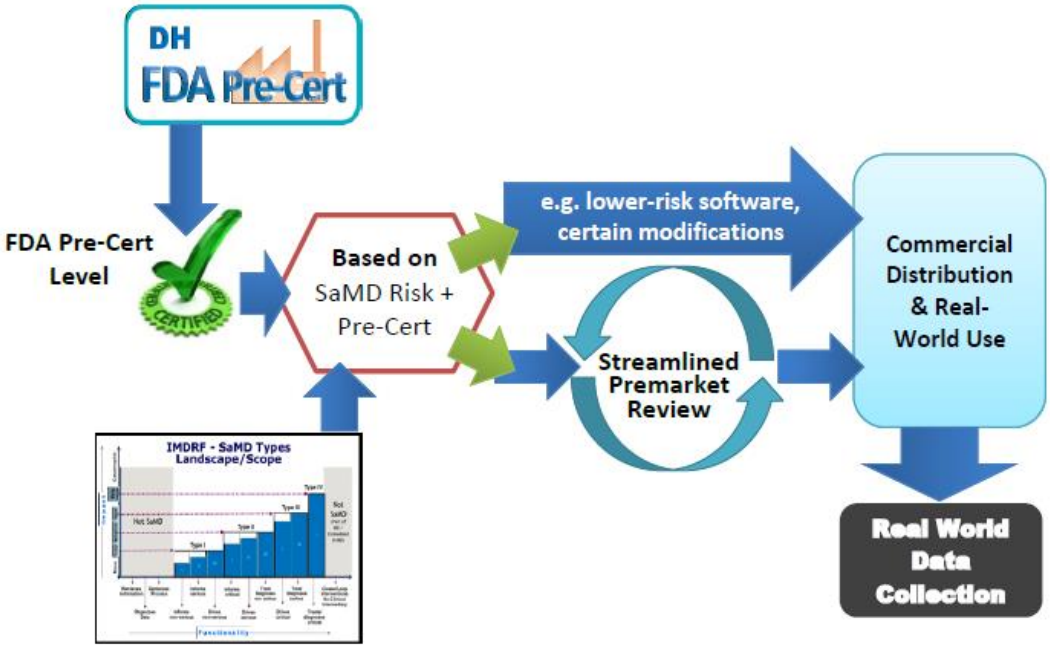
Understanding this, the FDA's Center of Device and Radiological Health (CDRH) has established Digital Health Innovation Action Plan. This plan lays out the CDRH's vision for fostering digital health innovation while continuing to protect and promote the public health, including:

- Issuing guidance to provide clarity on the medical software provisions of the 21st Century Cures legislation;
- Launching an innovative pilot precertification program to work with our customers to develop a new approach to digital health technology oversight (FDA Pre-Cert for Software); and
- Building FDA's bench strength and expertise in CDRH's Digital Health unit.

Although this particular plan is driven by the FDA, the approach can be adopted Globally, to other regulatory bodies. The FDA's Action Plan consists of issuing a new guidance, implementing legislation, and reimagining digital health product oversight. The regulatory authority recognition to 'reimagine' the oversight is much needed and welcoming news to pharma and product vendors in the digital space. This could set a clear expectation and guidance for development and implementation of digital technologies, not only in the US, but in other parts of the world.

To develop the new approach to regulation of digital technologies, the FDA CDRH implemented a pilot program, "pre-certify". This program seeks to qualify the device or the digital health technology manufacturer, rather than the individual product development. The pre-certified developer would qualify to be able to market their lower-risk devices without additional FDA review or with a more streamlined premarket review.

(Figure 5) **FDA Pre-Cert for Software**



According to the FDA publication, "the purpose of FDA's Software Pre-Cert pilot is to leverage customer input to develop a program that can help reduce the time and cost of market entry for software developers that the FDA determines reliably manufacture high-quality, safe and effective digital health devices while providing appropriate patient safeguards. Applying such an approach could improve support for continued innovation, allow for more rapid availability of new and updated software…" (Figure 5)

This method could aid the pharmaceutical industry tremendously. Pharma would be able to leverage the qualified vendor products and use their digital technologies in the clinical trials; while being confident about the compliance. For the clinical trial teams, the system validation effort will have significantly smaller scope since the devices, and the applications come from a certified vendor. The trial teams can then focus on specific intended uses, human factors, and usability in the narrower context of their clinical plans.

EDUCATION AND TRAININGS FOR CLINICAL TEAMS

According to a study conducted of 166 biopharma and life sciences industry researchers, executives and technology and software professionals carried out by Validic - 98% of clinical research teams plan to use digital technologies to collect patient data within the next five years. The study findings highlight the significance of digital technology utilization, especially in the patient communities.

The increase in the use of digital devices in clinical trials also increases the incorrect use of the mobile devices due to the new and changing technologies, indication specific and appropriate uses, the device care, tolerance, and dependence, etc. It is important to consider the proper education and training for the clinical teams when deciding to use a mobile device in a clinical trial. The incorrect use of the mobile devices, sensors, and apps could result in erroneous data collection for the trial.

The younger patients may be adept with the newer technologies, and senior patients may require extra training – nevertheless, it is important for the entire patient population involved in the study to receive adequate training and access to follow up training. Also, it is crucial for the site personnel to receive the training as well. The sites should be able to understand and monitor the devices throughout the trial for usage; for example, making sure the faulty devices are dealt with promptly, and the correct behavioral messaging is delivered to patients who are not adhering to the proper device use in the particular clinical trial.

CONCLUSION

The “Digital Transformation” is here and has been here for some time. The digital technology use is evident in our day to day lives, in our actions, interactions, and our routines. It is no longer a transformation, rather an adaptation. In the clinical trials arena, mobile technologies offer the potential for significant disruption by enabling access to focused patient population, data collection, monitoring and data insights, better patient engagement and experience, and the ability to serve patients beyond the clinical trial. With the increased use of mobile devices in clinical trials, it is imperative to adapt the digital technologies correctly to achieve the full benefit. The adaptation is a learning for the pharma industry. When determining to utilize devices in a clinical trial, the focus on the five areas (Human Factors and Patient Engagement, Use Cases and Fit for Purpose, Data Communication and Processing Pipeline, Industry Regulations and Compliance Requirements, and Education and Trainings for Clinical Teams) would ease the transition to **Connected Trials**.

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CONTACT INFORMATION

Abi Velurethu
Bayer Pharmaceuticals
100 Bayer Boulevard, PO Box 915
Whippany, NJ 07981-0915
Office Phone: + 1 862 404 3883
Mobile Phone: + 1 215 622 1524
Email: abi.velurethu@bayer.com
Web: https://pharma.bayer.com