MEDIDATA / Rave

WHITE PAPER

Decentralized Clinical Trials

What are they and what are the direct impacts to Data Management (DM)?

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Introduction

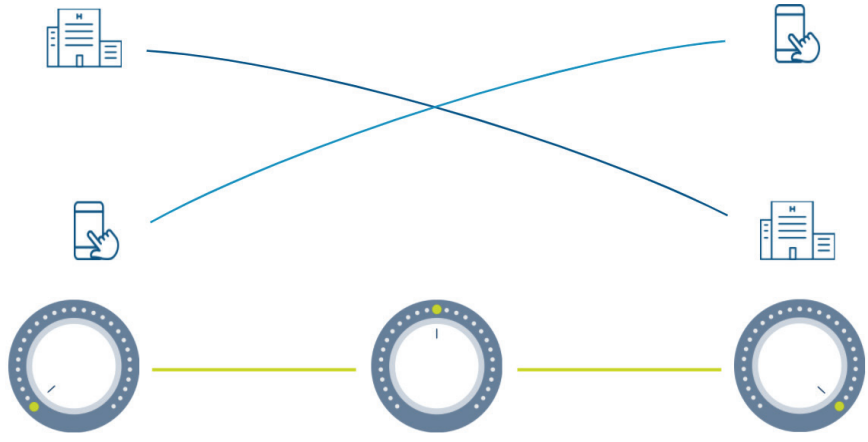
In 2020, after the COVID-19 pandemic surfaced, the need for alternative approaches to clinical trial execution and data capture became a reality overnight. The concept of implementing components of decentralization within a clinical trial became one of 'here and now,' versus a concept of the future. In many instances, the pandemic halted the patient's ability to go to a site. Recruitment, enrollment and retention rates were challenged; and a large percentage of clinical trials were delayed, and some terminated. As a result, the momentum around the concept of decentralization increased as did the need for capabilities supporting decentralization within a clinical trial. Organizations were ready to shift their business models and processes to support, test and pilot decentralization within their trials.

Before the COVID-19 pandemic, many biopharmaceutical companies, contract research organizations (CROs) and medical device manufacturers were exploring new ways in which they could reinvent the clinical development paradigm. This occurred by conducting pilots to digitally capture outcomes data or options to replace brick and mortar site visits by way of telemedicine, etc. Often these efforts occurred as one-off or siloed efforts within an organization and information was shared in pockets. However, looking back, these efforts were important in that they enhanced industry learning, helped to lower concerns associated with potential risks, and increased confidence associated with alternative ways to conduct a clinical trial. In essence, these pioneered efforts have become the keystone of our learning associated with remote data collection, data capture and decentralization.

But what is decentralization of a clinical trial? Commonly known as Decentralized Clinical Trials or DCTs, what does this mean? In the simplest form per Oxford Languages defines decentralization as: The transfer of control of an activity or organization to several local offices or authorities rather than one single one. If we apply this definition to a clinical trial, it means that one or more activities would be transferred from how/where it's currently being conducted to a different place. Ultimately, this allows the patient the opportunity to participate in clinical research in various environments.

Given protocol complexities and uniqueness, it would be difficult to apply a "one size fits all" decentralization model to every clinical trial design. Therefore, 'how much decentralization' should be taken into consideration per protocol and the risks defined upfront. The diagram below depicts the different degrees of decentralization from ***Traditional to Hybrid to Fully Remote or Virtual***:

Figure 1: Different Degrees of Decentralization



Traditional	Hybrid	Virtual
All trial activities are conducted at the clinical research site	Some trial activities are conducted virtually; while other are conducted at the site and/or through home health professionals	All trial activities are conducted virtually. Trial, supplies, and medicines are delivered directly to patient

Decentralization and Impacts to DM

With more data being collected directly from patients, either via wearable devices and sensors, electronic clinical outcome assessment (eCOA), and/or telehealth platforms, there is an urgent need to shift our thinking from reactive strategies into proactive planning and technology-based solutions to replace the query and listing-based reviews of trials past. Historically, data management would manually identify trends and data anomalies via data listings, dashboards, and home-grown tools that may or may not be interoperable. The process by which data managers would interact with their study data would be cased on the following concepts:

- EDC centric
- Linear
- One size fits all
- Site generated data - few integrations

The challenge for those in Data Management leadership and those working directly on trials themselves is how best to incorporate an ever-increasing list of data sources, novel data types, and analytic tools executing the core function of Data Management - ensuring that the clinical data collected is fit for purpose. Modern data managers command proactive planning and interoperable technology-based solutions to replace the query and listing-based reviews of trials past to stay ahead of the curve. Simply stated, data managers are now the center of the spoke responsible for all disparate data to harmoniously tell a complete patient's journey. Whether that be from the demand for telemedicine and decentralized trials or the further adoption of risk-based approaches (data, system and processes), we must evolve NOW.

How do we adopt new methodologies with old skill sets? Like your iPhone - it's time for an upgrade. We can't think that old ways will work in the new modernized DM. Clinical data management departments will need to prioritize upskilling their data managers and dedicate time and resources to expanding their analytical mindset, clinical skills, risk and mitigation processes. In addition, they must improve the understanding and use of real-world evidence, data trends and new clinical endpoints based on alternative EDC designs from DCT trials.

