Decentralized Clinical Trials (DCTs)

Version: #1

Release: April 2020

Author(s) and Reviewer(s)

- Patrick Nadolny
- Josh Wilson

Background

The Society for Clinical Data Management (SCDM) Innovation Committee seeks to provide Thought-Leadership to our industry and support the SCDM vision of "*leading innovative clinical data science to advance global health research and development*".

The SCDM Innovation committee strives to demystify what Clinical Data Science (CDS) is and support the development all Clinical Data Management (CDM) professionals, from subject matter experts (SMEs) working on clinical studies to CDM leaders setting the direction of their organizations.

The Innovation Committee will be publishing short briefs intended to serve as orientation guides on specific topics which are contributing directly or indirectly to the evolution of CDM toward CDS. The content of those topic briefs is primarily an extract from the previously published SCDM Reflection Papers[1,2] which collectively provide a cohesive and comprehensive overview of CDS.

Introduction

Decentralized Clinical Trials (DCTs) are often referred to as if they are a distinct clinical trial category, but this is a fallacy. The concept of a decentralized trials is essentially predicated on decoupling clinical research activities from a physical site location. The DCT model may also be referred to as a site-less or virtual study model, but recent trends suggest that the term "decentralized" is becoming the most widely used. This study model places the patients at the center of the trial with the aim to limit or eliminate the need for patients to travel to an investigational site. Those patient-centric trials are very disruptive for CDM especially when vastly decentralized (i.e. very few to no site visits).

This approach involves the use of technologies and processes, some of which we have been using for years, such as eCOA, web-based data collection tools and remote data monitoring. Other technologies are newer to clinical research, but are often already being used by consumers, such as wearables, and telehealth tools. Technologies and techniques used in DCTs often leverage a combination of active and passive data collection mechanisms:

- **Active data** collection includes case-report forms, eCOA instruments, and other means of data capture. It is data specifically collected for clinical research purposes and the patients are usually actively involved in its generation.
- **Passive data** collection refers to data that exists in a myriad of systems and generated as a by-product of real-world medical care processes or other patient activities. This data may not be collected specifically for clinical research purposes but can be curated and utilized in research. While patients are generally not actively involved in this process, they must consent, either prospectively or retrospectively, to their data being used.

Active data is collected, reviewed, and cleaned using more traditional CDM methods. However, in a decentralized model, the act of querying active data will be different, and passive data won't likely be queried at all in the traditional sense. There may be a need to use patient engagement portals or applications to reach patients directly in some instances. The query process in a decentralized model may not always allow for data corrections, especially if the data is collected directly from patients and considered source data. The data cleaning process may end up focusing less on correcting missing and inconsistent data and more on correcting the presumed behaviors that led to data issues to avoid them in the future. Methods such as analytics tools that use statistical algorithms to identify trends and anomalies are more viable ways to interrogate these types of data. This can highlight issues with the way data is collected, device malfunctions, patient behaviors, and potentially more. This may then lead to follow-up preventative actions to avoid future reoccurrences of the same issues.

Today DCT is used in a limited number of clinical trials. Some therapeutic areas and indications are more appropriate than others. Some protocols requiring complex procedures (e.g. Implant Procedures) or necessitating large diagnostic equipment (e.g. MRI) would not be practical at a patient's home.

Additionally, likely due to the immaturity of current technologies and risk aversion, many companies are only piloting some aspects of DCTs while keeping core visits and assessments at investigator sites (e.g. Dosing Visit and Exit visits). This may look simpler than a fully decentralized trial, but it is adding complexity by increasing the number of technologies, data sources and stakeholders on a study. The set-up of such hybrid studies (i.e. partially decentralized) requires careful planning leading to the set-up of multiple systems with complex data flows and integrations.

Short brief

As highlighted below, there are fundamental differences in the way data is collected in traditional trials when compared to DCT.

