PharmaSUG 2019 - Paper RW-238

Innovative Technologies utilization in 21st Novel Clinical Research programs towards Generation of Real-World Data and its articulation for Analysis & Submission

Srinivasa Rao Mandava and Cheryl Simon, Merck & Co, Rahway, NJ 07065

ABSTRACT

R&D budgets of Pharmaceutical industry have been increasing year after year with oncology and metabolic disease drug developments as lead engines. However, return on R&D investments reduced from 10.1 in 2010 to 3.2% in 2017. On the other side, Technology utilization is increasing in the same phase for better handling and cost & time reduction scenarios. Current $ 60 billion clinical research market is extremely slow and there by expensive in some ways. Outdated data technics, confusion and confrontation over eligibility, large numbers of subjects drop-out rates are the prime reasons for longer trial times of about 10 years. For the last few years digital technologies utilization across the industry is increasing with three focused areas such as 1. Engage 2. Innovate 3. Execute in dealing with three key groups such as a) patients b) providers c) payers. It is the key in acquiring more efficient and accurate data collection through all stages of trial life cycle in the current era of 21st century of novel clinical research. Digital technology allows passive collection of data from a variety of different sources including wearables that measure vitals, physical activities and also amounts of sleep. In this paper, we will discuss about utilization of digital and other innovative technologies such as AI, ML and Block Chain methodologies in trial processes and data articulation to achieve 21st century novel clinical research objectives.

INTRODUCTION

It is well evident that safety and efficacy data collected from randomized controlled trials (RCT) provide high quality data on restricted patient populations and has been standard for determining market authorization. However, this alone may no longer be sufficient to address the needs of key stakeholders (patients, regulators, providers, and payers) and guarantee long-term success of pharmaceutical products. This scenario heightened the interest of from the all the sections of stakeholders to focus on real world data (RWD), collected from registries, electronic health records, insurance claims, pharmacy records, social media, and also with digital technologies form real-world evidence (RWE). There are reasonable benefits in using RWE such as less time and cost to produce meaningful data, the ability to capture additional information, including social determinants of health that can impact health outcomes, detection of uncommon adverse events, and better utilization of innovative technologies such as AI, ML and Block Chain methodologies in trial processes and data articulation to achieve 21st century novel clinical research objectives. Digital Technologies could also helpful in the generation of subjects pharmacogenomic information and pharmacokinetic differences between individual subjects, reduction in differences between drug metabolism and race and ethnicity drug response variations which would be key for personalized and precision medicine scenarios. The main differences of the data collected with RCT and RWE methods are shown in Table 1.

Table 1. Examples of Differences in How Data from Conventional Randomized Controlled Trials and Read-Word Evidence are Utilized

Characteristics	RCTs	RWE
Standard of evidence	Gold standard	Complementary to RCTs
Cost	Costly to develop	Less Costly
Patient Population	Well-defined within constraints of specific inclusion criteria Results reflect outcomes in limited population	Broader and promotes evaluation of patients populations less often studied in clinical trials Patient data derived from other sources, including insurance claims
Sample size	Limited Requires sample size calculation to be performed in advance	Orders of magnitude larger
Efficacy	Randomized and blinding lead to minimized risk of data bias and confounding	Randomization and blinding may not be feasible Risk of unrecognized data bias and confounding greater
Adverse events	Only more frequently occurring adverse events revealed	Can reveal adverse events with much lower frequency and those requiring longer exposure to occur
Approval or Clearance of new medical products	Considered the gold standard necessary for new drug approval, and when feasible for new device approval	Not generally accepted for approving new drugs but can complement RCT findings, accepted for new device indications
Role in diabetes	Define efficacy and provide a preliminary safety profile in a well-defined and controlled population	Allows estimation of more realistic treatment effects of a wide range of diabetes interactions such as social determinants of heath and comorbidities
Other issues	May be less useful when strong signals are available form RWE or early-phase trials	Facilitates post marketing surveillance of adverse events and assessment of the product effectiveness Results may be less credible due when a control group is not included