If clinical data management commits to this cultural shift, they augment their daily activities with a new data governance toolkit that includes specialized tools for real-time analytics. Data management will be better equipped to provide engagement from protocol design, to data visualization development and patient-centric technology solutions in any phase of a decentralized trial.

Technology Solutions that Allow for Decentralization

1. **Patient Facing Technologies:** In any clinical trial scenario, the patient experience is paramount to overall success of the trial. Providing the patient choices, easy access to information, user friendly training materials, study supplies and materials, information sharing, video visits, etc., are all important components for a healthy clinical trial patient experience. In addition to individual patient needed technology enablers, broader information sharing within digital communities is possible within the technology platform. With that being said, patient-centric technology platforms that facilitate processes, provide easy web access to necessary information, trial updates, alerts, etc. and allow for the patient to provide input and feedback are all ways that one can improve the patient experience and increase study retention.

2. **Protocol Development and Design Capabilities:** In every clinical investigation a protocol is developed. In many ways, the protocol becomes the clinical trial study playbook. At a high level, it defines the study design, goals, objective, outcomes and activities that ensure patient safety. Regardless of the clinical trial type (i.e., virtual vs. traditional), the concept remains the same. However, it's important to determine the appropriate amount of 'decentralization' for a given clinical trial. How much decentralization is too much? To manage the amount of decentralization within a trial, it's important to consider the patient and site perspective including any concerns for privacy. For example, sensors offer the ability to remotely capture objective/bio measurements that would typically only be collected in on-site visits. However, introducing too many sensors for remote data capture may create unnecessary site and patient burden ultimately impacting enrollment and retention. Finding the right balance is important. Technologies that allow for an understanding of site and patient burden during the protocol development and design process is key to understanding the appropriate amount of 'decentralization' to introduce within a trial, increasing the overall probability of its success.

3. **Remote and/or Onsite Consent:** Traditionally, patient consent is a discrete on site event versus an event that allows for virtual information sharing. Depending on the trial type, from virtual to traditional, electronically capturing and automating the patient consent provides flexibility, consistency of information exchange and data capture. It's important to provide easy to understand information and the ability to access the consent throughout the trial, while maintaining the appropriate regulatory compliance.

4. **Outcome Data Capture Tools (e.g., eCOA, mobile technologies or sensors, wearables, apps, etc.):** The internet of things offers a plethora of consumer and medical grade technologies for remote data collection. So how does one decide on the appropriate tool(s) to use? To answer this question, consider as a first step identifying the digital measures of interest. For example, you may be exploring whether or not a digital measure(s) could be used as a biomarker to understand efficacy. If so, consider mobile technologies that help to understand elements of improvement or decline (i.e., number of steps, sleep duration, etc). Perhaps continuous safety monitoring is needed to support a particular component of a clinical trial design and there's a desire to provide patients the option to remotely capture these data versus capturing in the clinic. Introducing a sensor that monitors and generates digital data such as heart rate, temperature, etc. may be considered for inclusion. Regardless of the need or desire, defining the rationale, purpose, goals for inclusion can help to inform decision making associated with what sensors to include/not include. Simply said, it's finding the right tool(s) for the job. In addition to digital measures of interest and identifying sensors for inclusion, data interoperability, ingestion and access are all important technology considerations. Ultimately, a single data platform with a variety of available digital measures via various sensors is ideal. This allows for contemporaneous data collection in any environment, end to end data flow and access to unified data sources which results in faster, more robust clinical trial decision making.

5. **Data Oversight:** In a decentralized trial, data oversight and critical data elements and data sources may vary from the norm. For example, data sources may include electronic patient reported outcomes (ePRO), various sensors and/or home health procedures results (e.g., labs, etc.). Regardless of how/where data collection occurs, data platforms that allow for real time/remote access of all clinical trial data collected is important. In addition, depending on data oversight strategies, an individual's data oversight roles and skills may also look different than a traditional clinical trial. Defining strategy, roles and responsibilities associated with data oversight of the decentralized trial are important first steps. Three areas for consideration as part of data management strategies are:
   - Real time compliance monitoring to understand data completeness
   - Data monitoring for safety
   - Data monitoring for data quality and completeness

   In addition, utilization of risk assessment tools can also be useful to define and identify critical data elements, key risk indicators, quality tolerance limits and outlier processes associated with the task of monitoring data collection as part of a decentralized trial.

6. **Issue Management:** Once key risk indicators (KRIs) and quality tolerance limits (QTLs) are defined and data oversight technology enabler(s) are in place, the ability to evaluate clinical trial data becomes an event of real time (versus episodic) monitoring. As a result and in parallel, issues around data anomalies, quality and gaps will need to be identified and resolved in real time.. Thus the need for technology enabler(s) that allow for a consistent process and capture of data associated with issue management and resolution. This technology enabler will allow for an increase in overall data quality, an efficient and effective process and an automatic audit trail for transparency and awareness.

7. **Benefits to Patients:** By nature, decentralization of clinical trials provides the patient options as it relates to logistics and travel to the investigative site. Ultimately there's not a one size fits all scenario and providing options that allow for flexibility will naturally result in increased study enrollment and retention. This can only occur through technology enablers that allow for decentralization support from the beginning to the end of the clinical trial. Support, meaning support for the patient and those providing clinical trial oversight. As previously mentioned, the patient experience is paramount to the overall success of the clinical trial and creating a healthy, low burden clinical trial experience for patients, sites and sponsors is the key to success for execution of a DCT.