Traditional Approach		DCT Approach
Via observation / measurement	How?	Via connected devices and/or patient engagement tools
Brick and mortar study sites	Where?	Wherever patients roam or dwell
Patients and study personnel together	Who?	Patients alone physically (generally), sometimes visited at their home, but potentially with support through technology
Research-specific data only	What?	Research-specific and/or personal health-related data
Pre-specified intervals per protocol	When?	Pre-specified intervals, on demand, and/or continuously
For research purposes only	Why?	Sometimes for research, sometimes for patient's care

It is also important to realize that traditional EDC is not applicable for fully DCTs as all data are collected directly from the patients utilizing multiple eSource data collection modalities such as eCOA, Devices, Wearable, Sensors etc. All patient visits are either remote (i.e. Telemedicine) or conducted through home nursing. A pool of investigators may be available remotely to answer patient's emergencies. Figure 1 depicts an example of a visit schedule that a patient may follow in a fully DCT.

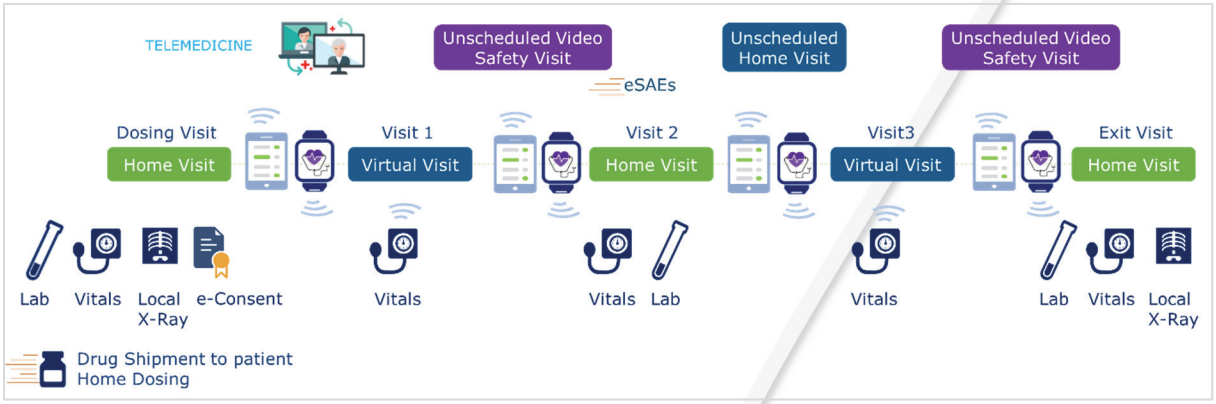

Fig 1. Example of design of a fully Patient Centric / Decentralized Clinical Trials

In this context, most of the traditional data cleaning processes are not applicable. Additionally, there are no site monitors to handle data-related issues upstream on CDM's behalf. Due to the limitation of addressing data issues after collection in a DCT model, the process heavily relies on technologies collecting error free data with quality checking at the time of data collection. Data processing would be focused on data consolidation from diverse technologies and sources rather than data cleaning. So, clinical data scientists should proactively assess data mastering and data reconciliation keys across modalities. Additionally, a risk assessment tailored to DCT could allow the implementation of a pragmatic risk-based study execution approach to data processing.

Additionally, CDM needs to wrangle and consolidate the data collected from the myriad of sources to enable the monitoring of data remotely. Pre-defined data handling strategies would be advisable to address illogical data (e.g. incompatible with life) since the source cannot be updated. CDM may also need to define a process to "disqualify" and/or "flag" such implausible data.

Overall, direct patient data collection supporting DCT is becoming more intelligent, bi-directional and interactive. Systems can share masked data with the patients to boost motivation while improving subject safety, compliance and ultimately, retention. While intriguing, this also highlights new elements and challenges around mobile device usage (e.g., BYOD or not), patient safety, ethical conduct, patient privacy, and shines a light on the quality of the clinical data being shared with patients including those from traditional CDMS. If we share data points that a patient (with or without their caregiver) uses to make a care decision, what are the implications and mitigations to consider within our clinical trials? Clinical data scientists will need to consider how patients interact with different types of clinical trial technologies. More critically, clinical data scientists will need to establish flexible data sharing, integration and cleaning strategies in an arena where ethical and strategic decisions play an even more vital role in patient safety and privacy.

