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Are we there yet? Evaluating new non-EDC data sources for clinical trial submission feasibility

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ABSTRACT

The current possibility that unlimited non-EDC sources of data (Wearables; Electronic Health Records; Smartphones; Custom Apps) will be available for collecting clinical trial data challenges the traditional methods of managing data for clinical trials. This paper discusses the work of the Data Engineering Project within the PHUSE Working Group; Educating for the Future; with a view to determine how best these data can be standardized and utilized for Clinical Submissions. This paper discusses how mobile technology data sources can be integrated (with the existing database), standardized and contribute to analyses that can then be utilized in submissions considering privacy and governance. Progress of the project will be presented during the conference with a chance to receive input from the audience.

INTRODUCTION

As members of Data Engineering project within the PHUSE Working Group "Educating for the Future", we have focused here on multiple data sources and corresponding use cases. In our previous presentation at PHUSE EU Connect 2019, we discussed an appropriate classification of data sources from a data engineering perspective, discussed the relation of the newly introduced FAIR principles with the existing clinical research widely known ALCOA+ data integrity rules, and looked at a use case where clinical data is combined with new data obtained from wearables and mobile phones. In this paper, we will focus more on the data obtained from mobile technologies (the types of data collected, the types of devices, data sources), data flow, Standardization and Integration, Analysis, Benefits and Challenges, Resources to refer.

MOBILE TECHONOLOGIES

According to the CTTI (Clinical Trials Transformation Initiative), mobile technologies are defined as "mobile applications and other wearables, ingestibles, implantables, and portable technologies containing sensors for the remote capture of outcomes data". Data collected from these mobile technologies can be classified as **Passive** or **Active**.

Passive Data is data collected *without* human intervention. For example, wearables which have accelerometers implanted to collect data based on the person's movement and other activities. Other examples are step count, heart rate, blood glucose, etc.,

Active Data is data collected *with* human intervention. Electronic Patient Reported Outcomes collected on mobile devices are active data, with typical examples recording Patient Global Assessment of Disease Activity, Disease Pain Intensity, Medication Intake, or questionnaires such as the ones used to determine subject mood and energy in cognitive impairment studies.

TYPE OF DEVICES:

Available devices fall into two major categories: those available to the general public and those specifically designed for specialist use (Research-oriented). Some pros and cons of these types of devices are as follows:

1. Devices available in the Market (Commercial devices, freely available)
    a. Pros: Pre-defined functions, Sleek aesthetic designs, easily obtained, user friendly
    b. Cons: Power usage, processing time, privacy, limited usability (step count, hours of sleep), software update during study, which might impact previous data collected. Measurements characteristics not confirmed for clinical research.
2. Devices not available in the Market (Specifically for Research):
    a. Pros: Raw data available for future research; More specialized data like ECG and electrodermal activity. Can build new algorithms to evaluate any new traits. In General, if any plan for Secondary use of the collected raw data, proper consent should be taken from participant. (Example: Skin picking, can be evaluated using gyroscope data monitoring from wrist sensors.) Known and confirmed measurement characteristics.
    b. Cons: Bulky design, less privacy, Subjects not aware of the traits that researchers working on. Relatively expensive – configuration for study, distribution to subjects, Usability.

DATA SOURCES (DEVICES/APPS)

There are number of devices and apps currently available that can collect active and/or passive data, all of which have the potential to be used in the clinical trial setting after undergoing a thorough validation and verification process. CTTI provide detailed criterion for selecting mobile technologies for data capture emphasizing the accuracy, precision, consistency, and uniformity of the data that device produces, and note that devices do not need to be approved or cleared as medical devices *per se* [2].

Available mobile technology functionality for remote or continuous monitoring is now extensive: for example, heart rate, heart rate variability, and other cardiovascular parameters; activity tracking (gait, balance, gross motor function); sleep parameters; glucose monitoring; haptics; sweat analysis; electro-stimulation; UV tracking; body temperature; galvanic skin response; blood oxygen saturation and so on. The physical forms of the technologies range from watches, rings, bracelets, patches, textiles, garments, but may also include ingestible or implantable devices. Currently most of the studies investigating these technologies are in the cardiovascular therapeutic area, but investigations in support of neuroscience, respiratory, sleep, stress, metabolic disorders (including diabetes and obesity) and rheumatology, pain studies have been made [1] [6].

