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12 Adhere.IO

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Introduction

Behavioral diagnostics can be a powerful force in persuasive behavior change and health. Our team at the MIT has developed and tested this new class of diagnostics aimed at improving medication adherence by remote for verification and persuasive incentives. Our platform called Adhere.IO began as a small student project called New Dots, later renamed XoutTB to reflect an application to improve tuberculosis medication adherence. Our journey into the use of mobile technology for behavior change began as a way of improving drug adherence to complex drug regimens, such as HIV and tuberculosis. We began by combining the latest findings from psychological and economic research and innovations in chemical and micro scale engineering to result in a combination diagnostic that uses lateral flow technology – the same biomedical technology that run pregnancy tests diagnostics – aided by mobile telephony.

Enabling patients to complete their treatment not only improves patient health directly, but also helps prevent the spread of drug-resistant strains of tubercular systems that are becoming more prevalent (Haynes, McDonald, Garg, and Montague, 2002).

Adhere.IO was invented at the MIT to introduce a new class of medical devices called behavioral diagnostics. Behavioral diagnostics combine emerging trends in applied behavioral economics and diagnostic design at the microscale wrapped in a telemedical application. Our application of behavioral diagnostics is a home-based test aimed at improving poor adherence of complex drug regimens such as HIV and tuberculosis, in low- and middle-income countries as well as high income countries. Our journey in developing behavioral diagnostics started with a challenge to improve TB medication adherence. We learned and are learning many lessons along the way.

The challenge

Tuberculosis (TB) remains a major public health concern more than sixty years after the first effective TB antibiotics were developed. According to the World

Health Organization (WHO), one-third of the global population is infected with tuberculosis bacillus, and 10 per cent will develop active tuberculosis. In 2010, there were roughly 8.8 million new cases of active TB and nearly 1.7 million TB deaths (WHO, 2011).

The conventional response: Treatment and adherence

TB treatment consists of a six- to nine-month course of antibiotics, usually a combination of isoniazid and rifampicin, taken orally (Centers for Disease Control and Prevention, 2009). Patients may often start treatment earnestly given that they may already be suffering from symptoms of the disease. As the antibiotics begin to do their job, the TB symptoms may begin to subside and the only remaining discomfort are the side effects of the medication itself. A qualitative visual representation of the problem is shown in Figure 12.1.

The system currently recommended by the WHO for tackling the problem of non-adherence is Directly Observed Therapy Short-Course (DOTS), which involves onsite, in-person monitoring of adherence with prescription drugs. Formal DOTS programs are often compromised and their performance is less than ideal. This is exacerbated by absenteeism and low attendance among community healthcare workers (Banerjee and Duflo, 2006; Chaudhury, Hammer, Kremer, Muralidharan, and Rogers, 2006). Furthermore, DOTS is a punitive measure that often results in a patient reprimand rather than peer support.

Community-based DOTS (CB-DOTS), using treatment partners as ‘social capital’ to ensure adherence, are protocols in which trained community members or peers observe the ingestion of each dose of medication (Ware, Idoko, Kaaya,

Figure 12.1 Visual representation of TB adherence

Biraro, Wyatt, Agbaji, Chalamilla, and Bangsberg, 2009); they have brought down the costs of DOTS but community programs vary considerably in their quality.

The WHO estimates that nearly 20 per cent of the world's population lives in areas still yet not covered by DOTS or similar programs (WHO, 2010). While most of these people will never develop cases of active TB, there exists a small portion who are at high risk for developing active TB because of latent TB infections or weakened immune systems. A cheap and effective monitoring technology that does not rely on health or community workers to see the patient every day has the potential to provide an effective yet inexpensive method for ensuring adherence in these vulnerable populations that do not have access to DOTS-like programs (Moulding, 2007). DOTS is estimated to cost US \$120 per patient (Wandwalo, Robberstad and Morkve, 2005), Adhere.IO can cost as low as US \$40–US \$70 per patient.

Adhere.IO's approach to increasing adherence

Adhere.IO creates an interactive feedback loop using reminders, monitoring, and incentives, as shown in Figure 12.2.

