Review Article

Use of Wearables in Clinical Trials

Kovvuri Navya*[1], C.S. Mujeebuddin[2]

*1. Intern at Clinosol Research Private Limited, 48-7-53, Rama Talkies Rd, Vegetable Market Road, near SBI, Srinagar, Rama Talkies, Dwaraka Nagar, Visakhapatnam, Andhra Pradesh 530016, India.

2. Founder and CEO of Clinosol Research Private Limited, 48-7-53, Rama Talkies Rd, Vegetable Market Road, near SBI, Srinagar, Rama Talkies, Dwaraka Nagar, Visakhapatnam, Andhra Pradesh 530016, India.

***Corresponding author's E-mail:** navya.kovvuri1998@gmail.com

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ABSTRACT

The development of ground breaking wearable technology in novel healthcare concepts and biopharmaceutical research and development has raised considerable interest in new means of data collection. This technology is a conflate of both science and engineering where it accomplishes analytics, health care, government, public acceptance, marketing etc. A variety of clinical areas have identified multiple applications for wearables; however, researchers face several obstacles in the field, including scientific methodology as well as administrative, legal and operational hurdles. To promote further assessment and acceptance of these technologies, we highlight methodological and practical considerations for clinical trial implementation including key elements of analytical and clinical validity within the specific context of use (COU). This overview article specifically addresses the concept of the antedate technology in clinical trials for all forms of participants that are involved in trial run. Along with the conceptual understanding of technology the basic requirements for improving the efficient treatment activity for participants and assemblage of valid data for any sort of applications. The wearable biosensors promises for improving the standard health of the patient. The wireless sensors, mobile biosensors that allow the assembly of real-time biometric data that may be used to collect valuable clues for treating even some of the most annihilating conditions. This study also discusses the technological advances that have been made so far, analyses the challenges which need to be addressed and suggests an outlook for future trends. Though selected works, it is possible that further studies are important to improve current techniques.

Keywords: mHealth, CTTI, Epro, FDI, Phenotype, Electronic data capture, COU.

INTRODUCTION

Wearables are defined as the accessories or implants that are worn in or on the body to validate the considered information. Wearables have shown significant wallop on the data available for researchers in clinical trials in numerous ways. The efficiency of these devices may vary but the sensor technology used has evolved for potential working. These are meant to capture the huge amount of patient related data including pharmacology, physiology, behavioural aspects, environmental conditions and data in convenient level that facilitates widespread of adsorption. Wearables enable for biometric entropy that provide distinctive insights into the long term, impact of therapies for treatment. There are also many challenges in using wearables that include access to the raw data, validation of data, processing and analysing of monolithic amount of wearable date, data security.

For a drug to come into market the estimation of cost is around $2.6 billion as per latest reports of Tufts in 2016 [1]. On the other hand, a 2018 report from Deloitte[2] estimated that the return of investment for new drug development had dropped from 10.1% to 1.9% in 2010. The basic process of drug development is clinical trials that play key role for approval of drug. As they are expensive to conduct and also the results are not accurate some times that causes pharmaceutical companies to invest in late-stage clinical trials.

The expenses for gathering data has always been a key for advancing clinical or biomedical research. We can predict that if collecting the data becomes substantially less costly, we can ultimately gain large quantities of data. Several larger observational patients, of same cohorts are already enrolling, such as the Precision Medicine Initiative, PCORnet[3], Human Longevity[4], 23 and Me, the P4 Initiative[5] and other initiatives internationally[6].

Individuals are involved in collecting data about themselves. There are several apps that helps in disease treatment management[7]. The advocacy groups are helping to perform the activity by themselves and organize data that will be available easily for researchers. From this viewpoint, wearables can provide an opportunity to capture both conventional health indicators and Novel data points such as frequent alerts, medication reminders, recording adverse events, instructional or coaching apps, and social networking. In particular, the current systems for determining compliance with medicines and recording adverse events are flawed[8-10]; therefore, there is potential for mobile applications in clinical trials to produce superior data for submission to an FDA.

TYPES OF WEARABLES

1. Mobile sensors:

Mobile health (mHealth) data are valuable; they contain scores of parameters evaluated non-invasively, at high frequency, and under real-world conditions, rapidly adding up to millions of data points that include signals that would otherwise be imperceptible with conventional drug research and development methods. The data can also make the creation of disease models and understanding the complex behaviour of biological networks much easier. Mobile health data, although unstructured and distinct from conventional clinical trial data, can be a valuable tool for drug discovery as well as for clinical research. For instance, while the data may inform about the state and output of monitored tissues and organs, it may not be sufficient to test specific hypotheses. Extracting knowledge contained in mobile health data calls for mathematical tools such as artificial intelligence, network analysis, and advanced multivariate analysis that have not traditionally been the drug industry's core competencies, and are likely to have to rely on the skills of specific scientific groups that have adopted open science to a much greater extent. This will help to change the drug research and development community from a proprietary mentality to one where competitive advantage starts with the ability to extract better knowledge from the open shared knowledge. However, mobile health data were not accepted for all their potential in favour of drug approval[11].

