medidata

WHITE PAPER

# Virtualizing Clinical Trials

# Patient Centricity in Clinical Trials

The backbone of drug and medical device development is the clinical trial process, which is regulated by regulatory bodies such as the Food and Drug Administration (FDA) and the European Medicines Agency. This is the lengthy and rigorous process by which new therapeutics are tested to demonstrate their safety and efficacy in human patients.

Historically, clinical trials have been steeped in esoteric language and opaque to the public at large. The process is run in top-down fashion, and managed in tightly controlled clinical settings. It is highly regulated; trials are subjected to strict validation rules for data gathering and analysis. And trial data generally flow from investigators back to the drug company/sponsor — instead of to the patients who were subjects in the trials.

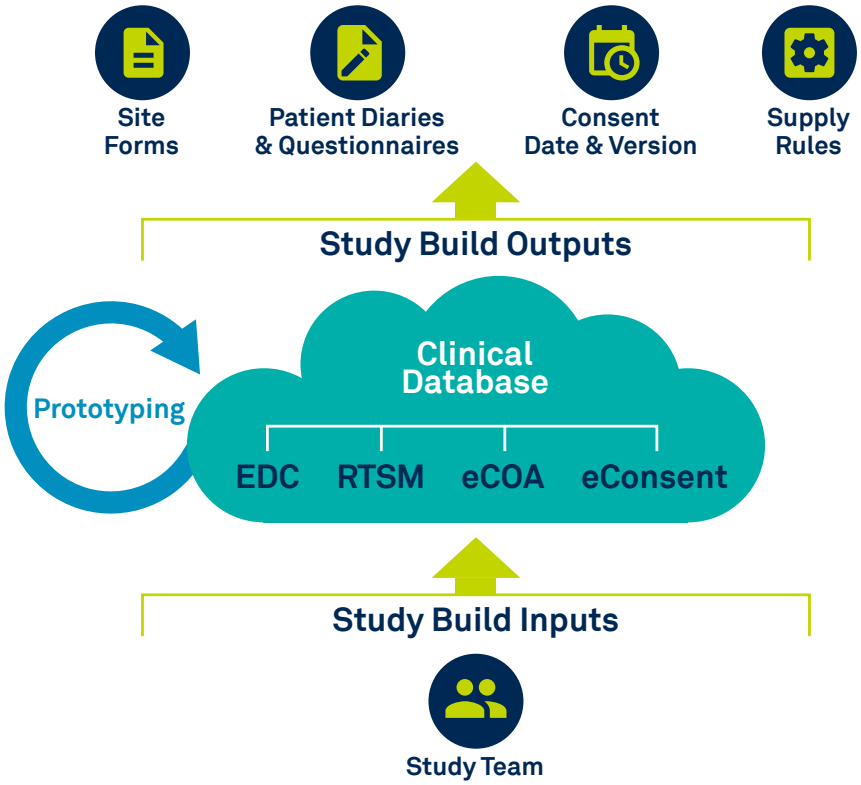
This last characteristic of clinical investigations is changing. A trend is emerging toward greater patient involvement in clinical trials — making them more ***patient-centric***.

Trial sponsors and clinical investigators are exploring ways to immerse patients in trials — including their perspectives and better informing them about risks, benefits, and disease progression. There are two recurring themes in these discussions: the user/patient experience and data quality.

The objective of a typical trial is no longer to just determine whether the drug causes the intended biochemical effect. Investigational drugs must be safe, effective and produce a positive outcome. Investigators, regulators and pharmaceutical marketers are increasingly interested in outcomes as measured from the patient's perspective. "Outcome" more broadly refers to the improvement in the patient's wellness or quality of life, and not just reversal of disease or extension of longevity.

The patient experience is an important consideration in trial design. The organizations that sponsor and conduct trials are identifying best practices and testing methods to get the patient experience right.

**Figure 1: Mobile health data captured in a clinical data platform**




Until recently, clinical trials have not emphasized the patient's perspective in data collection, but that is changing. Patient-centric data addresses different questions from those investigators have been asking in traditional trials. The data may be collected at home or at the patient's workplace — outside the traditional clinical setting. Managing the quality and the validity of those data is a new challenge.

Technology has made this evolution both possible and inevitable. The ubiquity of mobile technologies — like smart phones, tablets and wearables — and mobile networks has legitimized these devices as data collection sources that can generate reliable clinical information "in the wild" — outside the clinic, without investigator supervision.

