New Digital Trends and Technologies in Clinical Trials and Clinical Data Management

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ABSTRACT

Internet is a huge repository of information which is used to cater diverse needs of its users. Almost 5 billion people around the world now use the internet. The explosion of internet, Covid- 19 pandemic and social media expansion have been offered new digital trends and technological evolution in clinical trial operations and clinical data management sectors. We are going to discuss here, some of the latest new trends of clinical trial industry and challenges in these changing times and changing roles from data programmer to data scientist. Further, we are looking forward to the help from the industry in proposing a detailed curriculum for the current and future needs of career paths in clinical data operations and management towards a quick analysis and submissions of clinical data to regulatory agencies with quality for faster approvals using these technologies.

INTRODUCTION

When Alexander Fleming was discovered Penicillin in 1928, the average clinical trial time was 12 years. In 2020, the clinical trial time was reduced to 10 years without much change in industrial normal time. However, Covid 19 though disrupted almost around 40% scheduled clinical trials in the year 2020 especially oncological studies but offered new solutions with innovation especially usage and enhancement of digital technologies in clinical trials out of societal need and peer competition with quality quick delivery of drug products and vaccines.

Covid has changed the industry's mindset to think differently with possible usage of available digital options to reduce on going trial protocol schedule disruptions and recruitment of trail patents through social media and population foundations. Virtuality has become new norm and way of life for personal and trial conductance with virtual monitoring and there by home has become a trail site for sponsors, investigators, trial participants, coordinators, and data articulators. The main focus here is patient centric with the raise of tele medicine and also digital supply chain development and deliveries of trial medications, incremental patient drug adherence procedures and most of the manual operations such as patient travelling to clinical sites, have been replaced with new technological procedures and practices and there by paved a way of new industry setting with the usage of sensible and practical scientific procedures and norms and inform regulatory agencies rather than previous agencies policy dictate practices. In this way true meaning of cGXP (current good clinical, manufacturing, laboratory etc. practices) have been accomplished.

Thus, first time in a century, pharmaceutical industry got an opportunity to think differently, adopt new procedures and data standards, develop new clinical platforms and train personnel with new procedures, programs, software, and technologies to deliver the needs of new clinical development model which could reduce trial time and other resources while improving the quality aspect throughout the clinical trial life cycle. In this way, one can visualize and fully accomplish the notion that data is currency with modern technologies such as automation, AI, ML, NLPs etc. in R&D and clinical data analytics along with technically skilled and empowered manpower.

Therefore, clinical data management need to reciprocate to the changes outside and inside of the industry with new curriculum to for its personnel especially to programmers. The external changes are mainly originated from people, market dynamics, pandemic lockdowns, and urgency from the industry in reducing clinical trial spending using available new opportunities and technologies.

Sponsors and contract research organizations (CROs) have been pushing data management departments to collect clinical trial data more efficiently in terms of quality and time. As a result, CDM organizations have evolved meaningfully in two ways, 1. data deliverers working with closed systems, 2. data leadership working in digital environment with more strategic and extended functions.

Pharmaceutical clinical operations and data management are being enriched with data coming, nowadays, mostly from electronic sources, such as electronic case report forms (eCRF), wearables, electronic patient-reported outcomes (ePRO), electronic clinical outcome assessments (eCOA), electronic informed consents (eICF), new digital biomarkers, etc.

Recently, it was initiated in unlocking rich sources of real-world data (RWD) that can provide more accurate insights into the patient journey. These are data from claims databases, hospital records, mortality data, disease registries, consumer

data, pharmacy records, laboratory and biomarker databases, and even social media.

The expansion of digital health in clinical operations are in proportional to the use of electronic devices and smart phones by global population is shown below, in Fig.1:

Use of Technology	2010	2015	2020
World population (in Billions)	6.8	7.2	7.6
Devices (in Billions)	12.5	25	50
Devices (per Head)	1.8	3.5	6.5
Total No of Smart Phones, Worldwide, (in Billions)	0.5	3	6

International Clinical Trials Registry Platform (ICTRP) results show that the current registered interventional clinical trials region status as North America, Europe, Asia, and Sub-Saharan 35.2, 35.2, 25.0% and 2.3% respectively. Others were Oceania and Latin America and the Caribbean with 2.3%. ClinicalTrials.gov is the largest clinical trial registry, containing records for 306,775 trials from 210 countries as of May 2019.