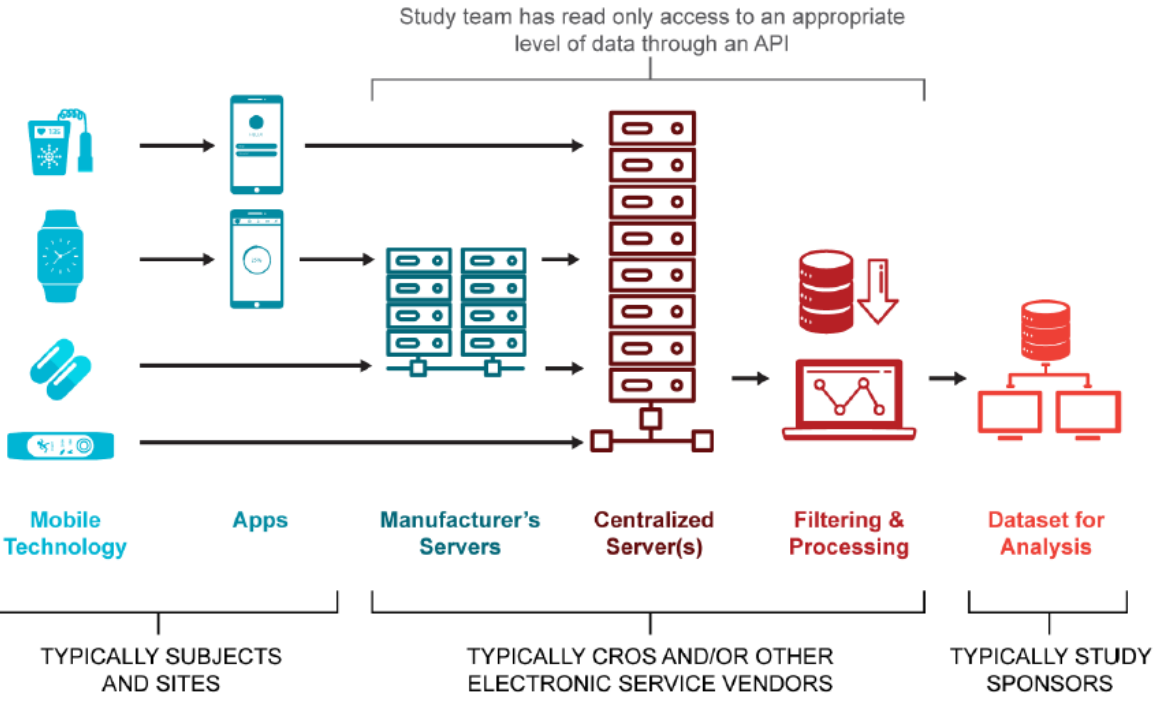
Depending on the type of study, type of device, sampling frequency, size of the data per day, the total size of the data collected over the course of a study can be huge. The example below, taken from a study measuring cognitive impairment [4] demonstrates the volumes of data collected under different circumstances.

Device and Data Stream	Sampling Frequency	Est. Size (MB) (per Participant/Day)
Watch - Accelerometer	100 Hz, while worn	> 200
Watch - Gyroscope	100 Hz, while worn	> 200
Watch - Pedometer	2-5 seconds	~ 0.1
Phone - Accelerometer	100 Hz, continuous	> 400
Phone - Gyroscope	100 Hz, continuous	> 400

SOURCE: Developing Measures of Cognitive Impairment in the Real World from Consumer-Grade Multimodal Sensor Streams, KDD' 19 [4].