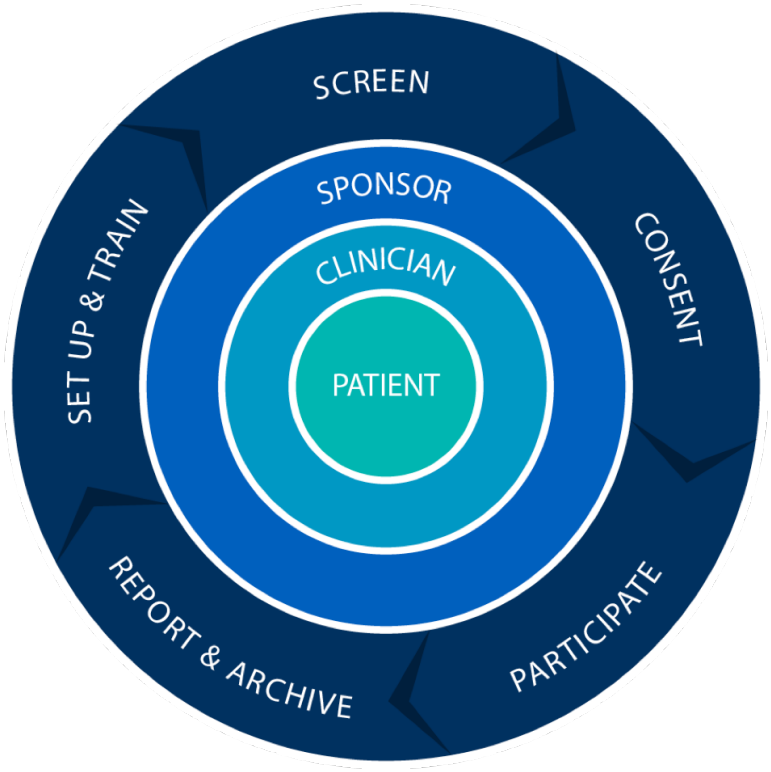
The use of smartphones is nearly universal in developed countries. Globally, we have seen an explosive proliferation of apps; a large percentage of smartphone and tablet users are accustomed to downloading and using them — not just to consume data, but also to enter it for a variety of purposes. And for app developers, the costs of developing and deploying them via mobile networks is low compared to the cost of conventional enterprise software tools.

Smartphones are more than just pocket-sized computers. They contain onboard biometric and global positioning systems that make them uniquely powerful passive data collection devices. As this paper will show, those features have been put to work in clinical investigations to monitor patients' vital signs, activity levels and mobility. Data have been shown to be reliable, reproducible and clinically meaningful.

Out of deep respect for patients, developers are looking for technologies that enrich and simplify the their experience. The immediacy and personalization of smartphone data make it uniquely relevant to the patient. Mobile clinical trials can turn the process of new drug investigation on its head — the ability to update a much larger database of patient experience and outcomes could enable unprecedented bottom-up development of huge volumes of data.

In order to work in the context of the trial, however, patients must see these devices and apps as seamless tools they can incorporate effortlessly into their daily routines. They will have value if they help patients better understand their diseases and make sense of what's going on in their lives.

We need to remind ourselves that we are working on investigational drug trials that involve a lot of risk, yet can offer a great deal of benefit to both the patient and to society. But the risks and benefits must be explained effectively to the patient, so that they can fully understand what is going on and give fully informed consent throughout the trial and over the course of their disease.



# Case Study: PatientsLikeMe

A key player in the growing market for patient-centric clinical data is PatientsLikeMe. The Cambridge, Massachusetts-based company has created an open, online community that is designed to give voice to a patient's story, and turn that story into data. Newly diagnosed patients find that there is clinical literature on their disease, some of which may be published in a format that is accessible to laypeople like themselves. But there are few resources that enable patients to learn from each other about their disease, its progression and how to live with it.

> **"We started with the assumption that patients had knowledge we needed, rather than we had knowledge they needed. We didn't have the answers, but patients had the insights that could help us collectively find them."**
>
> Jamie Heywood, Co-founder and Chairman, PatientsLikeMe

Founded in 2004, PatientsLikeMe has more than 600,000 members living with over 2,800 diseases. Its deepest resources are related to approximately 40 conditions which are underserved by the medical community — in that there is no effective therapy, or there are multiple therapies, and it is difficult for patients to make informed choices.

Access to the community is free for patients and their allies. PatientsLikeMe is supported in large part by the developers of new therapies, who draw on member experiences to inform their research.

The community lets users visualize the data meaningfully in profiles on the company's website and share the data with other patients, so that anyone sharing a common experience can learn from others.

