Can mHealth be Thought Of as the Default Solution for Accelerating Completion and Increasing Success Outcomes in Clinical Trials?

Clinical trials are the experimental foundation on which modern medicine is built. Human medicines cannot be sold without permission from a licensing authority, and permission will not be granted unless a clinical trial has demonstrated the medicine's success in treating the condition for which it will be marketed[1]. Clinical trials, in addition to generating valuable scientific evidence, also provide some patients with an important way of accessing products that have not yet reached the market, offering hope to those for whom existing treatments have failed. The necessity for a clinical trial to be performed before a medicine can gain regulatory approval means that trials are also big business.

As important as clinical trials are, they are, unfortunately, a painstaking but necessary process in bringing drugs to market. Clinical trials are costly, take a great deal of time, demand intensive effort, and can have a very high failure rate[2]. However, the return on investment can be huge if the medicine works, and becomes a blockbuster drug.

Clinical phases	Percentage of clearance	# Years taken to conduct
Pre-clinical	-	1-6 years
Phase I	30%	6-11 years
Phase II	14%	
Phase III	9%	
Phase IV (post-market surveillance)	8%	11-14 years

Table 1: Breakdown of the clinical phases according to percentage of clearance and years taken to conduct the trial[3]

According to Table 1, in a study conducted, about 30 % clear Phase I trials, 14 % clear Phase II trials and only 9 % pass through Phase III trials. (Phase IV occurs after the drug is approved.) This entire process may take anywhere from six to 10 years, which excludes time spent on preclinical drug research. (Disclaimer: There are other factors that contribute to the high cost of drug development which are not discussed here. This article highlights the most prominent ones.)

In 1975, the Tufts Center for the Study of Drug Development (CSDD) reported that the pharmaceuticals industry spent approximately $100 million in today's dollars for research and development of the average drug approved by the US Food and Drug Administration (FDA). By 1987, that figure had tripled, to $300 million. By 2005, this figure had more than quadrupled, to $1.3 billion. The true amount that companies spend per drug approval is almost certainly even larger today[4]. Now, it is estimated the global cost of drug development is between $1.2 billion and $1.8 billion per year[5].

Costs are Rising

Clinical trials have been regularly criticised for their high cost. In the overall process of developing new drugs, the clinical trial contributes to the highest cost. Approximately 90 % of the R&D development cost focuses on effectiveness and preservation, which is Phase III of the process[6]. This phase is usually the most extensive and expensive part of drug development. The rising costs of

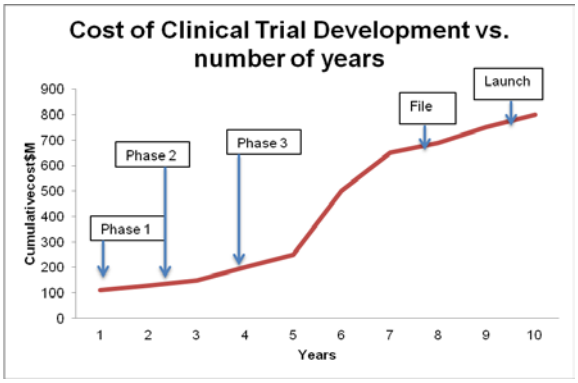

Figure 1: The different phases of drug development corresponding to its cumulative cost

clinical trials show no sign of declining, for many reasons.

According to the Pharmaceutical Research and Manufacturers of America (PhRMA), the total cost of Phase I-III research has increased by 250 % since 2001 – to slightly over $40 billion[7]. The table below shows a breakdown of the estimated cost for each clinical phase incurred while developing a drug:

Function	Dollars ($M)	Share of Total
Pre human/preclinical	$11,717.40	28.6%
Phase I	$3752.90	9.2%
Phase II	$7123.70	17.4%
Phase III	$16,300.10	39.8%
Approval	$2046.90	5.0%
Total R&D up to FDA approval	$40,941.00	100.0%
Phase IV	$5302.70	13.0%
Uncategorised	$197.80	0.5%

Table 2: Breakdown of the estimated cost for each clinical trial phase

Over the years, clinical trail research for pharmaceutical and biological products has increased globally[8]. All this research and development yielded an extensive amount of new drugs, making it increasingly difficult for pharmaceutical companies to prove their products are superior to those already on the market. This is because clinical trials development is becoming ever more complex, specifically from the regulatory perspective, with greater

emphasis on data and site/patient monitoring. The need to accumulate more data to show modest benefits has resulted in drug companies investing more in recruitment for clinical trials, which further increases the cost. In addition, the challenge of finding new products has led some companies to develop treatments for chronic conditions and degenerative diseases. The clinical trials for these types of drugs tend to be long, complex and expensive. More importantly, clinical trials commonly over-run their intended completion dates. In some studies, about 80% of clinical trials fail to meet their milestone.[9] These delays causes companies to lose between $600K and $8M each day a drug is delayed from the market[10].