Clinical trial data are usually obtained either during the clinic visit, from the electronic health record (EHR) or as patient-reported outcomes (PROs) from the patients. The EHR's procurement of data is beyond the reach of this study, but significant changes are probable as medical record data is made available by automated systems rather than through the existing manual curing into proprietary electronic or even paper forms. The analysis focuses mainly on patient data gathered outside of their standard-of-care experiences with the health care system. Such data form part of a larger body of what is also considered real-world data, which includes patient-related data and external data sources such as publicly available data sets and environmental data[12]. Real-world data includes EHR; PRO; or watch, sensor, and mobile device data as applied to clinical trials.

2. Skin Patch sensors:

The market for connected wearable patches is still in the early stages of development and commercial availability, but it does hold great promise, with the potential to improve patient health and lead to lower healthcare costs. Connected patches can allow patients and providers to diagnose, handle, and treat patients more easily, more efficiently, and more rapidly. There are more gaps on the market, and there has been significant change for certain groups in the regulatory and reimbursement areas. The introduction of wireless connectivity significantly increases the value for both clinical and non-clinical applications of this type of device. In the clinical setting, physicians and nurses have access to real-time, continuous data flow, allowing for the identification of patterns that may avoid patient deterioration. Through providing a more personalized experience, communication improves non-clinical uses. Advances in sensor precision, comfort, and demonstration of use cases have been made in both the clinical and non-clinical fields.

Applications for medical tracking, identification and diagnosis lead the market as regards shipments for both clinical and non-clinical use. There is growing awareness of the benefits that linked wearable patches can bring to medical professionals and patients. Managing and treating drugs offers a lot of promise, but the production and regulatory periods are much longer. Connected wearable patch devices that can help with adherence to medication will be of utmost interest, particularly from pharmaceutical companies and payers.

3. Smart Garments:

The smart garment will maintain its usual tactile properties by adding feature to the fabric and creating a tissue sensor. The nature of smart garments and the integration of sensors depends on the task, the needs of the users and the most effective steps (McCann et al., 2005). A clever garment must be appropriate for the consumer, for example a smart neonate jacket must be built for minimal stress when dressing.

Ideally, all of the components that constitute a smart garment would be textile-based and washable, including control, sensors and electronics. In fact, these components do have limitations. Progress in flexible batteries (Liu et al., 2012) and textile transistors (Barbaro et al., 2010) show promise for the future; however, electronic modules must be sealed or discarded until time. These should also be packed without sharp edges, which could be harmful, and should be ergonomically (biotechnologically) arranged. Sensors have calibration problem. Chemical on-body sensors especially need an active surface for reaction. One way to prevent calibration is to use low-cost, replaceable sensing components[13]. A sweat sensing system is an example of this, where the microfluidic chip can be easily replaced, while the optical and electronic components are reusable (Curto et al., 2012).

4. Wrist Worn Sensors:

A wrist-wearable system offers some potential advantages relative to other cardiac rhythm tracking systems. First, rhythm monitoring may occur passively without the patient having to perform any additional work beyond wearing and periodically charging the appliance. Second, by monitoring movement, sleep, heart rate, time, and more at the same time participants are likely to gain greater individual value than they would from a wearable one that records heart rhythm only. The additional value could increase patient interaction, allowing the device to be used for long term use. The system can be triggered outside the facility by the patient, thereby allowing for

constant remote monitoring without the costs and drawbacks of supervised surveillance. Such benefits make this system ideal for the proactive control of heart rhythms in both healthy individuals and chronic patients.

The feasibility of detecting AF via a photoplethysmography (PPG) signal relative to ECG was unknown at the time the mSToPS trial was planned, and this exploratory material was intended to provide early evidence of that ability. Since that time, however, significant progress has been made in the field of heart rhythm sensors, and although many unknown factors remain, AF detection via a wrist-wearable device has recently become the norm, integrating it into several commercially available smartwatches[14,15].

The goal of the research was to address the question of the efficacy of wearable sensors supported by the study in a group of older people who had already consented to be part of an AF screening trial. The RE-AIM system was used as a practical way to contextualize the research so that future studies based on the data from wearable sensors can be better designed by a deeper understanding of real-world experience with the reception and use in this digitalized product[16,17].

5. Smart shoes:

For mobility assessment purposes, smart shoes are a desirable category of smart devices for three reasons: (i) smart shoes have a predefined, rigid sensor position on the foot, providing accurate and versatile biomechanical analysis; (ii) smart shoes can be used to track gait, a highly stereo-type movement that facilitates automated measurement of practical biomechanics; and (iii) smart shoes allow technology adoption to be non-obtrusive and non-stigmatizing, eventually enhancing consumer tolerance and long-term adhesion. We do expect the sporting goods industry to manufacture an increasing number of sensor-equipped smart shoes able to track fitness and health condition. Current disadvantages of this device, including restricted consumer flexibility, limited battery run time, in particular constraints on a single shoe platform due to limited instrumentation capacity, will be resolved in the future once this mass market supply is assured[18].

