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White Paper:

Leveraging Technology to Reduce Costs in Clinical Trials

Introduction

Bringing a novel drug or a medical device to market is becoming more and more expensive, time-consuming and complicated. Yet the urgent need for more cures to both, treat well-known diseases more effectively as well as fight more rare diseases calls for faster and cheaper drug and device development processes, not slower and costlier ones.

Likely reasons for the recent rises in drug and device development times and costs seem rooted in the need to safeguard public health through more rigorous regulatory oversight, as well as to protect drug investments through more likely-to-succeed development processes. However, public safety and health as well as drug and device development companies' bottom lines all benefit when more patients can access more cures at lower costs.

How should societies negotiate those apparent contradictions between safety and efficacy on one side, and speed and cost on the other? We believe that recent advances in a variety of technologies will allow us to do both: lower the cost of development so more drugs and devices can be brought to market by more organizations more cheaply, as well as increase those device and drug development efforts' safety and efficacy.

In fact, we believe that we have never before been at the threshold of such a profound revolution in drug and device development capabilities that carries the promise of eradicating many if not most diseases within the foreseeable future. This paper explores some of these exciting possibilities, hopefully to the benefit of all.

What are the costs?

The most widely accepted all-inclusive cost estimate of developing and bringing a new drug to market by the Tufts Center for the Study of Drug Development placed the cost at $2.6 billion. The number of drugs coming to the market in the U.S. has dramatically slowed in recent years. In 2016, the United States Food and Drug Administration only granted approval to 22 new drugs, considerably down from 45 new drug approvals in 2015.

The radical reduction in new drug discovery has been blamed on a number of factors including soaring research and development costs, high rates of early phase failure (close to 90%) and increasingly common flame outs in later stage trials of candidates that seem like slam dunks but fail to perform in Phase IV.

Medical devices have enjoyed a swifter and less costly journey to market. The average cost to develop high-risk, novel medical devices was estimated at $94 million in a 2010 Stanford University report (the price is likely higher now but remains orders of magnitude below those of compounds). Devices can use far cheaper animal models deeper into the trial process and human trials tend to be smaller-scale than those required for novel compounds.

Under new regulations, the U.S. F.D.A. has dramatically accelerated approvals, but a wide-ranging investigative report by a coalition of hundreds of journalists found that device failures had been implicated in the deaths of 83,000 individuals since 2008. As a result, device approvals are likely to come under increasing scrutiny and possibly suffer greater delays on the route to market.

The U.S. pharmaceutical industry is pursuing several technological and methodological ways to accelerate and streamline the medical trial process for novel compounds and devices in order to cut costs, boost success rates, and get drugs and devices onto the market faster. Often technology makes the new methodology possible. As mentioned in the introduction, this paper is a survey of the various methods by which the companies are seeking to improve, accelerate, de-risk and economize the drug and device discovery process.

Three Vectors of Improvement and Why They Matter

If the goal is to bring more drugs and devices to market more quickly, there are principally three key levers that increase the volume and impact of new drugs and devices coming to market: time to market; reductions in complexity and errors; and reductions in cost of trials and development. Roughly speaking, these three vectors translate into speed, reduced complexity and reduced costs. In many cases, these three vectors are interrelated and complementary.

THE BENEFITS OF SPEED

Reducing time to market is critical for several reasons. For patients, the benefits of faster time to market are obvious: Potentially life-saving cures are available sooner to a larger group of patients. And for care providers there are likely benefits, as well: It is more rewarding as well as cheaper to restore a larger number of patients back to health, than to support them through prolonged ailments or disability. All of those are massive public health benefits.

However, for device and drug producers, the benefits of earlier time to market are compelling, as well: Compound development is increasingly concentrated in a handful of pathologies (oncology, liver disorders, metabolic disorders). Primarily, reducing time to market means pharma companies can more quickly recoup and profit from their investments as time to revenue is shortened. And there is a strong first-mover advantage in that later arrivals to the market may struggle to gain traction with PBMs, hospitals and physicians, particularly if the new drug is not markedly superior to existing treatments.

At the same time, reducing time to market can allow R&D resources to be more quickly repurposed for alternative or novel explorations. Pharmaceutical companies and research organizations may, at times, need to trade speed for cost, when it is viable to spend more upfront to accelerate time to market. In such cases, there is a careful calculation as to the cost-benefit of this tradeoff. For potential blockbuster drugs with multiple competitors on the horizon, it may make sense to spend more on trial recruitment or other possible inputs in an attempt to get to the market faster. For device makers, this tradeoff is less marked. Because testing is more straightforward and bounded, reduced time to market is almost always an unalloyed benefit that improves chances of financial success.