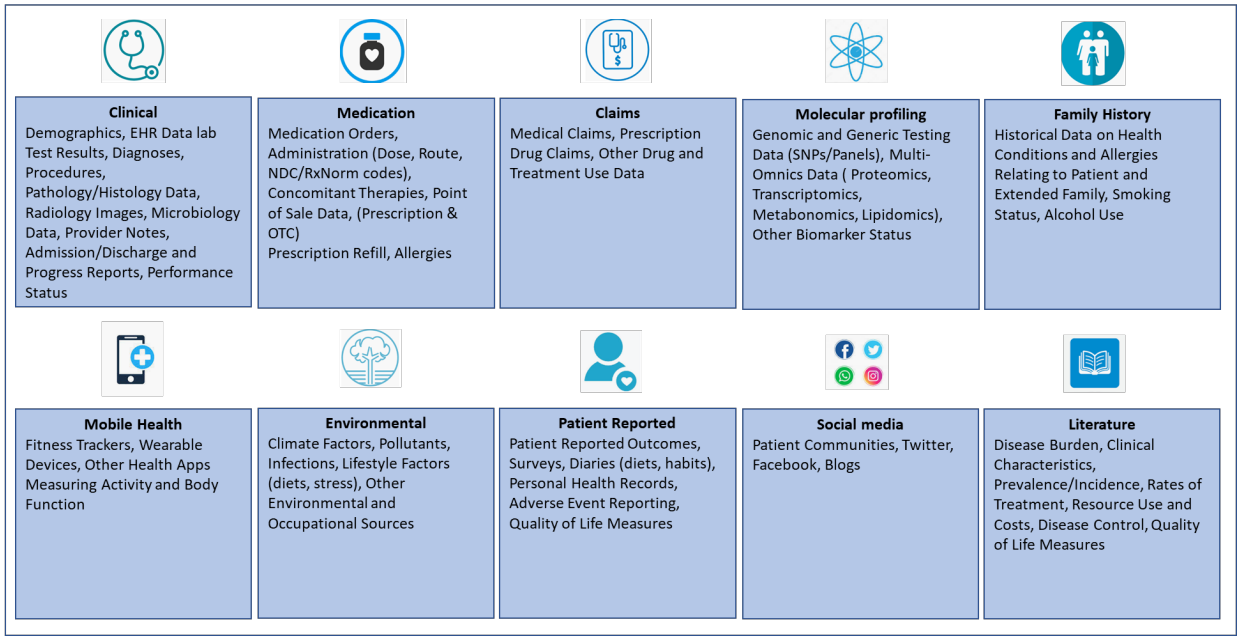
REAL WORLD EVIDENCE (RWE) AND REAL-WORLD DATA (RWD)

Real-world data (RWD) and real-world evidence (RWE) are typically used interchangeably. RWD usually refers to patient-level data gathered outside the conventional clinical trial setting. Such data may be generated in the course of normal clinical research practice or administrative claims processing or may be reported directly by patients. Examples include data from: patient charts, laboratory reports, prescription refills, insurance claims, subject registries, patients treated on- and off-label, patients treated through expanded access, pragmatic clinical trials, surveys, and mobile health devices, wearables, sensors, adherence tools, social media platforms, and online patient communities as well as other data from existing secondary sources used to support decisions concerning safety, quality, care coordination, coverage and reimbursement. Thus, RWD is both structured and unstructured data from the hosts of both homogenous and heterogeneous sources. This data includes, among others, phenotypic and genotypic data from discrete fields as well as clinical notes in electronic health records (EMRs), electronic health records (EHRs), electronic dairies and other molecular profiling data from biospecimen banks and bioinformatic platforms.

Real World Evidence (RWE) is defined as the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real-world data (RWD) as per the announcement of FDA in 2018.

Some Examples of Real-world data are shown in this Figure 1 below

Figure 1



FDA's 21st CENTURY CURES ACT

The 21st Century Cures Act of 2016 (Cures Act), is congressional bipartisan public policy designed to accelerate the discovery, development, and delivery of new cures and therapies and treatments for disease came into law on December 13, 2016. As part of the act, there was authorization to include $500 million over a decade to provide budgetary appropriation to the agency to cover the cost of implementing the changes in the law. Among its goals, the act intends to modernize and innovate the clinical trials towards the generation of safety and efficacy data collection and analysis. FDA is currently framing new policies, programs, processes and methods and utilization of new digital technologies in achieving this goal.