At the heart of the system is a colorimetric diagnostic that reveals an alphanumeric secret code when exposed to the metabolites of a drug. In order to produce such metabolites, the drug has to be ingested and a sample, such as urine, placed on the test. Within minutes, the code is revealed as the chemicals from the test

Figure 12.2 The Adhere.IO system

react with the metabolites. The test only reacts with the medication's metabolites, and only those metabolites, voiding the possibility of revealing the code without taking the medication. The patient will then send that code via SMS to a number linked to a database that matches the code to the expected answer. The patient receives a reward based on the correct codes that they send in (Gomez-Marquez and Hanumara, 2010).

Adhere.IO uses established lateral flow technology with a twist interactive diagnostics. Chromatography paper is formed into paper fluidic channels and embedded in chemicals that result in a colorimetric reaction not unlike a variant of the standard pH dipstick test. The technology is affordable, designed to be locally manufacturable, and because it is based on paper which is highly ubiquitous, easy to scale and distribute. It is also instrument free (as in the previous paragraph). In order to detect whether a drug is there, thus allowing the patient to reveal compliance at a distance, we need to detect one of the following, the metabolite of the drug, the drug itself, or potentially a tracer embedded on the drug, or an indirect ingredient already found in the drug. As a launching pad we chose to detect a metabolite commonly found in isoniazid which is isonicotinic acid which is excreted in urine. The reaction is commonly described as the Potts-Cozart reaction and is based off of many available commercial tests. We modified the published test into a paper diagnostic.

In practice, patients are given sets of test strips that they use every day to prove that they have taken their medication. Unlike DOTS where a healthcare worker intervenes to monitor, the patient sends his or her proof code via an SMS to a central processing database that tracks the patient's compliance rates. For each week that the patient succeeds in taking his or her medication, they receive a reward in the form of cellphone minutes (immediately transferred electronically to their cellphones). These short-term incentives aim to keep patients engaged in their long-term treatment. What this provides is a private benefit to the patient (an incentive such as cellphone minutes) as well as a public benefit to both the patient (increased chance of survival) and society (decreased infection rates). What economists have long known is that people are more responsive to short-term private benefits faster than they do to public benefits. Economists call this hyperbolic discounting (Ainslie and Monterosso, 2002).

The evolution of our approach

We outline a few key findings on how the project has evolved from a response to a student challenge into a multicountry clinical trial project, shifting established community health paradigms.

Mobile as a lens for paradigm shifts and disruptive innovation

Exploring a paradigm shift taught our group to analyze the problem with a new lens. The lens can be technological, systemic, or a combination of the two. The resulting view may undermine established agendas among players.

At the inception of Adhere.IO, the challenge of patient noncompliance was brought forth by a group of public health experts who had been heavily invested in DOTS, the current standard of care. Our response was perceived as radical since it could bypass the community healthcare worker altogether. We were proud of our technology, our impression of their reaction to it was that it represented a threat to their establishment. Traditional stakeholders seemed to label the approach as heretic in private, and based on responses to the press and our own introductions, amateurish. Had we followed their advice, the project would have been very different today. We heard reasonable suggestions for undermining the idea:

- ‘You don’t have to go through the trouble of giving them a test, just give them food.’
- ‘The problem is that community health care workers don’t get paid enough. Instead of spending the money on a test, just pay them more.’

We had the luxury of employing a new lens toward the problem because we were not beholden to any stakeholders:

- **No one in the team was being funded to develop the project.** While funding was nonexistent with the exception of a few hundred dollars from the MIT to test out some key concepts, we were completely autonomous.
- **There were no jobs at stake.** All participants either had a day job or were full-time students. This was a completely separate activity with very little overlap, and no shared oversight. This provided a truly free space to explore new approaches. In the long-term, this would later prove to be one of the most difficult aspects of maintaining a healthy continuity of the project.
- It was **not part of a tenure track research agenda.** No one held an academic position at the time of inception. Adhere.IO is interesting from a systems integration and public health perspective. However, the very nature of its simplicity makes it a poor candidate for an engineering or basic science publication on which to base a tenure agenda. The chemistry was known and established in 1972 (Ellard, Gammon and Wallace, 1972). Lateral

flow technology has been around for decades. SMS reminder and healthy behavior messaging systems had already been widely used. In academia, all the above are translated into ‘it’s already been published’. Had we followed that agenda, the project may have never taken off the ground.