DATA FLOW

The process of data collection in these wearables to data usable for clinical studies is complex. This diagram (from CTTI [2]) shows the typical device data flow from the time of collection to the final data being available for analysis. It shows that for any particular device the path from device to analysis dataset may include several intervening steps, each of which requires careful consideration and confirmation before data can be unquestionably used to support clinical decision making.



SOURCE: CTTI [2]

STANDARDIZATION AND INTEGRATION

The CTTI data flow diagram (above) shows how different mobile technologies data may pass through different servers (Manufacturer's servers, Centralized servers etc.) prior to being available for analysis. Data from wearables is often first transferred to a mobile device like a phone. Other wearables may send the data directly to a general server which is hosted by the service or phone provider. This data needs to be picked up, selected, standardized and transferred to a clinical study database. In addition, the linkage between the patient data from the commercial service provider and the clinical study data needs to be set. Finally, the data can be put in a recognizable format and can be used for analysis within the clinical study. This needs to be done with proper strategies by authorized individuals and technologies. For example, using QR-codes to anonymize the patient details, using data encryption and selecting defined data as agreed in the informed consent. Standardization of data and a clear description of data flow using data schema's and descriptions is key in this process to make the data FAIR (findable, accessible, interoperable and reproducible).

As the data is often (a) high volume and (b) sensitive personal data, it requires high security standards by strictly following protocols to comply with regulatory requirements and to protect privacy of the individuals.

The specifications in the study protocol and informed consent should define what data from the wearable devices can be used for the clinical study given the privacy regulations. In addition, to make the huge amounts of data handleable it may have to be transformed; for example, taking moving averages, removing gaps and spikes etc., Selecting the correct data and describing the data selection and data transition processes will be needed to make the analysis data reproducible. Close cooperation between study statisticians and the data engineers is required to ensure the right data will appear in the study database.

A number of third-party vendors offer technology platforms for managing, selecting and transforming mobile technology. These include:

RADAR-base (Remote Assessment of Disease And Relapses) is an open source platform to leverage data from wearables and mobile technologies. The focus of RADAR-base is seamless integration of data streams from various wearables to collect sensor data in real time and store, manage and share the collected data with researchers for retrospective analysis [8].

ANDROMEDA, data platform from Evidation Health, A comprehensive platform to turn raw, high frequency everyday behavior data from sensors, devices, speech, video, and other sources into new knowledge about health and disease [9].

These kinds of platforms, like RADAR-base include visual representations of the data which make it possible for data engineers and statisticians to make decisions on what data can and may be included in the clinical study and provides the mapping tools to standardize the data. They can also ensure, via their independent access-controlled environments, that only the correct data is made available to authorized users (see study team section in the figure above).

ANALYSIS

According to International Conference on Harmonization (ICH) E9 guideline “Statistical principles for clinical trials,” which states that data collection should focus on the data necessary to implement the planned analysis, including the context [7] [2]. CTTI recommends against speculative “data fishing” and strictly analyze as per protocol, which by implication suggests that only that device data required by the study should be made available to the study team regardless of the range of device data collected. Considering the amount of data available from these mobile technologies, there is a good scope of identifying personal traits as well as high chances of mis-interpreting the results. Hence, in the clinical setting, analysis must be limited to the extent of the consent obtained from the participants.
To get proper validated novel endpoints and analysis techniques based on mobile technologies data that can be used for registration studies, exploratory studies are necessary. There are number of studies reported in the academic world taking care of this, which will enable us in the future to use the data for clinical trials.

BENEFITS AND CHALLENGES OF USING MOBILE TECHNOLOGIES IN CLINICAL TRIALS

BENEFITS

1. Increase in Subject enrollment and retention
2. Avoid trips to Clinical sites, which helps in enrollment of remote/difficult to reach population
3. Reduces cost and time
4. Increases convenience
5. Much larger patient groups can be studied
6. Increase both patient compliance (alerts for completing active data) and the quality of the data

7. Can avoid some site induced inaccuracies (For example: Whitecoat hypertension)
8. Novel endpoints – Room to develop novel endpoints (Mobility as a measure of quality of life)
9. Real time Safety monitoring, Scope for quick action and to avoid worsening of Adverse Events
10. Increase in Medication adherence with proper device alerts