The global clinical trial market was estimated at $ 44.3 billion in 2020 and is expected to be grow at CAGR of 5.7% in coming 5 years. Oncology segment dominated by trial market by 36.3% in 2020 with an industry spending of $38 billion. Now a days, any delay in clinical trial costs the sponsors potentially ranging from half million to 8 million dollars per day. Recent Pandemic lockdown brought devastating impact on outpatient clinical trials through temporary site suspensions, reduced subject recruitment and trial delays. Around 40% of oncology trails were suspended in lockdown. However, every calamity will also offer some opportunities to thrive. Covid has offered good opportunities for pharma industry in the form of virtual, blind, or remote trial propositions along with digital transformation at an unprecedented rate to innovate to overcome the challenges. At the same time, global regulatory bodies encouraging the industry through paved way of end-to-end trail digitalization, including the FDA's latest guidance in last June, which allowed for innovations and adaptations that were successful throughout the lockdown to be implemented for use outside of the pandemic.

Some of the digital trends in clinical trials are described below:

1. eConsent
eConsent is the use of digital methods to request, confirm and document informed consent of the subject.
FDA and the OHRP, HHS have agreed eConsent in clinical trials since 2016, in a guidance document which states that "electronic processes to obtain informed consent may use an interactive interface, which may facilitate the subject's ability to retain and comprehend the information."
A recent 2019 Industry eConsent Survey supports that eConsent is a valuable technology for many organizations in improving clinical trial processes efficiency, and quality, and to generate a better patient experience impacting patients' comprehension and ongoing engagement, improved patient retention, and reduced regulatory risk and audit findings. The top drivers identified were similar between biopharmaceutical company respondents and CROs. Even prior to the pandemic there was an increasing trend to utilize eConsent within biopharmaceutical companies and CROs, which has only grown more substantially since Covid-19.

2. Digital Biomarkers
Digital biomarkers could be used virtually to monitor patient health reducing the need for the patients to attend the clinics. For instance, a smart phone tapping test app has been developed to monitor status and conditions of patients in Parkinson's therapeutic area clinical trials. In another example, Merck has tapped recently Evidation to explore whether data collected from smartphone apps and wearables can help to diagnose Alzheimer's disease early. The remote monitoring data on pathophysiological changes, as well as subtle changes in cognition, sensory, and motor function associated with disease onset are providing new compelling opportunities to identify novel endpoints and digital biomarkers for Alzheimer's disease.

3. Patient selection and recruitment

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Every clinical trial needs certain requirements of participating patients with regards to eligibility, suitability, motivation, and empowerment and diversity of patients. 86% of all trials do not meet enrolment timelines, and close to one third of all Phase III trials fail owing to enrolment problems. Usually, Patient recruitment takes up one third of the overall trial duration. For example, Phase III trials carry 60% of the total cost of the trial because they require the largest patient cohorts. The internet is first resource that people like to use after cancer diagnosis. In modern times, patients, physicians, healthcare providers, regulatory bodies, sponsors and CROs and communities are on common platform, social media. Social media is an obvious avenue to help educate and share information about clinical trials without "spamming" those that are not interested. This is more efficient than mass mailing. Crowdsourcing is an evolving clinical trials development paradigm with cooperative group of clinical trial investigators who can influence in reaching to the right patients in time. In recent social media trends, we have seen increment of Spotify ads in trial recruitment (each ad costs about $250 and ad will be created within one hour).

On the other side, Twitter, and other certain other platforms are helping minority and other diversified population recruitment in clinical trials especially in anti-viral trials. In 2020, across all geographies, the click through rate is up by 20%, patient engagement rate is up 13% and registration rate is up by 80% with digital advertisement. AI- and ML-driven systems can help to improve patient cohort composition and aid with patient recruitment through extract and analyze relevant information from a patient's EHR records, compare with eligibility criteria for ongoing trials, and recommend matching studies.

Deep 6 AI uses NLP to extract clinical data such as symptoms, diagnoses, and treatments from patient health records. Its software can even identify patients with conditions not explicitly mentioned in EHR data, improving the match rate between patients and clinical trials.

4. Expansion of Telemedicine

Telemedicine is broadly defined as the use of telecommunications and software to monitor and treat patients in lieu of patient's visit to trail site and hospital. Telemedicine was the most mentioned and adopted technology during Covid 19 and used for routine follow up to identify adverse events especially in phase 1 studies. Digital medicine simulates the kind of face-to-face interactions that help build trust between patient and provider and lower the burden on the patients. Decentralized trials will improve the patient experience by making necessary in-person visits local and adding in digital measurement tools. Automated patient screening, triage and routine care are the main use cases will continue in moving beyond urgent care and expand in other areas such as women's health and tele-mental health.