Subjects/patients are the most important assets of a clinical trial. And the number one cause of delayed completion is patient recruitment and retention, as well as the clinical trial process itself, which is the main discussion of this article.

Since clinical trials contribute the biggest cost percentage in drug development, it is clear there is a need to reduce the cost of clinical trials in order to reduce the cost of medications for patients. Drug manufacturers are under pressure to cut the cost of drug. As the recent controversial review of the UK Cancer Treatment fund, drugs perceived to be expensive can be dropped without consultation or warning[11]. Reducing the costs of trials is absolutely crucial for the public good. Reducing the cost of clinical trials and time to market is the ideal scenario, however, reducing time to market will be discussed in more detail in future articles. Reducing the duration and cost of clinical trials increases the potential to make profit on a drug, whilst also driving down the cost of treatment, and ultimately improving the outcomes for patients. Strategies for reducing cost already include offshore trials and outsourcing. Now, mobile health also has a role to play in clinical trial efficiency, and ultimately reducing the cost.

Offshoring and Outsourcing

The increasing cost of clinical trials is affecting the drug industry in several ways as more organisations are using different and innovative ways to make the process more efficient and cost-effective. One way used to cut costs includes companies conducting clinical trials in other countries, such as China and India, where costs can be as much as 60% lower. Because the apparent clinical trial processes can be complicated, a new industry has arisen to drive the studies through the tangled regulatory underbrush; commercial contract research organisations (CROs). Revenues for CROs will reach $32.73 billion in 2015, with the industry pursuing this route thanks to its ability to drive cost advantages and offer regional expertise by way of its research service providers[12].

Mobile Health (mHealth)

As feasible as all of these ways are, it is important to note that mHealth is also one way that clinical trials can reduce costs. Technology, particularly mobile technology, should always be considered as an option to streamline the processes in order to reduce cost[13]. Studies have shown mHealth can reduce cost . So, can mHealth be thought of as the default solution for accelerating completion and increasing success outcomes in clinical trials?

As mentioned previously, the number one cause of delayed completion is due to patient recruitment and retention. Since this is one of the significant reasons why clinical trials are delayed, it is important to see the reasoning behind it. There are various initiatives and organisations that have been set up to offer patient and volunteer recruitment to clinical trial sponsors and some CROs claim to have a high rate of patient recruitment. Despite this, it still remains the number one reason for delays. Why is this still happening? A possible reason is that they fail to track recruitment efforts. According to Lopienski (2014) one of the biggest mistakes that can be made in patient recruitment is not tracking the results[14]. It is important to ask each subject/volunteer how they heard about the study and document the information and how it is obtained. Sites can use metrics and analytics with mHealth giving hard data to justify why they need an increased advertising budget. Examining what was effective and what did not work helps plan future recruitment, knowing what to continue doing and to avoid making the same mistakes.

Using mHealth in Recruitment

Integrating mHealth with patient recruitment websites and having tracking software can help track such information to innovate the recruitment process. Patient accrual in clinical trials relies heavily on effective patient recruitment, but enrolment goals are not met for a variety of reasons. No matter the cause, delays in clinical trials affect sponsors, CROs, and sites. Making improvements to recruitment efforts and working more as a team can increase the efficiency of clinical trials to keep studies on track.

Using mHealth in Retention

In the issue of retaining the patients, this comes to the subject of patient engagement. A growing body of evidence[15] demonstrates that patients who are more actively involved in their healthcare experience better health outcomes and incur lower costs. It is clear how important patient engagement is. This concept can be, and is already being, extended to the clinical trial space. As a quick brief, “patient engagement” is a concept that combines patient activities with interventions designed to increase activation and promote positive patient behaviour, such as obtaining preventive care or exercising regularly16. Patient engagement is a strategy to achieve the “triple aim” of improved health outcomes, better patient care, and lower costs.

But Who Provides the Device?

More and more people now own mobile phones, tablets and gadgets and are using apps to regulate their daily lives and routines. With smartphones, roughly 5% of the

Case Study

As an example, in a patient engagement study published in *Health Brief*, patients who received enhanced decision-making support* ultimately had overall medical costs that were 5.3% lower than for those receiving only the usual support*. They also had 12.5% fewer hospital admissions and 20.9% fewer preference-sensitive heart surgeries. Using this similar concept, incorporating mobile technology to engage patients in the clinical trial setting, the same cost savings concept can be applied.