5. Contact Lens Sensor:

Potential biomarkers are still being developed for the early detection of diseases and disorders. Registered biomarkers are currently being tested for POC applications in biosensors, ranging from on-chip sensors to practical, embedded sensors, such as contact lenses. Because a large market has taken shape in diabetes management, contact lens sensor research and development have mainly focused on the glucose-related field. As the sensing technology advances, the number of diseases that can be tracked and identified by biosensors in contact lenses will expand. Continuous surveillance for many diseases may not be needed, and contact lens biosensors may also serve as a diagnostic tool for one-time use. Contact lenses can normally absorb tear components during use in this situation and may be examined during use. It would be possible to identify the occurrence and development of certain illnesses by incorporating the identification of common biomarkers, such as cancer, or dry eye, the incidence and development of certain diseases could be established[19]. This section addresses the main new methods of identification based on contact lenses, such as fluorescent holographic, colorimetric, and electrochemical. Provides a performance analysis of the different types of contact lens biosensors. Cutting-edge technologies which might have integration potential will also be discussed in the following.

6. Smart Glasses:

Smart glasses are wearable web-connected computing devices which enable multiple types of data to be transmitted and projected in the field of vision. There are many applications smart glasses can be used.

They provide most of a typical computer's features, but head-mounted displays will respond to voice remarks, eye movements, motions or basic tactile commands in this situation. A hands-free system can usually be particularly useful in medical practice, where clinicians are often occupied with hands, sometimes even in the sterile area. In comparison to the wearers ' world, smart glasses provide an interactive or virtual reality. These can be used, among others, for broadcasting, streaming video, teleconferencing, data transmission, telementoring and in the process of education.

Google's Glass has been one of the most widely recognized smart glass styles since it was launched into a small market in 2013. It has high wearability, a portable interface, and is running in a well-established android system. In person-to-human interaction, it's almost non-obtrusive. Certain systems such as Epson MoverioBT-200 or Atheer Lab DEV kit still have minimal applicability in clinical settings due to wearability (cables), lack of friendly operating system, large-scale front-end, obstructive human-to-human interaction and cost[20].

Smart glasses can provide clinicians with information such as patient data, vital signs or imaging results in their field of vision so that they can be used at the same time as performing other tasks or procedures. This can be very useful in all types of procedures when a doctor or nurse needs to work on the operation. This helps to avoid looking at different displays or walking away from the patient to check at test results.

7. Smart Rings:

As many wearables are developed the smart ring also plays a prominent role where it is comfortable to wear and that helps to know the awakefulness of the person, heart rate and the regular functioning of the body. Compared to smartwatches, smart rings use built-in sensors to provide exercise and health tracking. For example, phase and heart beat tracking[21], temperature

and sleep tracking (by measuring heart beats and movements) and blood flow[22]. The smart ring form factor has enough space to accommodate the same components as smart watches. Nonetheless, owing to size constraints, smaller parts are usually used in existing smart ring products on the market, such as smaller and less precise accelerometers and smaller batteries that lead to lower battery life than smart watches.

Example: Oura ring is widely used that helps in sleeplessness.

8. Smart Bandages:

These are useful to identify the severity of wound in case of pressure ulcers, venous leg ulcers, diabetic foot ulcerations, wound healing, inflammation, proliferation, tissue remodelling[23].

Some of the examples of wearable sensors are shown in the table 1:

Device type	Data collected	Examples
Wrist worn	Actigraphy, HR(Heart Rate), BP(Blood Pressure), EDA(Electrodermal activity)	ActiWatch Spectrum by Phillips, ActiGraph Link by ActiGraph, E4 by Empatica, ViSi Mobile by Sotera Wireless
Skin Patches	ECG(Electrocardiography), actigraphy, skin temperature	BioStamoRC by MC10, HealthPatch by Vital Connect, BodyGuardian by Preventice
Cuffs	BP, HR	Intellisense Digital BP Monitor by Omron Healthcare
Finger worn	HR, SpO_2	$iSpO_2$ Pulse Oximeter by Massimo
Clothing embedded sensors	HR, HRV (Heart Rate Variability), ECG, Breathing Rate, actigraphy	Smart shirt by Hexoskin
Headbands	EEG (Electroencephalogram), EMG (Electromyography)	EMOTIV EPOC by Emotiv, 4D FORCE by 4D FORCE
Smart Rings	Gesture-based controller, heart beat tracking	Oura

The mostly used devices for the clinical trials are:

1. ActiGraph, GT9X Link
2. ActiGraph, wGT3X-BT
3. Apple Watch Series 4 GPS
4. Empatica E4
5. Fitbit Ionic
6. Garmin Vivomove HR
7. Huawei Band 3 Pro
8. Oura
9. Nokia Steel HR
10. Polar A370
11. Samsung Great Fit 2 Pro
12. Spire Health Tag
13. Striiv Apex HR
14. Atlas Shape
15. Vital Connect Vital Patch
16. MCIO, Alive Car

There are more than 160 brands in the market but the mentioned above devices are mostly recommended, in several factors based on scoring rubric, price, form factor, battery life, connectivity, flexibility.

OPPORTUNITIES AND POTENTIAL BENEFITS OF WEARABLES IN CLINICAL TRIALS

1. The additional interest in clinical trial is being impelled by the welfare that can be received by the patients and sponsors. This is because of the effective way of using the devices to collect the clinical data in efficient way that causes low consumption of time and money.