5. eSource

Right process design for collection of RWD is essential in a clinical trial to facilitate analysis and prove drug efficacy, and this must be handled at design stage. Clinical Registries, Electronic Health Records (EHR) and post-authorization reports are just some of the sources for RWD. It is important for sponsors, CROs and tech companies to have pre thoughts and ideas on how to use these data and to be aware of latest technologies for processing and analyzing such data. An efficient and reliable tool are needed which connects EHR to electronic data capture (EDC) systems, and RWD data, eSource, and all other EDC systems could be centralized in one platform for analysis.

Some of the most promising eSource technology advancements for future research are consider are:

- AI/ML-based platforms that support enrolment of subjects in clinical trials
- AI-based medication and protocol adherence support
- Innovation in electronic clinical outcome assessment (eCOA) technology to facilitate a more patient-centered approach to trial design and administration
- Interoperability: Platforms that enhance interoperability between various electronic data capture systems like EDCs, EHRs, mHealth, RWD sources, etc.
- Centralized Data Platforms: Smart technologies that integrate data from various streams to expedite analysis and understanding of the data.

6. Patient Centricity

The current industrial clinical trial trend is patient centricity approach. From technology adoption to data security, all emerging trends in this decade will be focused on creating a better experience for patients.

The biggest patient centric takeaway is to treat patients as partners in clinical trials, not subjects. Including patients in trial design while understanding and empathizing with their current health conditions may better protect and build trust between patients and biopharmaceutical companies. By showing more kindness and empathy, researchers will better protect patients and build trust — one of the most important elements of conducting a trial. Additionally, patients deserve access to their own data now more than ever. They deserve to know more about their contributions to society, and easier access to data is one way we can provide that. By sharing data with

patients, we are making them part of the research process, not just a means to an end in a trial.

7. Electronic Trial Master File (eTMF)
Electronic trial master file (eTMF) system is a Trial Master File in electronic or digital format. It is a way of digitally capturing, managing, sharing, and storing those essential documents and content from a clinical trial. It utilizes both hardware and software to manage clinical trial data. Benefits in clinical trials include saving time, cost-effectiveness, and an increased visibility to repair and discover document errors. It is also helping with recruitment, as patients can opt to be contacted for trials that are relevant to their medical conditions while reducing regulatory risk along with fast submission advantages.

8. Wearables
The use of wearables in clinical trials continues to rise. Wearables, or wearable technology are smart electronic devices worn close to the skin that collect data digitally and automatically.
Wearables offer remote data capture over longer time periods, providing more detailed, granular data. This aligns with decentralized trials and can improve patient safety while reducing the patient burden of traveling to sites. The ease of use makes wearables patient-centric, which improves recruitment and patient retention. Wearables could help deriving digital endpoints in tracking daily activities and algorithms from the data collected such as flights of stairs climbed, or time spent not sitting. These endpoints are more relatable to the patient, having a direct correlation to an improved quality of life. It is predicted that 70 percent of clinical trials will incorporate wearables by 2025.

9. Data Scrapping
Collecting online data from social media and websites in the form of unstructured text is called scrapping, web harvesting or web data extraction. Social media clinical trial data provides rich raw data access to clinical research advancements and challenges to computer scientists, sponsors, and other funding bodies to develop innovative methods, tools, and software.

10. Safety Monitoring
Harnessing the ability of digital tools in collecting the data continuously, which can be transmitted directly to clinical researchers, investigators and administrators, might improve the detection of infrequent events or those that are situation-specific and unlikely to occur during a study visit. The speed at which adverse and safety events can be identified and reported may have a significant impact on the timeliness of completion and reporting of clinical trials.

11. Drug Adherence
Ensuring medication adherence among patients is commonly an ongoing challenge during clinical trials, and it is becoming increasingly difficult as treatment regimens become more complex. Adherence ensures that the effect of an investigational drug is fully reflected in the data. Some adherence tools use facial recognition to confirm that a medicine has been ingested and generate non-adherence alerts to investigators.

12. Digital Supply Chains
Digital supply chain (DSC) can be defined as the development of information systems and the adoption of innovative technologies strengthening the integration and the agility of the supply chain and thus improving customer service and sustainable performance of the organization. DSC will integrate innovative technologies such as augmented reality, big data analytics, Blockchain technologies focusing on drug suppliers/sponsors/patients while reducing intra and inter-organizational costs and create more value for organizations. It will also improve visibility, robustness, resilience, and trail performance.