**Enhanced support includes a patient who is engaged by health coachers over telephone, mail and Internet (which is higher coaching versus the usual support)*

global population owned a smartphone in 2009. That number is expected to hit 35%, or 2.5 billion people, by the end of 2015, which is approximately the population of China and India combined.[17] Considering the ever-quickening pace of technological innovation and the shrinking cost of processors and microchips, it can be projected that by 2017, half the world will be hooked up to the internet with portable devices. Practically everyone will "always be online" on data connection or 3g/4g Wifi, even in developing countries. It is the connectivity and not just the device itself that provides the opportunity for real-time clinical monitoring and data collection. Smartphones, tablets, other wireless devices and "going online" have radically changed many aspects of our everyday lives, from banking to shopping to entertainment. Many devices already feature biometric sensors such as heart rate monitors, and medicine and healthcare is next. Hence, it makes sense that we integrate these devices with mHealth applications. Doing so puts the savvy patient in sync with their daily lives when it comes to managing their health, and now the opportunities are spreading to embrace this technology proactively, in particularly with clinical trial subjects.

Since most people have a smartphone, it can be proposed that trial subjects can possibly use their own devices, in this case a smartphone in a clinical trial setting. As a result, the "bring your own device" (BYOD) approach may be able to reduce clinical trial cost. BYOD allows participants in a clinical trial to use their devices (with which they are already familiar) to access and respond to study-related questionnaires. Moreover, the connectivity of such devices affords an opportunity for real-time data collection and reporting. So theoretically, clinical trial sponsors would not need to supply a specific device when using mHealth in clinical trials, and this is seen as a way that may lead to cost reduction. Of course, if the patient does not have a device to use, the sponsor could provide it, but the cost of this is expected to be considerably smaller (with the assumption that most clinical trial subjects own a mobile device).

As in the workplace, the use of the patient's own device in clinical trials or any medical setting is controversial. Cost is perhaps the least significant factor, as reasonable reimbursement could be made for the provision and connectivity of a suitable device. More significant objections stem from the security and protection of the personal data. Hence it is important to take appropriate measures in a similar way to mobile banking, or the payment card industry (PCI). Best practices include end-to-end encryption of the data, and working with mobile apps that are developed to a standard of assurance for use in the medical sector.

In engaging the patient, we look at streamlining the clinical trial processes. When looking at streamlining the clinical trial processes, a further problem area that mHealth can help with is the initial and ongoing capture of data. In most trials, data capture continues to be done via paper. The clinical trial subjects are the key element in the studies as the data coming from them is most valuable, however self-recording using paper is prone to error and inevitably introduces delays. Data required from the subjects include: dosage of drug taken, timing of dosage taken, questionnaires, side-effects and many others. However, errors in capturing these very important data results in the further increased cost of clinical trials. Patients may forget to take the drug or even perhaps take it at the wrong time, and may forget or delay to fill in the questionnaires after taking the drug; all of these lead to delays, which have a cost value to them. In addition, when taking data on paper, the turn-around time for the data to come back to the clinicians (from the patients) may take a few days, as it is not on real time (patient may need to travel back to the site and so forth).

Data collection has been improved with electronic data capture (EDC) packages such as ePro[18], where patients are able to do this on a website via a computer with internet connection. However, it seems that it is still not enough to fully streamline the clinical process because of delays between data capture and data entry, i.e. sometimes because the subject just tends to forget or delay them; ultimately the data is not on real time. Having a mobile application will make the patient more engaged (vs. using paper or website) because real-time automated data capture allows the patient to submit data on the spot – for many of us, devices like our smartphones are among our most valuable possessions that we cart with us everywhere we go. It is a more accessible device compared to the computer. Hence, it is important to integrate a mobile element to these web elements in order to make data capture real time, which can streamline the clinical trial process.

Wearable Tech

The emergence of wearable technology and popularity of patient-centric applications for them also provides a great opportunity for pharmaceutical manufacturers to engage patients and create a customised, direct relationship with them. The clinical trial space provides an excellent channel to leverage these technologies. The integration of wearable and mobile technology in new clinical trial design and business strategy development holds promise for aligning site and patient needs with faster study execution and reduced costs. In relation to

this, the application of statistical analysis to biological data, i.e. biometrics, could be a great advantage for some trials. Using a wearable tech, specifically in clinical trials (and not just for fitness) like a handheld electrocardiograph or a blood regulator microchip patch, and consolidating the data collected via an app, would be useful in streamlining the process. These biometrics can be especially useful for clinical trials that are conducted on subjects that have two or more chronic conditions like diabetes and heart attack, or patients with degenerative diseases like Alzheimer's, as tracking and measuring data from them (people who need a long-term commitment to measuring and tracking their health) would be useful for pre- and post-clinical trial studies.

Hype or Hope?

The hype of leveraging mHealth in clinical trials has stirred some drastic movements within the industry. The pharmaceutical and drug development industry will either choose to go digital or be forced to. Earlier adopters of digital may already be realising the future potential, impact and benefit that mHealth has to offer in cost reduction and streamlining the clinical research process. The laggards may be more established, enabling them to compete for longer with their old models, but sooner or later all players will be adopting digital. This can be seen in an example from a CRO perspective. CROs specialise in optimisation of the trial process, therefore a proper strategy to use mHealth is vital. This creates a good business strategy for the CROs to develop their own business because more and more clinical research is looking to go digital.