THE BENEFITS OF REDUCTIONS IN COMPLEXITY

The traditional process of bringing a drug or medical device to market has numerous input stages where opportunities for failure exist. Data collection and capture, study administration, dosage accuracy, sample pollution (with external environmental factors), and compound degradation (due to logistical problems) are just some of the areas where even well-structured trials can go wrong. Additional complexity comes from having to maintain traditional double-blind trials with placebos, simply because this doubles and triples the logistical requirements and the surface area for potential problems.

Reducing complexity across any or all of these potential failure modes can have numerous beneficial effects: improved accuracy and reliability of trial data; faster recognition of non-viable compounds based on early-stage results; reduced cost due to increased viability of smaller sample and trial sizes; simplified and less costly logistics; reduced manpower requirements and potentially reduced time to market. Most importantly, reductions in complexity should confer a higher degree of confidence in every stage of the trial process.

THE BENEFITS OF REDUCED COSTS

As outlined above, both reduced time to market and reduced complexity can contribute to reduced cost (and accelerate time to revenue). And, in many cases, cost reduction is a corollary to improvements in the other two vectors. The most obvious benefit of reduced costs is that it makes development of novel compounds and devices more efficient and allows more organizations to test for more cures. Testing for more cures ultimately will save more lives.

Reduced costs will also allow changes in market dynamics that may democratize compound and device development. By lowering the threshold for developing and testing FDA-regulated products, many more companies or research laboratories may embark on development efforts. Reduced costs should accelerate the velocity of discovery, as well, by generating more “bang for the buck” for each dollar invested into drug and device development. In short, the crux of driving future innovation is reduction in cost.

Technological Improvements in the Trial Process

Unlike other fields directly impacted by information technology, the drug and device development industry has not yet derived significant benefit from improvements in technology. This is largely due to a slow regulatory process and a resulting comparative reluctance to embrace change, and not due to the lack of available technologies to utilize. The pace of change is understandable; lives are at stake. That said, the incredible power of new waves of technologies are unlocking previously unimaginable possibilities to improve the development process.

This section provides a brief overview of some of the most prominent among them. This overview is by no means exhaustive but it is representative of the wide array of new methods and capabilities that are either being experimented with or are being developed to improve drug and device development along the three core vectors.

Virtual and Hybrid Clinical Trials

Virtual trials eliminate the need for study sites by using distributed technologies for compound delivery, subject management, and data collection. Virtual trials are related to hybrid trials, which have physical locations which may be more broadly distributed or only serve as a primary point of focus even as trial execution and data capture is geographically distributed. By bringing the trial to the subjects and eliminating the physical overhead associated with rigid trial centers, this new modality for running trials can significantly reduce complexity and cost, as well as increase trial velocity and iteration. Virtual trials are often combined with newer methods of data capture and electronic records, due to the difficulties with paper data capture in distributed operations. This newer form of data capture streamlines study processes dramatically. By using a virtual platform, coordinators may conduct video recruitment interviews across multiple geog raphies. During the course of a trial, investigators can conduct video patient check-ins with patients to address emerging issues and improve compliance. This may reduce dropout rates.

Enabling Technologies for Virtual and Hybrid Trials

Several technologies make virtual and hybrid clinical trials feasible. Nearly ubiquitous data connectivity simplifies information transmission from distributed collection points to centralized study repositories. We are actually in the early stage of this trend, as connectivity is poised to improve and expand due to the rollout of more powerful 5G data networks and the deployment of several low Earth orbit Internet connectivity satellite constellations by companies such as SpaceX, Amazon and Facebook. Secure and compliant cloud computing from large providers such as Amazon untether trials from physical technology locations. These cloud platforms enable interactive response technology (IRT) which provides a centralized application and database that offers easy asynchronous or online access to capture and present trial data.

Additionally, an increasing number of medical devices and sensor platforms – such as automated blood pressure cuffs, to name one – allow patients to more easily capture and provide their own data. So-called e-PRO instruments are specifically designed to empower patients to record and report well specified and reliable observations electronically. This is called Direct Data Capture. It is increasingly used to capture data with no clinicians present and without requiring a specially equipped tablet or smartphone. Underlying these improvements as well is the constant and steep cost reduction of technology hardware and sensors. The silicon chips and storage systems that power the technology behind this transformation are continuing on a "Moore's Law" pace, with prices declining by roughly 50% every 18 months even as the power of the silicon systems roughly doubles during that period. For sensors, medical grade sensors that formerly cost hundreds of dollars now cost a dollar or less and are readily available for integration into medical (or, increasingly, consumer) devices.