13. Recruitment of trial personnel through data analytics
Demand for experienced and knowledgeable talent in clinical research has never been greater due in part to a confluence of economic, pandemic and healthcare trends. The rush to hire clinical research associates (CRA), clinical trial managers, statisticians, clinical data programmers, project managers and other key roles has led to a significant talent shortage due to increasing competition, changing regulations and the impact of. The U.S. Bureau of Labor Statistics (BLS) projects that demand for life sciences talent is growing faster than all other occupations. Sponsors are using social media as a valuable tool for sourcing and recruiting prospective candidates. Social networking allows organizations to build their employment brand and awareness, expand the breadth and depth of their network, target top talent in a large range of skill sets, and improve the effectiveness of their recruiting efforts. Creating a visible presence on websites such as Indeed and ZipRecruiter, Spotify ads, reaching out to associations, organizations, EBRGs and foundations and networks like LinkedIn, Twitter and Facebook will be imperative for attracting top talent. Tools like these not only allow you to have greater visibility when you have job openings, but they can also lay the groundwork for hiring future candidates as jobs come available.

According to social media, 60% of all job searches in America originate from a mobile phone. Businesses have been taking advantage of video chat tools such as Facetime, WebEx Zoom and Skype in the wake of the COVID-19 pandemic and seems to continue further.

14. Augmentation of brand value of organizations through social media
The brand is the name around which any modern organization wants to build its entire business especially in drug portfolio development of a pharmaceutical organization. Although pharma has been active in social media for some time, the industry is still in the relatively early stages of social media maturity.
In a digital age, patients are much less dependent on investigators or physicians for advice, increasingly able and willing to take greater control of their own health. Social listening is a key first step in effective clinical trial planning and design. An extended monitoring program will help clarify the dynamics of the study indication area in question and thus help ensure recruitment and retention of the right clinical trial participants. Specifically, to identify what content formats and messages resonate with patients and caregivers to ensure trail sponsors are speaking the patient population's language (questions, concerns, areas of interest), to uncover where conversations surrounding the disease state and related topics are taking place. In other words, the communication channels through which patients will be most receptive to trial messages, to understand the patient journey including the key decision points along their journey and map the influencers in the indication area (patient organizations, advocates, trade bodies, news sites, etc.) and assess who's central and who's peripheral to the conversation.

Some of the latest and future requirements of regulatory guidance on above issues are given below:

Clinical trial issue	FDA 2020 guidance	Post-COVID-19 roadmap
Requirement of in-person consent.	Can obtain signed informed consent remotely.	Make electronic remote consenting permanent.
Requirement to use clinical trial–specified laboratories and imaging.	Allowed use of alternate laboratories and imaging centers.	Allow use of any laboratory and imaging center that meet specifications.
Recording of safety and clinical assessments based on in-person visits at investigator sites and investigator-based recording.	Allowed alternative methods for safety and clinical outcome assessments (e.g., virtual visits, phone contact).	Add Patient Reported Outcomes (PROs) and telehealth approaches to routine clinical trial methodologies.
Administration of investigational products exclusively at clinical trial sites.	Alternative delivery/administration methods of investigational products.	Increased use of community-based network sites as opposed to clinical trials sites only.
Requirement for in-person visits to receive investigational oral products.	Allowed home delivery of investigational oral products.	Direct-to-patient investigational product (oral drugs) and concomitant medication reporting via digital tools.
Requirement for in-person visits to receive investigational in-fusional products.	Allowed at-home or local health care provider infusion.	Aspire to 100% remote infusions and monitoring when feasible based on a risk assessment.
Limited clinical trial access for underserved populations.	Shipping of investigational product intended for infusion to a local health care provider for administration.	Decentralize clinical trial conduct and make it more accessible to rural areas and underserved populations: • Increase funding mechanisms for trials conducted in underserved communities. • Markedly broaden trials available for patients with wide range of comorbidities.
Requirement to administer "experimental clinical trial products" even if the same drug was approved and available commercially. Commercial procurement by patient of investigational product already.	Commercial procurement by patient of investigational product already approved for other indications.	Discuss mechanisms for use of clinical trial products obtained as commercially approved drugs.

The current trends in clinical data management are highlighted here below:

The strategic and operational aspects of clinical data management (CDM) are rapidly changing with advances in exponential software technologies, evolving shift from disease-centric to patient-centric approaches, increasingly stringent compliance requirements, incremental demand for decentralized clinical trials and changing submission requirements of regulatory bodies. The traditional data collection processes are not robust enough to support the volume and velocity of data generated during the product development life cycle.

The augmented usage of wearables results in gigabytes of real-time data which requires contemporaneous dynamic coding and reconciliation while ensuring data integrity. Secure data storing and enabling effective processing towards regulatory compliancy is also a biggest challenge.