Time for a Lean Approach?

In the entrepreneurial world, the sooner a failure can be identified, the more productive time can be devoted to successful ventures. Because of the high failure rate in clinical trials, adopting the lean method may be equally beneficial for the process. Using digital and mHealth can facilitate this "lean method" in clinical trials. If you were to fail, fail at the early stages. Reducing product failures at the later stages of the clinical trial process has also been stressed as a way to reduce costs. mHealth can enable the leaner approach to clinical trials as real-time data enables earlier visibility of side-effects and risks. So if the drug is not working, this will become evident sooner, allowing earlier failure, which can reduce cost and help them to pivot (make a structural course correction to test a new fundamental hypothesis about the product, strategy and engine of growth) to a different solution.

Because mHealth has been shown to be able to streamline the clinical trial process, pharmaceutical companies realise the benefits of mHealth, hence they are even putting aside special budgets for their pilot projects in mHealth. Pharma giants such as Novartis, Pfizer, Astra Zeneca and GlaxoSmithKline are betting big on leveraging mHealth technologies in the drug development process, so we should expect the increased use of mobile health tools in clinical trials in the near future.

This goes to show that pharmaceutical companies already believe in the importance of using mobile technology in the drug development process, specifically for patient engagement, and hence the mHealth industry is projected to grow even more in the very near future.

Data is in the Cloud

As more data are collected, study timelines grow longer, patient recruitment and retention grows more difficult and drug development costs increase (CSDD)[20]. This is because of the collection of data from various centers and is also due to the way data is collected, i.e. in paper form, there are still data being collected by paper. This has a negative impact on the bottom line. The cloud has proven to be a useful tool in consolidating data and collecting data via technology. Further falling costs are also predicted as the cost of cloud computing and storage[21] drops. Also, data loss is much reduced when compared to paper systems. This effort has already been initiated with the NHS patient data is already in the cloud, under a project with Microsoft UK patient records, which are stored in the Azure data centers in Ireland[22].

In addition, collection of data from various resources e.g. multi-trial centres causes data fragmentation, and would cause data retrieval to be difficult. Answering key questions regarding a study is time-consuming and has a negative impact on the bottom line. Consolidating data in the cloud could streamline the multiple clinical trial centre using the same study, so all healthcare professionals involved in the study will be able to have access. Technologies for analysis of cloud-stored "big data" are also making great strides, which can only help accelerate the efficiency of data capture, analysis and reporting, whilst cloud providers such as Google and Microsoft are making great strides to overcome concerns about data security and privacy.

Conclusion

It has been demonstrated that integrating mHealth in clinical trials can reduce cost. However, are these cost savings enough to make any significant impact revenue-wise in the long term? Clinical trials are still the basis for deciding how good and safe new drugs are, and that's true even more so now than in the past. The challenges that mHealth has to overcome in the industry are primarily due to regulations, so working together with the regulatory landscape will be best to push mHealth to fully leverage mHealth. mHealth, mobile and cloud technology and BYOD opens many opportunities for improving clinical trials provided the concerns are overcome. Trends in healthcare and technology are driving the adoption of mobile health, but many obstacles remain. Risk is big issue in clinical trials - risk of things going wrong, risk of adverse reaction, and risk of the drug failing. However, risks associated with clinical trials can be managed more closely with the immediate and real time feedback from embedding mHealth.

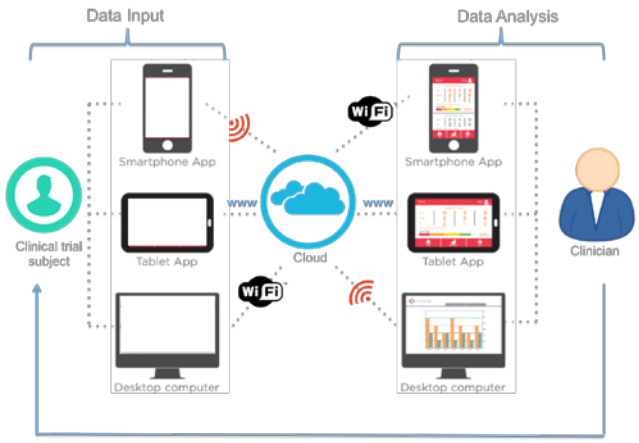

Figure 2: Integrating mHealth into a clinical trail study

To capture mHealth's full potential, industry stakeholders will need to act in a coordinated fashion to redesign their approach in streamlining the clinical trial process. Working with a trusted developer that has the experience and capability in medical deployment is also key to a successful outcome in mHealth in clinical trials.

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