Patient profiles look a bit like electronic health records. Data are codified using ICD 10, SNOMED, MedDRA and other common schemas. The database enables PatientsLikeMe to manage patients' stories as a form of qualitative research data, useful in answering questions like, "What's daily life like for someone with Parkinson's?" The company applies social science principles to analyze, in ethnographic fashion, what kinds of people visit the site. PatientsLikeMe found that users fit a finite number of patient personas, and their concerns boil down to a handful of common questions.

The company developed a taxonomy of plain language terms from the many colloquial expressions that patients used to describe the way they feel, and experiences that could represent important events such as drug side effects and markers of disease progression. The taxonomy, drawn from hundreds of thousands of experiences, is intended to normalize this terminology so that it can be translated into clinically relevant data.

PatientsLikeMe is based on the principle that the patient's lived experience can be translated into data to help drive decisions about their care, product development and regulatory action. The company has been working with the FDA since 2015 to help establish the value of patient-generated data in influencing regulatory decision-making.

The company is in early-stage testing of DigitalMe — essentially a virtual avatar of the patient, based on standardized profile data, qualitative data and clinical data from biological samples. The data combine to create a comprehensive, digital picture of the individual patient, designed to predict the outcomes of various therapies; essentially, DigitalMe would allow patients in partnership with their clinicians to "try" alternative interventions such as a new drug, in electronic simulation, on the digital avatar first before selecting the one likeliest to succeed.

# Bringing trials into patients' lives

One of the most important new insights is that patient-centricity requires an individual's deep involvement in understanding his or her own condition, and the objectives of the trial — which must engage the patient on a daily basis. Several recent trials provide concrete examples.

## ADAPTABLE

About one in five Americans takes aspirin either every day or every other day; about half of Americans over 65 take aspirin. The purpose, of course, is aspirin's potential to prevent blood clots that can cause heart disease — myocardial infarction, clot-related strokes and other, similar diseases.

Aspirin addresses a very expensive healthcare concern very inexpensively in industrialized countries. In 2013, 611,000 Americans died from heart disease. One of every six dollars spent in the US healthcare system goes toward prevention and treatment of heart disease.

In the US alone, Americans take about 30 billion aspirin annually. The issue for clinicians, however, is that we don't really know the right dose. There are two that
are commonly prescribed:

- Full-strength aspirin — About 60% of patients take a 325 mg dose; and
- Low-dose aspirin — An 81 mg dose, sometimes referred to as baby aspirin

There is not a good consensus as to which is the appropriate dosage. Low-dose aspirin may not provide a full preventive effect, but there is evidence that full-strength aspirin could put patients at elevated risk of bleeding. There is no one answer to the question of which dosage will provide the better outcome. Each patient's experience may be different.

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The Patient-Centered Outcomes Research Institute (PCORI), an independent, federally funded, not-for-profit research institute based in Washington, DC, is running a trial that is adaptable and completely virtual. Led by a team from Duke University, the researchers are focused on patients with a history of heart disease. They are identified by their electronic medical record (EMR) profiles. They register online and go through an identity verification process. There are multimedia rich tools to explain the objectives of the trial and obtain their online consent. Over a 15-month span, the patients report on their use of aspirin and their health outcomes as they perceive them.

The trial is ADAPTABLE in name (Aspirin Dosing: A Patient-centric Trial Assessing Benefits and Long-Term Effectiveness) and adaptable in design. It is intended to collect data from a variety of different settings, in and out of the clinic.

The idea is to make the tools on the process easy, and fit neatly into their lives. No doctor visits are required. But despite its simplicity, the trial has the potential to answer some profound and highly personal questions:

- How much aspirin should I take each day to reduce my risk of another heart attack or stroke?
- Do the benefits of taking aspirin every day differ based on the dose?
- Do the risks differ based on the dose?
- Based on my health, age and other circumstances, what's the best dose to protect my health?

PCORI plans to enroll 20,000 patients in this trial, which is attractive for its low-cost, adaptable and scalable format, to answer questions in a way that is directly relevant to the individual patient.

## NEUROLOGICAL DISORDERS

Recent neurological disease trials have tried to more seamlessly integrate remote assessments based on patient-generated data. In trials involving conditions such as depression or bipolar disorder, traditional trials have relied heavily on subjective physician assessments of the status or severity of the patient's disease. Developers of new therapies have been interested in more objective measurements of cognitive function — metrics like attention, working memory and executive function.

What has been done using questionnaires can be replicated with apps on tablets or smartphones, allowing those assessments to be much more seamlessly integrated into a patient's daily life. But this approach does not simply replace older assessment techniques. It can, however, be more objective, relying less on the physician's impression or how the patient remembers feeling. The ubiquity of smartphones allows data collection in real-time. But the pervasiveness of smart phone usage is just the beginning.