Strengths and Weaknesses of Virtual / Hybrid Trials

Virtual and hybrid trials should reduce costs on multiple fronts including recruitment costs, travel costs, and technology and physical plant costs. By making it easier to assemble cohorts, these trials can accelerate drug and device trial design and execution. Possible negative impacts are less and lower quality communication with the clinical team and error introduction if patients are not proficient at collecting their own data.

eSource and Electronic Data Capture and Transport

eSource and Direct Data Capture is the use of any device, such as laptops, tablets and smartphones, to collect trial data directly in an electronic format and upload that data securely into databases. These systems can function both synchronously and asynchronously (when not connected to the Internet) to streamline data collection and improve data quality by eliminating paper from the clinical trial process. eSource solutions can increase efficiency at virtually every point in the clinical trial journey, from patient consent to data collection to patient diaries.

eSource obviates the need for transporting, reading, verifying and storing paper as was previously common in clinical trials. With the elimination of data entry and transcription from paper, so too go virtually all associated errors. In instances in which patients are recording vital signs with medically-approved home devices, or in which sensors attached to clinicians' smartphones or tablets can directly transmit data, then eSource means reporting directly into trial databases without any human intervention at all.

Real-time remote data sharing, as enabled by eSource, can allow research organizations to far more easily conduct trials at multiple sites around the globe or collaborate across time zones, asynchronously. And instant access to trial data enables organizations to make better, more informed decisions much more quickly. By eliminating paper from the trial process, research organizations can not only improve data quality but also reduce errors, save costs of researcher time, and accelerate the trial process significantly by automating multiple time-consuming tasks and alleviating clinicians and researchers from repetitive, manual tasks.

Strengths and Weaknesses

eSource provides benefits along all three major levers for improvement. By accelerating data capture and interpretation in trials, as well as facilitating communication and allowing teams to function on a 24-7 basis with real-time data sharing and collaboration, eSource accelerates the time required for trials to achieve a clear positive or negative outcome. By eliminating paper, eSource can eliminate associated costs including transportation, storage, and manual data quality verification prior to recording. For newer, iterative research designs, eSource is essential; the study sites would drown in paper if required to capture and store all information. By removing numerous intermediate steps, eSource reduces complexity and the likelihood of errors. On the negative side, cybersecurity becomes paramount when the only records are electronic and capture of data is widely dispersed across numerous devices, including some operated by patients in the trials.

Internet of Medical Things (IoMT)

IoMT is simply a health-centric version of the Internet of Things. The declining costs and improving accuracy of sensors, paired with cheap connectivity and improvements in usability driven by consumer-friendly smart devices such as the FitBit and the Apple Watch, has created a new and highly efficient way to judge ongoing efficacy of clinical trials and collect highly accurate, objective data on those trials.

Device Types

Types of IoMT devices can be broken down into three main groups; smart technology sensors, connected and intelligent medical devices, and wearables.

Smart Technology Sensors

Smart technology sensors can capture biological data when connected to or embedded in mainstream technology platforms. For example, there is the AliveCor, an FDA-approved EKG capture device that jackets a standard iPhone. Additionally, data captured through existing sensors on smart phones is increasingly useful for investigators. For example, image capture is now good enough on iOS and Android devices to allow for accurate clinical diagnoses of dermatological conditions. By extension, this data is good enough for use in clinical trials. This development is driven, in part, by the increasing array of attached sensors and sensing programs using existing sensors in the smart phone platforms that measure biological data but were not driven through the FDA approval process.

Connected and Intelligent Medical Devices

Designed for home use, these devices are increasingly automated and can capture accurate readings when operated by trial subjects with minimal risk of errors. Blood pressure cuffs, blood sugar measurement kits, and many other systems that patients use to measure their conditions are also useful for drug and device trials. For example, the Omron-3 blood pressure cuff is highly accurate, fully automated and can indicate to users when the reading it has captured is valid or invalid. IoT-enabled smart pills are ingestibles that carry sensors and data recording or transmission capabilities. These systems have only in recent years become both small enough and cheap enough to be useful for clinical trials. Because these pills can collect data in situ from within the subject's body, data capture is highly relevant. When enabled with data transmission capabilities, it is possible for investigators to track detailed time series and even real-time information.