2. Patients who are visiting the clinical site have their data noted before so as the investigator can make out early decision. And patients that are unable to visit the clinical site can be easily guided in person.

3. Data assembly from wearables provides massive opportunities for observational studies. This hypothesis causes future interventional studies that probably lead to improve patient care that provide new treatments.

4. Also used for Post-market studies.

5. Wearables are commonly used for: Cardiovascular, neuroscience, respiratory, sleep, stress, metabolic disorders, obesity, rheumatology, pain.

WHY DIGITAL DEVICES CONSIDER USING IN CLINICAL TRIALS?

Use of wearable devices has skyrocketed in recent years. They identify wearable devices on smartphones and tablets as sensors and/or software applications (apps) that can capture health-related data remotely, i.e. outside the office

of the healthcare provider. The data may be passively collected or may require an input from a user. The accelerometer mounted in a wristband or cell phone is an example of a sensor collecting data passively about the physical activity and movement of an individual. Technology (e.g. ePRO (electronic Patient Reported Outcome) will issue a patient report collecting information related to health; Collected via a cell phone app or a web interface. For addition, some devices, such as smart-cap bottles designed to track adherence to medication, may use a combination of sensor and data collection depending on the application. A user activity (opening the bottle) triggers event recording but the data is passively transmitted from a sensor to a server through Bluetooth. A cell-phone app mediates the transmission.

Ten years on from the launch of the iPhone, we've seen an almost total change in how people connect with each other, access media / information, and engage with that content. Most notably this transition has contributed to a complete change in the standards around event coverage in healthcare and beyond. Digital disease monitoring has changed outbreak detection timeframes via social media from months to hours[24]. The US Food and Drug Administration (FDA) is now promoting notification of adverse events through mobile apps. Hospitals use inpatient Fitbits to track recuperation and mobility. Patients communicate with health-care facilities online daily. Twitter and other social media are able to report and post views on products and services much faster and wider than nearly any company[25,26].

At the same time, rising healthcare costs are of tremendous concern and a persistent buzz has heralded the prospect of virtualization of healthcare through digital devices. For remote monitoring of cardiovascular parameters, movement (including gait, balance, and many other types of motion measurement), body temperature, galvanic skin response, blood oxygen saturation, and multisensor / multisystem monitoring[27], advanced research and development of wearable devices is continually improving. Specific shape factors include wearable watches / armbands, patches, textiles and apparel. All of these sensor systems are designed with the ability to monitor and communicate data continuously in real time or intermittently. Although maturity, ambition, and efficiency currently vary greatly, these sensors and technologies clearly have the potential to become an integral part of healthcare and biopharmaceutical growth in the future.

CHALLENGES AND CONSIDERATIONS FOR WEARABLES IN CLINICAL TRIALS

1. Depending on the type of device used, the potential and the cost varies. The types of data to be updated in the device, the infrastructure used during collection, the number of participants needed.

2. How the data is transferred to other devices, how that device send information to the clinical trial database that challenges across multiple platforms. The raw data access can be difficult to come by, the change in the output also interpret the raw data.

3. The other particulars to be considered are the size, shape, battery life or modulations, convenience to wear, the disturbances in daily activities when wearables are used.

4. Most of the wearable devices in the market today have their own systems of algorithms with no access to the raw data on which they were based. Without raw data there is no way to determine the anomalous result is real or if it is causing any issues.

5. The challenges include that the participants in the trial are asked to remember to change the device, wear a bulk or uncomfortable wearable that often leads to compliance issues.

6. Comparison of the data from various participants and commercial graded wearables will vary among devices related to body placement and other factors.

7. Comparison across the devices has shown that it is relatively accurate for most wearables for 18-39 years old but more variable in old age group[28]. The difference in acceleration values between hip and wrist placement of the same wearable[29]. The comparison across eight different wearables showed error rates between 9.3% and 23.5% in the measurement of daily energy expenditure[30].

8. The second concern, data provenance, is the source history and the data lineage. Raw data can be difficult or impossible to collect directly from most wearable devices; rather, the data is converted and analysed on the devices before being processed on the connected mobile device before being transmitted to the server of the manufacturer. Only a few devices provide kits or protocols for software developers to directly access the data. Where this is not an option, the data must first pass through the proprietary software and/or hardware of the manufacturer, and be forwarded to the server of the manufacturer. Only then can it download the data for further review. The data may be aggregated, compressed and/or transformed during this process, and these operations are invisible to the researcher, making it difficult to evaluate and interpret comprehensive data. This concern is particularly problematic for consumer devices as few provide the ability to track data to a particular device and instead have to be retrieved on the manufacturer's website through a user account. However, there are worries regarding patients or others who tamper with data; some wearable technology firms have introduced data encryption to eliminate the ability to manually alter data[31].

Blockchain technology may also provide a way to enhance data security and data provenance[32].

9. The regulatory issues are the third major concern regarding the use of wearables and other devices in clinical trials. These issues raise questions as to how easily the FDA can approve the data when it submits in support of a new investigational drug application. The FDA has given guidelines on the use of wearables and mobile devices and

their uses in clinical care but not clinical trials. A lack of guidance for clinical trials may underlie the pharmaceutical industry's resistance to wider adoption of mobile technologies. The rate of adoption continues to rise despite the lack of FDA guidance, with wearables included in at least 300 trials in 2015 [34].