In that process, Agency launched, the Real-World Evidence Program, to promote the use of RWE as part of its regulatory decision-making processes for drugs and therapies in the month of December 2018. The guideline document consists (1) provision of definitions for both RWE and RWD, the basic establishment of information and its analysis and evidences respectively (2) current uses of RWD for evidence generation in safety and efficacy areas of regulatory studies and nonregulatory or non-randomized studies (3) examples of trials using RWE for nonregulatory purposes to assess comparative effectiveness of treatment regimens and (4) future plans for clinical data standards and governance. However, this roadmap document covers only drugs and biologicals only and excludes medical devices

RISE OF DIGITAL HEALTH AS INNOVATIVE TECHNOLOGY

The term digital clinical research refers to technology/ies that can receive and transmit electronic data which can be used, directly or indirectly, to produce, collect, generate monitor or enhance clinical information and data or coordinate clinical research processes. The expansion of digital technologies in healthcare and clinical development are shown in the Table Below.

Expanding use of digital health technologies

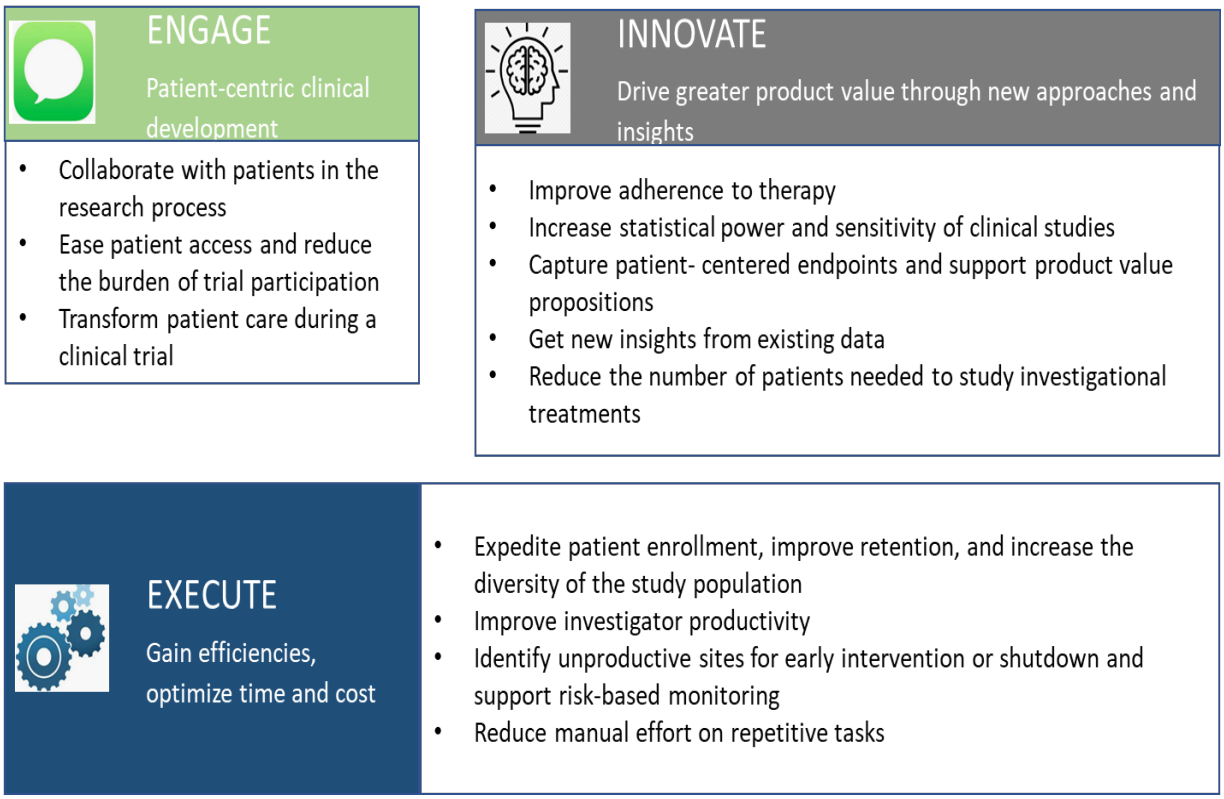
Use of Technology	2010	2015	2020
World population (in Billions)	6.8	7.2	7.6
Devices (in Billions)	12.5	25	50
Devices (per Head)	1.8	3.5	6.5
Total No of Smart Phones, Worldwide (in Billions)	0.5	3	6