Furthermore, the volume of data collected using these tools can be vast, and the desired use of this data must be considered prior to collecting it. For instance, if actigraphy devices will be used to measure the number of steps and hours of sleep, is the intent to compare a single participant's day-to-day activity, or to compare activity across participants? While it might be tempting to compare activity from patient to patient, with the relative variance of the data from these devices due to the device itself and user habits, it may not be possible to compare absolute measurements. Trends may be observed within a patient as to whether activity is decreasing, increasing, or remaining the same over time. Clinical data scientists may apply statistical monitoring methods, machine learning or other forms of signal detection to proactively detect such trends where fast response is required.

This is just one simple example of the need to rationalize the data collection methods as well as how the data will be used. In that context, what will the CDS role in reviewing this data be? Clearly, the data from a device can't be queried in most instances. An elderly patient will likely not know if they really walked 3,235 steps yesterday when they may only have walked from 1,500 to 2,000 steps a day before. But, if there is wide variability in the data day-to-day, there may be value in detecting them and sending questions or reminders to the patient through an engagement app, such as, "*how many hours a day do you wear your device?*", "*did you forget to wear your device yesterday?*", or "*Please, remember to wear your device tomorrow*".

The use of apps and devices is a critical technology component that must be leveraged effectively to achieve the goals of data collection in decentralized clinical trials. Connecting to a patient without the use of physical clinical sites does require utilizing patient-centric applications and devices that are easy to use and, ideally, require little training and maintenance. The value of data collected using a device is only realized if the patient is using the device consistently, correctly, and if the data is transmitted regularly to be monitored and analyzed.

Best practices currently suggest that the use of clinical grade devices is most appropriate for clinical trials[3]. However, the use of commercial-grade devices has been accepted in some instances[4] such as the Apple Watch to detect atrial fibrillation which has been approved by the FDA[5]. The larger sample set

that can be achieved in a decentralized trial may allow for a greater tolerance of variability than in a traditional trial, which is important due to the higher likelihood of missing data[6].

The need to benefit from decentralized trial methods has never been greater, and the industry is likely to continue pursuing ways to introduce more aspects of decentralization into trials. Being prepared for the downstream impact to CDM organizations moving toward CDS will ensure that once other obstacles to adoption are overcome, we will be ready to handle the data regardless of how it is collected

References

1 SCDM, June 2019, The Evolution of CDM to Clinical Data Science – A Reflection Paper on the impact of the Clinical Research industry trends on Clinical Data Management. Available at https://cdn.fs.pathlms.com/a1AnYc9xSiu8GbVj4bHi?cache=true

2 SCDM, March 2020, The Evolution of CDM to Clinical Data Science (Part 2: The technology enablers) – A Reflection Paper on the impact of the Clinical Research industry trends on Clinical Data Management. Available at https://scdm.org/wp-content/uploads/2020/03/SCDM-Reflection-Paper-Evolution-to-Clinical-to-Data-Science-Part-2.pdf

3 US National Library of Medicine, 2018, Elena S. Izmailova, John A. Wagner and Eric D. Perakslis, Wearable Devices in Clinical Trials: Hype and Hypothesis, Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6032822/

4 Clinical Researcher, April 2019, An Overview of the Prospects for Using Wearables to Improve Clinical Trials, Available at https://acrpnet.org/2019/04/25/an-overview-of-the-prospects-for-using-wearables-to-improve-clinical-trials/

5 Marco V. Perez, and Al, Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation, New England Journal of Medicine. Available at https://www.nejm.org/doi/full/10.1056/NEJMoa1901183

6 Jenifer L. Hick, and Al, Best practices for analyzing large-scale health data from wearables and smartphone apps, NPJ Digital Medicine, Available at https://www.nature.com/articles/s41746-019-0121-1

Main abbreviations

BYOD	Bring Your Own Device
CDM	Clinical Data Management
CDS	Clinical Data Science
DCTs	Decentralized Clinical Trials
EDC	Electronic Data Capture
eCOA	Electronic Clinical Outcome Assessment
SME	Subject Matter Expert