Promises in health care

Wearable devices can collect data in natural settings on a 24/7 basis, while people go home and work on their daily routines. Digital diaries detailing key personal health and lifestyle features will improve the data collection. Consumer fitness trackers collecting mobility and some vital sign data are the best-known wearable devices[33]. Similar wearables cannot be sold as medical devices unless the device accuracy has been developed prior to release onto the market. This is a big step forward compared with conventional data collection methods related to health. For example, basic physiological data, such as vital signs and telemetry, are usually only collected during doctor's office visits or as part of clinical trial protocols for the medical product. Such details are a very small snapshot of the phenotype and physiology of an individual. Inferences about a person's health are made on the basis that such a snapshot is extrapolated over extended periods of time, possibly weeks and months. This extrapolation is also focused on the recollection of patients recalling events that followed a visit to the hospital. Decisions on the health, medical status, and therapies of the patient are made comparing data collected in doctor's offices with population statistics, which may or may not be applicable to a particular person.

Moreover, there are well-known issues related to the in-clinical assessment of vital signs, like white-coat hypertension[34]. There is increasing awareness that population-based values need to be modified for factors such as age, gender, drug status, ethnicity and other factors[35,36]. Such changes can be made if data are available for different subpopulations of concern. This can also be achieved using the individual's own longitudinal data collected over extended periods of time, which would allow for an approach to specific medicine. Frequently collected data over long periods of time can provide a deeper understanding of the variation in illness, which is likely to be an important contributor to variability in the response to care. Having larger and denser datasets can help characterize variation within and between patients. Furthermore, there is growing evidence that replacing paper diaries with electronic versions can dramatically improve the quality of subjectively recorded outcome data[37,38,39], such as pain and functional status, by ensuring enforcement, timely data collection, avoiding secondary data entry errors and raising administrative burden[39]. The replacement of paper diaries and patient memories with electronic data collection methods is likely to continue and grow with future technological advancements. In addition, wearable device data combined with other data such as genomics or other high-throughput technologies have the potential to create a detailed multilayer image of a person's health and may deepen our understanding of how genotyping can be combined with deep phenotyping.

Promises in drug development

The above-mentioned applications are also appealing in early and late-stage clinical trials for the drug development. Collecting dense data from participants in the trial using wearables in natural settings— often not otherwise collectible — may radically change the way clinical trials are planned and performed. In the early development of pharmaceutical drugs, the collection of detailed physiological data that detect early safety issues and advise dose changes and dosing rates, or may contribute to the discontinuation of certain drug candidates. The subjects of the research would not need to be continuously confined to the units of pharmacology to have the data collected. Creating new endpoints through wearable devices has implications in several disease areas in the late stages of clinical development. Such novel endpoints can provide more precise measurements of disease activity compared with conventional measures, allowing for quicker and more accurate readings in clinical trials. In addition, sensors can provide objective measures of typically subjectively reported results, such as pain and fatigue, complementing or even replacing self-reports altogether. Another attractive function includes portability to home settings and simplification of conventional hospital interventions. Sleep data collection using actigraphy will serve as an example[40]. Essential sleep parameters, such as period of sleep and number and duration of awakenings, can be obtained using wrist-worn actigraphy tools. This could substitute sleep studies that are impractical for long-term monitoring and provide data collected in natural home settings that are more likely to represent the regular sleep habits of a person. Although actigraphy data do not provide information on a deeper level, e.g. sleep phases, the procedure is very non-invasive and easy to apply. Actigraphy-based sleep data also highlights the need for new wearable-based endpoints to be clinically validated.

You can see other exciting wearable technology in phone / tablet applications. The best-known examples include tracking adherence to medication, remembering medication, and communicating with patients. Medication adherence is a significant area of concern in many clinical areas[41]. The causes for non-adherence are multifaceted and include socio-economic factors, access to health care, means of communication with healthcare professionals, awareness of patients and understanding of the effects of non-adherence to the results of treatment[42]. In addition, cell phone applications can provide data to track medications adherence and assistance with prompt action by medical staff and carers[43]. Drug notification systems, augmented by warning personalization and accessible to both patients and caregivers, have been found to increase drug adherence[44]. In addition, a range of digital technologies have been created to capture objective adherence data using smart-cap bottle and blister pack

technology. Nonetheless, in well-powered, controlled studies, the efficacy of these innovations in enhancing patient adherence has yet to be verified[45].

Cell phone apps and web-based interfaces are increasingly being used in clinical trials for remote patient registration, patient approval, and retention, making the process more efficient and allowing for greater outreach to remote patients. Clinical trial retention of patients may be improved by offering app-mediated alerts, providing information about future visits and operational updates on execution of clinical trials, promoting compliance, facilitating contact with medical staff, and facilitating participation logistics.

The entirety and combination of applications can provide a foundation for telemedicine and allow clinical trials to be partially or completely remote, taking drug development to populations that are difficult to reach. Diminishing the number of clinic visits and potentially preventing the use of other expensive medical equipment such as telemetry may minimize time and costs. Time, ease, and cost savings are great potential benefits of wearable devices, although the cost of development and implementation is currently counteracting these savings. Nevertheless, wearable technology data have the potential to improve the identification of treatment effects and show how these effects contribute to the underlying characteristics of the disease, strengthen our understanding of the treatment-response relationship and enhance the personalized medicine.