- We had the **benefit of being outsiders** who could look at the problem with a **fresh perspective**. None of us had a public health background. We were designers who had no idea which aspects of the project might run into ‘sacred cows’ and which questions were naive. Being an outsider allowed us to explore what might be a familiar territory to others.
- **Extensions and expansion of DOTS (the current standard of care) were not part of our metrics for success.** Looking back at the inception of the project, we suspect that some of the promoters of the challenge might have been looking at a method to augment or accelerate the current approaches to tuberculosis compliance in the field. In the end, we took note of those approaches, and became particularly impressed by the high rates of absenteeism presented by Banerjee and Duflo (Banerjee *et al.*, 2006). Our approach shifted the locus of power from the community healthcare worker to the patient.

The structure of the disruption

Previous remote approaches at dealing with lack of adherence have used various methods including reminder systems, incentives, supervisor incentives, and verification. To date, there is no widespread system that combines verification and incentives.

Table 12.1 Conventional approaches to adherence persuasion

	DOTS	DOTS Incentives	xHale	Proteus Helium	Health Honors
Reminder					X
Patient incentives					X
Supervisor incentives		X			
Verification			X	X	
Healthcare Professional centric	X				
Patient centric			X	X	X

Figure 12.3 Detection and Reporting Method

Many approaches focused on empowering the healthcare worker instead of the patient. This resulted in misdirected incentives, healthcare-centric verification diagnostics, and a declining relationship between the healthcare worker and the patient: less caretaker, more supervisor. Our design for the Adhere.IO ecosystem aims to create a system in which the supervisory role and the caretaker role are decoupled, as shown in Figure 12.1. In order to do that, the patient has to gain a relationship with a third party – the incentive mechanism – that serves as a proxy for supervision and monitoring.

The mobile as a reader

Adhere.IO is part of a growing group of mHealth technologies coupling the communications power of a phone with onboard diagnostics. These are technologies that strive to be independent of a system. We have noted an overwhelming number of mHealth approaches that focus on novel transmission of patient data packets. This approach assumes that we have obtained the right information in the first place. There is space for more innovation in the field for creating these types of hardware apps. Since Adhere.IO's invention, the field of hardware apps on mobiles has grown. In 2009 and 2010, a number of significant innovations in pairing vital signs with mobiles emerged such as ThinkLabs stethoscopes. In 2011, we saw a surge in technologies aimed at pairing wet lab sensors with mobile phones such as the ESTI2 research consortium that develops

mobile phone STD tests (Sutter, 2010). Solutions like Adhere.IO strive to take advantage of the phone's ability to do more than serve as a portable database. This creates additional opportunities to interact with a patient's health status, opening gateways for positive behavior change.

Cross-functional team formation

The XoutTB project assembled a team that focused on creating a biosensor-driven system coupled to a telecommunications platform. It required a multidisciplinary team that included chemistry, mechanical engineering, policy, economics, and clinical experience. Beyond creating diversity within the group, we forced cross-functional tasks to avoid attacking the problem conventionally. In fact, we did not have an IT person at the inception of the project.

We applied a Solution Architecture (Gomez-Marquez, 2010) approach to tackling a problem in which we had limited expertise and limited funds. In this way, we sought out help as needed.

Solution architectures

Designing projects for the developing world can attract many forms of assistance both in-kind resources and subject matter expertise (SME). The latter is critical at every stage of a project. It can be helpful to understand the types of expertise you will need to seek and bring together to realize your design. This involves grouping technologies and ideas. It also involves assembling individuals who may be part of your team and other may be participating as mentors.