Wearables

Wearables are growing in popularity primarily for fitness tracking. Pioneered by FitBit, wearables increasingly capture more detailed biological data such as heart rate, blood pressure and body temperature. Future generations will also capture blood oxygen levels. Researchers are already using wearables as a mass recruitment tool. Doctors at Stanford University teamed with Apple for a large-scale heart study with tens of thousands of participants who are owners of an Apple Watch. The study already has proven a success; several people with abnormal heartbeats were notified of the condition due to data captured on their watches and analyzed with artificial intelligence algorithms designed to spot anomalous heartbeats.

Strengths and Weaknesses Of IoMT

Positive impacts of IoMT include vast new potential for continuous and near-immediate feedback, direct data capture that is more accurate and new types of data capture and research that were previously not possible, all with a relatively low bar for compliance. Potential negatives of IoMT include over-reliance on remote data capture without direct human observation, unintended behavioral changes induced by the presence of IoMT and lack of sufficient compliance or misuse of devices by trial subjects.

Real-World Data Incorporation

To evaluate real-world product effectiveness, more information is often needed on how specific treatments perform within different age groups, genders, races, and ethnicities, as well as how they perform when patients have differences in disease severity and/or co-morbid conditions that require other medications. This is an additional layer on top of traditional randomized controlled trials (RCT) that provide crucial insights into whether a treatment will work or is working in a real-world setting. Potential sources include social media, smart phones, activity trackers, electronic health records, insurance claim databases, patient registries, and health surveys.

This real-world data (RWD) can provide important health information about patients in the social context of their day-to-day lives. An accurate description of RWD is any health-related data collected outside of the trial construct. Because RWD is often unstructured, semi-structured or poorly-structured data, machine learning / artificial intelligence systems provide critical support in making this data relevant for medical research purposes. The collection and use of RWD is complementary to the construction of Synthetic Control Arms, relying on some of the same evidence types and information.

Strengths and Weaknesses of RWD:

Positive impacts of RWD include better understanding of whether tested treatments are working in real-world situations and whether compliance is challenging outside of a more restricted clinical trial environment. Additionally, RWD gives investigators insights into outside factors that may impact trial results such as lifestyle patterns. Negative impacts on RWD are that it is noisy, prone to errors, poorly controlled, and difficult to capture. For example, insurance and medical records can be fragmented and hold conflicting or unclear records of physician visits and treatment regimes.

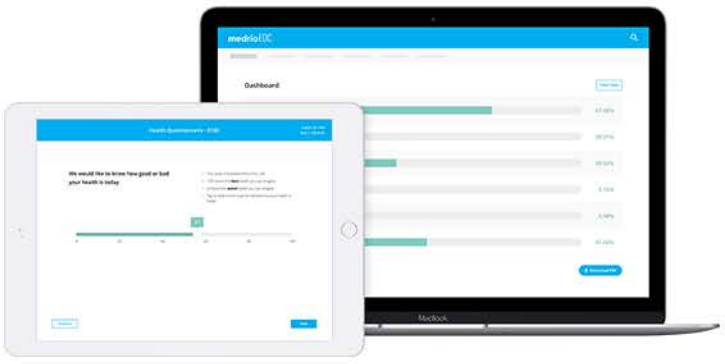
Better, Faster, and Cheaper Trials Lead to More Cures and Saved Lives

Over the past two decades, novel technologies have radically rewritten the rules of the game for industry after industry. From Uber rewriting the rules for transportation, to Tesla reorienting the automotive business around the idea of software and batteries, to Apple putting a super powerful sensor platform in the hands of the masses with its Watch and iPhone, to SpaceX making rockets reusable, technology is accelerating business innovation, slashing prices and quickening the tempo of progress and development.

The healthcare industry and the drug and device development space are now poised to make similar leaps in productivity, cost and pace of innovation – if it embraces all the new technologies and methodologies coming available and exploits them to their fullest potential. From IoTM to adopting cloud computing and distributed technology to drive trials, logistics and infrastructure, opportunities for improvement are broad and deep.

To harness the use of these new technologies more quickly, governments around the world have demonstrated that they want to accelerate drug and device trials and embrace new forms of validation to help speed the delivery of new cures and therapies to patients in need. Clinical research organizations, pharmaceutical companies, research laboratories, and all others who presently work in this field but fail to adopt and adapt may risk being bypassed by other, more innovative alternatives. The future of drug and device development is brighter than at any point in recent memory.

Now it's up to the industry to truly embrace modern technology and modern approaches and deliver more and better cures, faster and at a lower cost. At stake are the lives of millions who will benefit from being treated with more new drugs and devices sooner.



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