The promising potential of wearable devices has drawn tremendous interest, including the launch of experiments[46], and a number of agreements between biopharmaceutical, contract research organization (CRO) and device companies have been announced[47,48]. However, the major impact on biopharmaceutical R&D anticipated from digital technologies has not yet materialized[49]. The reasons behind the lack of wearable devices have not yet materialized.

Scientific

Most devices, especially consumer-grade ones, are advertised with promises to improve health and wellness with no scientific evidence behind this claim[33]. Properly designed, well-powered experiments with a clear statement of a medical problem are needed, rather than technology-seeking applications[50]. Biopharmaceutical R&D scientists, on the one hand, are generally unfamiliar with devices which pose a barrier to the adoption of wearable technologies in clinical trials for drug development. On the other hand, product engineers are not familiar with the process of drug development and regulatory requirements regarding drug approvals. The solution would be to bring device engineers into the production of drugs to educate biopharmaceutical R&D and to allow product technologies to be implemented.

Regulatory

In the US, the approval routes for the sale of medications and products are different, and the regulation is carried out by various FDA divisions. Most wearable devices are known as510(k) approved Class II devices, which require technical performance compared to a predicate (i.e. legally marketed) device that uses a similar engineering solution. The criterion does not include creating a correlation with a clinical outcome such as a diagnosis of the disease. This condition only occurs for devices with510(k) de novo where no predicate system is available. Therefore, in order to establish an affiliation with a disease condition, a device under review must be evaluated in a specific population similar to the statements on the product label. If such a 510(k)-cleaned device is intended to support an efficacy argument on a drug label, a connection needs to be established in the context of drug development between the device's readings and an efficacy parameter of interest. It must also be balanced by the analytical performance data of the system which indicates that the device is suitable for an intended use. Furthermore, a lack of shared understanding of the methodologies and terminology plagues the area. A similar issue in the field of laboratory biomarkers has been successfully addressed with the widely accepted principle of "fit-for-purpose validation" and well-developed and common terminology[51,52,53]. The same strategy can be applied in the field of wearable devices, and several pre-competitive projects have made significant progress towards achieving this objective[54,55].

Data infrastructure, processing, analysis, and interpretation

The challenges around infrastructure are multifaceted. Clinical teams involved in drug discovery are not familiar with the massive amounts of 24/7 data to be analysed and combined with the rest of the data from the report. Compared to traditional data collected at predefined time points by clinical sites, the sensor data structure is very different and consists of multiple layers: raw unfiltered data, raw filtered data to remove invalid data according to scoring algorithms, data consisting of secondary derivatives, and data extracted from secondary derivatives to interpret. The outstanding questions include: who is the originator of the data, what constitutes the source data, which databases are required to maintain an audit trail, and what the final result should be published. These are the issues that the industry and regulators are discussing, but the guidelines that would help harmonize the field have not been established. In addition, the collection and analysis of massive data, as well as the visualization and interpretation of information, presents a formidable challenge. Machine-learning approaches for automated data processing and enhanced signal detection have been shown to be useful in solving this problem[39]. In addition, there are no well-developed guidelines that would help organize, annotate, and standardize data and provide electronic data capture (EDC) databases with data mapping instruments. The lack of data requirements for mobile technology is exacerbated

by the fact that wearable devices often report variables related to the same phenomenon (e.g., mobility), but use different terminology, and algorithms for data processing are not reported. The solution should include industry-wide data and terminology guidelines, criteria for processing similar data sets, and specifications for accountability around data processing algorithms.

Ethical and legal

This category of challenges involves data ownership and sharing, conditions for consent, privacy, protection, and major geographic differences in approaches to tackling these challenges. US and European law tend to be going in different directions as to reach, approval, data sharing, and processing[56]. Consumer and medical devices are regulated differently in the US. HIPAA protects the data obtained through medical devices and includes permission from the patient to collect and share the data. On the other hand, although it may include legitimate health information such as disease diagnosis, lifestyle, biometrics, mobility, and behavioural patterns, the data obtained by consumer-grade apps may be transmitted in a detected, aggregate manner without clear provision as to who will have access to the data. In the EU, new General Data Protection Regulation (GDPR) regulations do not differentiate between device types and cover all data generated in the medical context by wearable devices or apps[57]. However, the EU needs clearly defined reasons for data usage, data reuse and sharing consent, and enables patients to withdraw their consent at any time.