The mobile as a walkie-talkie

By placing much of the innovation on the sensor, we ended up with a system in which reception of the coded message by the patient can be done in a number of ways, not just a mobile phone. By focusing on the intricacies of the other aspects of the solution, we refused to be tied down to many IT-laden challenges and prevalent discussion points such as debates about open sourced code, data storage mechanisms, SMS versus Data, cloud-based apps versus in-phone software.

During our period of system development, we were able to focus on aspects of chemistry, mechanical engineering, and behavioral economics that would ultimately tie-in to a telecommunications system. This led to telecommunications neutrality. Our aim was to create a messaging and incentive system in which the patient could use a number of communications devices, not just mobile phones, to verify their adherence behavior.

It is conceivable that if we had started with a smartphone, a team of software developers, and a mandate to create something specifically for mobile health, we may have invented a complex piece of hardware and software with rigorous smartphone requirements. Allowing the team to treat the phone system as a walkie-talkie directed the flow of ideas toward the initial sensing and behavior reward scheme.

Bottom-up innovation leads to a change in the incentive scheme

In August 2007, our team arrived in Nicaragua for our first engineering field trial to test the manufacturability of our system. One of the first changes in system design came from Ezequiel Provedor, head of CARE's health division: Use cell-minutes as a reward instead of microfinance credits. That decision shifted our 'telecommunications neutrality' to a definitive bias toward mobile phones. It was a decision based on the incentive system as opposed to the choice of communications technology. The decision created a mobile-centric evolution to the process. At the same time, it swept the project up in the popularity and promise of mobile health. One of our fundamental aims is to separate the hype around mobile technologies for health from the core innovations that create behavior changing technologies.

Surviving the double valley of death for emerging technologies for global health

Appropriate technologies for health can often leave researchers in a quandary: technologies must be simple and affordable, but often simplicity leads the research agenda to be considered less-than-cutting edge for traditional grants and academic funding mechanisms. Our lab describes this as the 'Double Valley of Death'. In medical device commercialization, the Valley of Death is recognized as that period that a technology has to survive in between academic research funding and pre-revenue commercialization activities. In global health, an often overlooked Valley of Death is the period beyond early stage seed funding and mid-stage research where the uncertainty of an idea is still as high as its promise. Adhere.IO has been a classic case of a technology going through both Valleys. The project received an early stage award of less than US \$10,000 to develop a refined prototype that included field testing. Additional funds from private donors doubled that amount to a manageable budget for materials and incidentals, but not equipment. After creating reputable bench prototypes, a small US \$50,000 NIH Award allowed the project to continue development, and in 2009 a major award for a clinical trial in Pakistan was awarded. The award was later revised to pay for evaluation costs but

not for implementation costs. In practice this meant we could pay to evaluate the technology, but we could not pay to actually develop it. This scenario occurs far too often in global health technology research. As more funds are placed in ‘mezzanine level’ awards instead of early stage awards, promising technologies may simply be abandoned for more sustainable projects. To counteract this trend, we embraced several tactics:

Vintage technologies. Instead of reinventing the chemistry, we scoured proven assays that had worked before and focused on re-contextualizing the solution with today’s available technologies – such as mobile phone and paper microfluidics.

Lean prototype fabrication strategies. Our laboratory has specialized in the creation of affordable prototyping methods for a variety of biomedical and diagnostic devices. For instance, early in the project we recognized that instead of expensive filter paper sold by specialty chemical suppliers, we could use generic coffee filters as a substrate.

Trickle-Up Applications. Adhere.IO began as XoutTB, a diagnostic platform intended for tuberculosis adherence. After failing to get early stage funding interest from parties in global health, we took our platform that was already as simple as an interactive diagnostic could get, and applied it toward domestic uses. In the United States, nonadherence costs the healthcare system approximately US \$290 billion a year in follow-up costs, according to the New England Health Care Institute. The promise of a technology that is simple, affordable, and universally compatible with most telecommunications systems is now very attractive to domestic markets – without losing its soul and intention to help patients in the poorest of countries who are trying to get well from diseases that just need them to change their behavior to stay healthy.

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