There's a great deal of interest in using the "exhaust" that is produced by the smartphone itself. That is, the user's interaction with internet-based tools, the speed with which they jump from one app to another, their tone of voice, the number of pauses in their speech and how that evolves over time all represent measurable data that can be correlated with cognitive function.

With patient consent, those data can be collected seamlessly over the course of an organized trial without interrupting the patient's life. In one example, studies conducted by Seton Hall University professor Sona Patel focused on Alzheimer's disease and the potential to track the progression of pauses in speech — using this as a potential leading indicator of cognitive decline.

## mRHYTHM STUDY

The Heart Rhythm Society's 38th Annual Scientific Sessions recently published results from a University of California, San Francisco trial called mRhythm, using the Apple Watch to detect atrial fibrillations. Arrhythmia often goes undiagnosed because patients who suspect they might be experiencing it generally must go to the clinic — hospital, a doctor's office — and get an electrocardiogram. If they don't happen to be having an arrhythmia while they are strapped to the EKG, the test will be negative.

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The Scripps Institute and a company called iRhythm Technologies (irhythmtech.com) published a 2015 study showing that in patients wearing a continuous cardiac monitoring patch for two weeks, there was a far greater likelihood of detecting arrhythmias. The logic of continuous cardiac monitoring is fairly obvious — an intermittent arrhythmia is much more likely to show up over a 14-day period than during a one hour scheduled EKG. This sort of device is typically applied, calibrated and tested in a clinical setting.

By contrast, the Apple Watch study involved patients who use the simple app and an off-the-shelf wearable device. Despite its relatively casual application, the Apple Watch detected atrial fibrillation with 97% accuracy when compared with the gold standard for this patient population. It demonstrates the potential for an ordinary consumer device to integrate clinical data into a patient's life.

# Create tools that help patients better understand their disease

As we have seen, mobile devices that are everyday tools in ordinary Americans' lives can be powerful data gathering systems and can help clinicians diagnose and monitor disease progression; they can also be used to conduct meaningful clinical trials of new therapeutics in nontraditional settings. This is important to investigators and to the developers of those new therapies. Other studies have shown that these research techniques can help the patients themselves understand what is happening to them as the trial progresses.

In inflammatory disease, immunological disorders and neurological conditions, clinicians still rely heavily on subjective measures and the ability of investigators to interpret the patient's characterization of, for example, pain and stiffness. Medidata's data scientists have been working with investigators to determine whether trials could incorporate remote tools — devices patients could use in their own homes without supervision — that measure disease progression more objectively.

## JOINT FLEXION

GlaxoSmithKline designed a study to measure the severity/progression of arthritis incorporated an iPhone and an app developed using an Apple Research Kit module. The app was designed to provide a simple wrist test, measuring tension and flexion in the wrist. Such a test could be used in a variety of disease states. But the investigators needed to know first whether they could obtain good quality data from patients at home — flexing their wrists while holding their phones.

Trial sponsors have typically assumed that the advantage of conducting a trial of this kind in a clinical setting is that the method is controlled — instruments are calibrated, staff are trained and the data can be trusted. It remained to be proven that unsupervised and untrained patients could report valid data in their homes and furthermore, that the data would actually mean something.

In the test, the data scientists took data from the phone and modeled its 3-D movement in space. They were able to determine whether the subject was holding the phone steadily, moving only the wrist — which is what the Research Kit Module instructs the patient to do, as opposed to doing something like a bicep curl which would yield bad data — showing almost nothing about the extension and flexion of the wrist.

While the patients didn't always perform the test as required, the app was able to distinguish between good and bad data, and to inform the patient whether it was getting useful information. As a result, the test can produce a very solid and clean data set in the wild, as opposed to a controlled clinical setting. Furthermore, the data were valid and revealed much about the patient and the progression of the disease — based on precise measurements of the pitch, roll and yaw of the phone as the patient flexed.

## DUCHENNE MUSCULAR DYSTROPHY

Another interesting candidate in the development of mobile health tools is Duchenne Muscular Dystrophy, a degenerative disorder characterized by muscle wasting.

Currently, the most common primary endpoint in a Duchenne muscular dystrophy trial is the six-minute walk test, which at a minimum requires the patient to be ambulatory. But many Duchenne muscular dystrophy trials run into difficulty because the patients are not ambulatory — rather, they are in wheelchairs. In the clinical trial development community, this is known as one of the more extreme examples of an irrelevant endpoint. Unfortunately, this paradox has slowed the development of effective therapies.