Data security

It can be helpful to distinguish enforcement from privacy and security in the practical consideration of privacy, protection and compliance, as compliance appears to be retrospective in nature, but maintaining privacy and security must be proactive and forward-looking[58]. Much has been written about general and advanced privacy and security with regard to medical data and devices[59,60]. Luckily, recently published guidelines by the US National Institute of Standards and Technology (NIST) outlines new families of privacy and security measures that can be used as the basis for design and auditing. Focusing specifically on wearable sensors and apps, the guidance finds it important that all personally identifiable information (PII) and all personal health information be used. The key generic concerns include: the computer protection of any mobile devices, tablets, and cell phones used to capture, store, or transmit information; the potential complications of combining research sponsor-collected PHI on a participant's personal device; secure data transmission and receipt; secure account management; data encryption; data blinding; data backup and device fedility. Depending on the exact software model, the actual device operating system, the intended network connectivity procedure, the intended data capture and processing strategy and many other variables which will be study-specific, specific solutions will always be needed[61]. The take-home message here is clearly that cyber security is becoming more complicated, but also understandable and manageable. Success needs a detailed specialist evaluation of the benefits – risks just like any other medical intervention.

SPECIAL CONSIDERATIONS FOR CLINICAL TRIALS

The use of wearable devices in clinical trials and in drug development is close to that of biomarkers in the early 2000s. There was some uncertainty over the proper use and confirmation of biomarkers at that time. Huge efforts have been placed into biomarker activities resulting in streamlined methods, in particular the definition and process for analytical validity, clinical validation and qualification[52,53, 62]. Considerations for the use of wearable devices in a clinical trial should specifically involve scientific considerations with a patient-centered approach in mind. Operational factors, such as patient and site staff preparation, patient and patient compliance system acceptability, data collection, and transition and management are essential to obtaining accurate and interpretable data. Furthermore, there is a critical role in the use of wearable devices for testing, both analytical and clinical.

Scientific considerations

The scientific approach will begin with an important health condition or health feature for patients that has not been treated to a satisfactory level by current standards of care for the management of disease. Once it is established, a scientific hypothesis to determine the nature of an experiment to be performed should be formulated. For example, the existing morning stiffness and sleep evaluations in patients with rheumatoid arthritis (RA) are based on self-reports. The standard data collection methods provide patient self-reports focused on memory recalls and patient diaries during doctor's office visits. Objective data representing these safety criteria can be very helpful for the management of patient care including adverse event control, dosage and dose changes. Once the scope is established, the next step will involve finding an appropriate technology for capturing the data of interest. In the case of RA, the study results suggest that wrist-worn actigraphy tools can differentiate RA patients from healthy controls and can provide valuable mobility information in the drug treatment context[63,64]. The hypothesis should be evaluated as one of the aims in a clinical study. The hierarchical order of a significance purpose, e.g. primary, secondary, or exploratory, may depend upon the intensity of evidence to support the hypothesis. The research can be done through an observational or interventional analysis. If there are no data or limited data on the relation between a disease / health aspect and device-derived readouts, an observational study would be sufficient. An interventional research is more suitable if the purpose is to create a mechanism for the collection of wearable data in the context of drug treatment and to support arguments for effectiveness or direct decisions on care. Additionally, a system should be optimal for a given study population.

The general process for validation requires a declaration of need, usage background (COU), analytical validation, clinical validation and certification, if necessary, for a regulatory reason. A need statement is a descriptive and consistent explanation of the knowledge gap or the need to develop drugs (e.g., improved safety monitoring) and interfaces with the wearable's scientific aspect. A succinct overview of how a wearable is meant to be used in drug development is the COU, which also deals with the technical aspects of a wearable. Analytical testing determines if the performance characteristics of the system are appropriate with a specific COU. Analytical testing or technical performance developed for510(k) clearance purposes will require setting performance parameters of the system under conditions that are as close as possible to real-life use. This goal can be accomplished by comparing system output with a standard data collection tool if available[65], or another well-established performance device[35]. Some of the analytical validation parameters may already be known by the device manufacturer during device calibration and may include important information such as gold conformance and sensor precision. Knowing the performance characteristics is necessary to determine whether a system can quantify what is required in a given COU. If a medical device is being considered, output of the device is identified for clearance purposes. In a targeted study population or COU, however, it may not be necessary. Of example, if a device has been tested in normal healthy volunteers but is intended of potential use in a particular disease, it is necessary to establish both the hardware and software output in the disease context to make the system usage fit for purpose. The lack of testing in the intended study population can result in inadequate data processing and even data loss[66]. Clinical validation also ensures that the wearable device acceptably recognizes, tests, or forecasts the concept of interest with a specific COU. Clinical validation requires creating an affiliation with a specific disease condition to ensure that the results are interpretable and provide useful information for the management of patient care[65,67]. Both analytical and clinical validation can be conducted in dedicated product assessment studies or can be integrated as one of the endpoints in clinical trials for drug development. Several devices can be tested in the first scenario with adequate controls inserted in the test, e.g. medications that modulate blood pressure for devices monitoring the blood pressure. The downside of this type of study is the lack of system impact assessment on other regularly conducted research procedures in the drug development, such as repeated blood draws for pharmacokinetics (PK) or imaging procedures. In the second scenario, the introduction of devices as exploratory endpoints to clinical drug development trials provides an opportunity for the study participants and sites to determine tolerability and acceptability of the system in the light of other study procedures. Such concerns are a starting point, but need input from stakeholders and further discussion among the biopharmaceutical industry, device manufacturers and regulators. It is possible that wearables, similar to surrogate endpoints, would eventually require certification. Within the specified COU, based on a structured regulatory process, it is a presumption that a drug development tool can be relied upon to have a clear definition and application in the production of medical products and regulatory review. We are not aware of any wearable use instances that require that level of support.