Digital technologies include a wide range of different technologies that can be used in trail processes including categories such as mobile applications, information technology (IT), wearable devices, sensors, platforms, and advanced analytics, such as connected devices, artificial intelligence, machine learning, and robotic processes. Other terms such as mHealth, eHealth, social media and the medically-related Internet of Things[2] are sometimes used interchangeably because there are no globally agreed upon definitions.

As pharmaceutical industry and other organizations look to apply these technologies either individually or in combination to perform operational activities, such as recruiting patients, improving adherence, and capturing and analyzing data to wards generation of RWD, it could, however, be useful to conceptualize digital not simply as a platform or technology, but as a way of doing things differently. Thus this innovative technologies provides enormous opportunities in engaging both subjects and sponsors through targeted end goals and unified user experiences in meeting their needs and fostering long term good relational ships, innovation of new methods in drug discovery process that provides value for patients, health care providers, and payers using data and innovative platforms such as digital endpoints and real-world evidence and efficiently execution of digitizing and rationalizing programs to drive efficiencies, cycle time reductions and cost effectiveness.

Some of the value leverages for digital technologies are shown in below Figure 2.

Figure 2. Value levers for digital technology in clinical development



The significance and scope of potential RWE use cases requires rigorous quality assessment, especially when used for regulatory decision-making. Therefore, we propose a checklist for robust, regulatory-grade RWE: 1) High quality, 2) Complete, 3) Transparent, 4) Generalizable, 5) Timely, and 6) Scalable. As suggested by potential use cases in cancer, the up-front investment in establishing regulatory-grade standards will pay dividends as RWE gains importance in medicine.

CONCLUSION

Declining research and development (R&D) efficiency is one of the biggest challenges the pharmaceutical industry is facing today. The traditional approach of three discrete, fixed trial phases designed with RCTs for testing mass-market drugs often is not viable in today's increasingly competitive, value-based therapeutic markets with quality. It lacks the flexibility, analytic power and speed required to develop complex new therapies targeting smaller and often heterogeneous patient populations. As a result, the perspective of clinical trial processes is changing. Digital disruption in the form of new wearables, sensors and medical devices enable pharmaceutical and medical device companies to generate new types of datasets. Artificial intelligence and machine learning can generate new insights and digital biomarkers that have the potential to be more clinically responsive to change. However, to run a successful remote/digital trial, a complete end-to-end solution is required. Carefully selected technology, combined with the right trial design and operational excellence, will increase the likelihood for success.

REFERENCES

Krause, JH, Saver, RS. Real-world evidence in the real world: beyond the FDA. Am J Law Med. 2018;44:161-179

Sherman, RE, Anderson, SA, Dal Pan, GJ. Real-world evidence—what is it and what can it tell us? N Engl J Med. 2016;375:2293-2297

Network for Excellence in Health Innovation. Real world evidence: a new era for health care innovation. 2015. Available at: http://www.nehi.net/writable/publication_files/file/rwe_issue_brief_final.pdf. Accessed February 21, 2019

US Food and Drug Administration. Use of real-world evidence to support regulatory decision-making for medical devices: draft guidance for industry and Food and Drug Administration staff. 2016. Available at: https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf. Accessed February 21, 2019

ACKNOWLEDGMENTS

I would like to thank Sandeep Tanwar for reviewing the paper and giving valuable input.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Srinivasa Rao Mandava
Merck & Co
610-505-8557
srmandava@hotmail.com

Cheryl Simon
Merck & Co
908-468-8537
khabirah@aol.com