Recently, the Clinical Trials Transformation Initiative (CTTI) attempted to determine what would be a more relevant endpoint — one that would not require patients to be walking but could show whether patients' conditions are improving.

The measure proposed by CTTI after extensive research with patients was total arm movement. After extensive interviews, it turned out that it is really important to patients to be able to feed themselves, dress themselves (to the extent they can), and remain as independent as possible despite being wheelchair-bound. CTTI is now evaluating various sensors for their ability to measure total arm movement — most directly, the ability to lift the arm up and down. As the joint flexion study suggested, this kind of application should be well within the capability of common mobile devices like smart phones.

## RECOVERY TIME AFTER SURGERY

What the studies above have in common is that they measure patient activity, which clinicians have presented as a useful indicator of patient well-being. Another area where this can be applied is in the study of postsurgical recovery time — e.g., after orthopedic surgery, or insertion of a stent or an interventional procedure like angioplasty.

Trial sponsors have investigated whether patients are active, leaving their houses, traveling and the like. They are looking for a more objective way to study quality of life as a measure of the surgical outcome. That metric can have a direct impact on the reimbursement profile for the therapy, and the comparison against other therapies.

There is a great deal of interest in using basic consumer-grade trackers. They are not necessarily looking for sensor data, e.g., on cadence or balance, although those things are clearly of interest. They are interested in a general measure of quality of life. New studies are likely to attempt to validate this combination of user experience and data quality using inexpensive, simple and wearable technologies. Again, the attractive aspect of this is that clinicians can extract data from patients going about their ordinary lives. The data would be relevant to activities and quality of life elements that patients genuinely care about, and the cost of such data-gathering would be low.

## HEART RATE VARIABILITY

Heart rate variability can be measured and tracked inexpensively and remotely, using EKG data or a remote pulse oximeter. The data are relevant to cardiovascular and neurological diseases. A number of studies have shown a correlation between low heart rate variability and high morbidity in cardiovascular disease. Low heart rate variability also appears to be correlated with a higher propensity among veterans who suffer from post-traumatic stress disorder (PTSD).

These correlations are not conclusive. But there is a great deal of interest in heart rate variability as a subclinical measure — one that can be measured and analyzed easily and inexpensively — and might be used to risk-stratify patients or help improve our understanding of the early stages of disease.

# Use technology to enrich and simplify the trial experience

Patients involved in clinical trials need and deserve to better understand what is happening to them, and how their disease is progressing. One specific area where technology can play a role is in securing the patient's informed consent. Medidata has been involved in developing simple, multimedia-rich methods that respect the patient and the patient's right to know what is going on in the trial.

While the protocol itself may not be that complicated, the patient needs to understand concepts like randomization. It may be difficult for the patient to grasp that they are engaged in a drug trial, but may not be getting the study drug. The trend is moving away from using heavy legal documents to obtain informed consent, toward multimedia content that explains concepts like randomization clearly and respectfully.

Technology also allows us to give more day-to-day insights on the disease back to the patient. One of the early Apple Research Kit apps was used in an asthma study, published in *Nature Biotechnology.* Among 50,000 patients who downloaded the app from the app store, a large number did so casually and never followed up on using it — went through informed consent, completed a questionnaire, used the app for more than a week and so on. There were about 2,500 patients who were characterized as "robust users." They used the app for months, entering data almost daily and completed most of their tasks.

The investigators asked: What makes someone become a robust user?

It turned out that robust patients tended to have the most severe disease, as measured by ER or hospital visits where they were intubated for exacerbations of their asthma. They told the investigators in focus groups that they were finding the app useful in explaining why they were experiencing these exacerbations; causes that emerged during the focus groups included local wildfires, and patients recognized a correlation to their alcohol consumption. These were patterns that patients could see visualized in the app. The investigators concluded that the more tangible a pattern patients could see in the app, the more likely they were to become a robust user and to continue contributing data.

## Conclusion

The evolution of clinical research toward a more patient-centric model will require intensive research by clinicians and data scientists, support from trial sponsors and ultimately the blessing of a regulatory body, such as the FDA. But the patient-centricity trend in clinical trials is real. As we have seen, real-world experience with clinical data collected by the patients themselves "in the wild" is accumulating, and clinicians are taking these studies seriously. The mobile technology needed to collect the data is already in patients' pockets.

The trend will open new opportunities for drug and medical device developers to create therapies that alter outcomes — indeed, change the entire concept of "outcomes" — in ways patients can experience and evaluate first-hand.