Device choice and logistical consideration

In clinical trials in drug development, both commercial and medical-grade instruments may be considered. Medical devices need less testing before they are included in clinical trials, because their output can be assessed for certification or approval purposes and the information is available on the label of the product. Having said that, it is necessary to consider the expected COU before applying. Nevertheless, consumer-grade products may not yet have accuracy identified, so product analytical and clinical validation studies are needed to assess whether a device of interest is fit for purpose. The availability of raw and derivative data from the system should be carefully considered, as often only secondary derivatives and summary data are available; this could provide an incomplete audit trail. Acceptability of apps by subjects of study is crucial to a successful implementation. Device technological features such as scale, wearability, battery life and effect on day-to-day activities should be carefully considered. Such characteristics that require input from patients prior to initiating the study to ensure a technology is successfully implemented. When consumer acceptance of technology is not established before the start of the study, a small pilot test may be needed to obtain such results, because acceptance will have a major impact on compliance with patients.

We found that having practical experience directly involved by clinical scientists in the design and execution of clinical trials is highly beneficial. This speed up the implementation of devices by clinical teams and helps scientists to rule out early devices which are unlikely to be readily adopted by participants in the study and may not have interpretable data. Before the start of the study, when customer acceptance of technology is not developed, a small pilot test may be required to obtain these results, as acceptance will have a major impact on patient compliance. We found that having practical experience involving clinical scientists directly in the design and execution of clinical trials is extremely beneficial. It speeds up clinical teams ' deployment of technologies, and lets scientists rule out early devices that are unlikely to be readily embraced by study participants and may not have interpretable data.

Devices are typically operated by staff at the clinical site, qualified to pass information on to the participants, and available to help when study subjects encounter difficulties. Before the study starts to assess the effect of data flow on study participants and other clinical trial procedures, the data process flow should be identified, in addition to subject and site staff training. Types include having a data synchronization cell phone, different app-compatible

phone models, translations where necessary, data synchronization frequency, and specific system docking computer models. Enforcement should be checked for subjects contributing data to the study. Interventions such as the topic alerts should be introduced in order to improve enforcement if it falls below a certain level.

Decisions on the sequencing of data processing into secondary derivatives and data analysis need to be made at the front. When data needs to be checked in near-real-time, the collection, interpretation and visualization of the data must be developed and evaluated before the start of the study. Follow-up treatments, if necessary, must be defined as part of a protocol for clinical study. Retrospective data processing and analysis are better suited for exploratory endpoints, as they provide more space for experimentation with alternatives for raw data processing and visualization, and can be achieved iteratively. The use of data should be clearly defined in the study protocol and whether such use has any effect on patient care or any other study procedures should be stipulated. In addition, decisions on how to treat subjects that may have an allergic or other adverse reaction to wearable device components would need to be made. Based on the intended use of the results, subjects with documented adverse reactions to system components may be removed from the study or permitted to participate in other research procedures; this is appropriate where consent to the portion of the study's wearable device is voluntary and lack of participation does not have a significant impact on the overall study data integrity. Considerations are multidimensional for including tools in the clinical trials. R&D and healthcare institutions have a range of hurdles to overcome, rendering the introduction of wearable technology a standard procedure. The advancement of analytical and clinical testing methodologies and the broad acceptance of devices under the fit-for-purpose concept will continue to be crucial to future success.

GUIDELINES:

1. Use of mobile technology for data capture in clinical trial do not typically need to be approved or cleared as medical device.

2. In CTTI (Clinical Trial Transformation Initiative) the initial step explains that what we want to measure should be pre-selected, so that to avoid unnecessary data.

3. It also states that the individual sponsor’s decisions are not considered regarding technology to be used. The correctness of the technology should be justified through verification process.

4.CTTI’s stance on data management states that the data should meet ones priority.

CONCLUSION

Wearable devices are innovative and have the ability to fundamentally change the advancement of health care and medicines by changing the way health data are obtained, interpreted and visualised. Potential applications are complex, effective in many clinical fields, and are expected to rapidly develop. The ultimate goal should be a better understanding of the nature of the condition, reactions to treatment along with a decrease in healthcare costs and an improvement in clinical trial performance. Furthermore, introducing new ways of gathering remote data will bring new therapies and services to all patients in need. Wearable devices are innovative and have the ability to fundamentally change the advancement of health care and medicines by changing the way health data are obtained, interpreted and visualised. Potential applications are complex, effective in many clinical fields, and are expected to rapidly develop. The ultimate goal should be a better understanding of the nature of the condition, reactions to treatment along with a decrease in healthcare costs and an improvement in clinical trial performance. Furthermore, introducing new ways of gathering remote data will bring new therapies and services to all patients in need. The problems faced by the introduction of wearable devices are not trivial. The scientific community would benefit from regular exchange of information to share the results and learning experiences; this would promote the creation and acceptance of best practices for application of technology, data collection, analysis, and interpretation. The field is currently full of enthusiasm but more evidence from rigorously designed experiments are required to displace the hysteria and follow empirical methodologies to produce and test scientific hypotheses.

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