CHALLENGES

1. Device performance not as specified by manufacturers
2. Privacy and Data Security
3. Infrastructure necessary for handling large volume of data
4. No acceptable endpoints available for many indications for immediate use
5. Technological devices not available as per study requirements to evaluate endpoints
6. Biopharmaceutical companies and device companies are separate and exploring mutual requirement is a challenge
7. Challenges at each level: scientific, regulatory, ethical, legal, data management, infrastructure, analysis and security

RESOURCES WORTH REFERRING BEFORE USING MOBILE TECHNOLOGIES IN CLINICAL TRIAL

1. CTTI Recommendations: Advancing the Use of Mobile Technologies for 2 Data Capture & Improved Clinical Trials
2. Feasibility studies data base: https://feasibility-studies.ctti-clinicaltrials.org/
3. Atlas, an evidence-based catalog of connected technologies. https://elektralabs.com/
4. RADAR-Base, Open source platform for remote assessment using wearable devices and mobile applications. https://radar-base.org/index.php/home/about-us/
5. FDA Mystudies app: https://www.fda.gov/drugs/science-and-research-drugs/fdas-mystudies-application-app

SUMMARY AND CONCLUSIONS

“Are we there yet?” Context of this question is to understand whether the data collected from mobile technologies is currently used by any sponsor to support primary or key secondary endpoints of clinical studies and whether submitted to any regulatory agencies or not? Per our understanding, most of the clinical studies mobile technologies data available currently is being collected under “feasibility” terms of reference. Several academic studies using wearables have been reported but it is not clear if this data would be acceptable as part of a clinical submission.

In order to see mobile technology data in submission packages, there needs to be a huge transformation in all areas to address scientific, regulatory, ethical, legal, data management, infrastructure, analysis and security challenges. Among all these, data management, infrastructure, analysis and security challenges can be adopted from other industry use cases where the amount of data that is generated/utilized in much larger volume. Scientific and regulatory challenges involve the development of novel endpoints accurately reflected from mobile technologies, which need to be developed by scientific community with close collaboration with regulatory, which can eventually provide/update guidelines, framework. Ethical and Legal challenges can be streamlined and can be avoided with proper determination of data utilization and by adhering to the consent obtained.

To conclude, “Are we there yet?”, not yet, but we are on our way.

REFERENCES

1. Wearable Devices in Clinical Trials: Hype and Hypothesis. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6032822/
2. Clinical Trials Transformation Initiative, CTTI Recommendations: Advancing the Use of Mobile Technologies for Data Capture & Improved Clinical Trials. https://www.ctti-clinicaltrials.org/sites/www.ctti-clinicaltrials.org/files/mobile-devices-recommendations.pdf
3. Feasibility studies database: https://feasibility-studies.ctti-clinicaltrials.org/
4. Developing Measures of Cognitive Impairment in the Real World from Consumer-Grade Multimodal Sensor Streams (https://evidation.com/wp-content/uploads/2019/08/developing-measures-of-cognitive-impairment-in-the-real-world-from-consumer-grade-multimodal-sensor-streams.pdf)
5. "Collecting and Analyzing Millions of mHealth Data Streams." Proceedings of the 23rd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining. ACM, 2017.
6. https://valencell.com/blog/2019/04/wearables-in-clinical-trials-opportunities-and-challenges/
7. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. E9: Statistical principles for clinical trials (Step 5) 1998. Available from: http://www.ich.org
8. Ranjan Y, Rashid Z, Stewart C, Conde P, Begale M, Verbeeck D, Boettcher S, Dobson R, Folarin A, The Hyve, RADAR-CNS Consortium. RADAR-base: An Open Source mHealth Platform for Collecting, Monitoring and Analyzing Data Using Sensors, Wearables, and Mobile Devices. https://radar-base.org/index.php/home/about-us/
9. Evidation: https://evidation.com/product/#data-platform
10. https://www.imarcresearch.com/blog/using-wearable-devices-in-clinical-trials

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