Most of the current data management systems are legacy enterprise systems which are not interoperable and there by yielding relatively poor performance in data capture, process, analysis, archive, and exchange data in an efficient and cost-effective manner.

Manual transfer of different types of clinical data such as demographic, safety and visit is cumbersome and prone to errors when the exchange involves numerous stakeholders within the clinical trial ecosystem. Furthermore, merger and acquisition activities and intensive re-engineering has increased the complexity of operations with multiple versions of data management processes and disparate technologies used across in-house, outsourcing, and offshore operational models. Data confidence is a constant battle and the organizations need to ascertain that the data collected is standardized and trustworthy.

Now a days, sponsors are looking to modernize their clinical data management process on the following areas:

- **IT simplification:** Driving holistic programs focused on process reengineering and IT rationalization, and make the IT landscape leaner, smarter, scalable, well designed, incorporation of clinical standards and business optimization and future growth.
- **Data centricity:** Implementation of enterprise data lakes such as data repositories, investing in building capabilities in advanced analytics, and improving data quality and accuracy by adopting simplified and straight forward standard approaches and next-generation technologies.
- **Better collaboration:** Creating synergies between ecosystem partners such as technology partners, providers, preferred vendors, CROs, for better seamless trial data outcomes.
- **Change management:** Adopting forward-looking change and risk management solutions, and redefining and formalizing data management policies, procedures and SOPs etc.
- **People Empowerment and management**: Investing heavily in recruitment of skilled and experienced science/software personnel, onboarding, and training to incubate and inculcate new skillsets such as EDC, big data, artificial intelligence, machine learning, cloud infrastructure management, data standards etc.
- **Cybersecurity:** Building foolproof data governance structures to ensure privacy, security and ethical handling of clinical data including genomics data, HEOR data, and data collected through Bring Your Own Devices and other mobile devices.

The famous digital trends in data management are discussed below:

1.<u>Artificial Intelligence</u> and other smart and intelligent Automation
AI is replacing conventional labor-intensive and time-consuming processes in data management with rapid, remotely accessible, and real-time solutions for development of software platforms, application programming interfaces (APIs), and other digital products. Other technologies such as robotic process automation (RPAs), machine learning, and natural language processing can be leveraged to augment data standardization. Smart automation can enable their organizations to achieve greater efficiency, ensure compliance and better utilize their resources. AI and ML can be incorporated into advanced, cloud-based life sciences technology platforms to support trial design, data monitoring, and safety case management.

Generally, the data trends and anomalies could be identified through edit checks, listings, and dashboards. These simple and repetitive tasks will be automated with RPA, ML based automations. The potential areas of data management automations could include, serious adverse event reconciliation, automated clean and eligible patient tracking, auto-generation of edit check specifications, automated loading of 3rd party data, automation of clinical data reviews, analysis and reporting system process triggers (scheduler) and automated quality reviews etc. Software robots can conduct menial tasks like data entry or quality control very fast and with maximal accuracy. Also, bots can perform a large-scale interpretation and processing of clinical trial data, for instance, radiology reports, and facilitate the identification of high-risk abnormalities in images.

2. Data Analytics and Visualization

With so many data sources, having an integrated data viewing process is a needed requirement. CRAs, medical monitors or even investigators will be able to see all the available data in a single EDC system. Companies will need to implement a data visualization strategy to facilitate overall data viewing, on-demand patient profiles and medical monitoring, as well as provide a central database of record for the clinical trial.

With real-time access to all data points, presented in concise graphical displays, data safety monitoring committees can make patient safety decisions more quickly fully harnessing the power of all collected data. This translates to reduced trial time and better safety oversight for patients.

3. Data Strategies

Clinical trials can have more data sources such relational trial management systems (RTMS), central laboratories, biomarker data, genomic data, medical imaging data, EHR/EMR data, ePRO, eConsent, EDC systems and digital devices, such as wearables.

The other data strategies will include how to best collect the data, how efficiently manage, and integrate the data, and how and where to store the data. Many companies may even develop a specific digital-data strategy to specifically manage data collected from wearables. A digital-data strategy should include multiple facets from device provisioning to data collection, reconciliation, and cleaning. A comprehensive strategy will also include a data-focused risk assessment and management to fulfill ICH requirements and reduce the burden associated with the necessary oversight.

4. Augmentation of Metadata Management

Newer technologies are emerging to adjust and keep information base administration more straightforward and errands like data quality and metadata management will be mechanized with expanded data management techniques. With AI investigation and programming methods, metadata management could be well organized and data storage will be well tuned and revised. Augmented data management uses ML and AI techniques to optimize and improve operations. It also converts metadata from being used in auditing, lineage and reporting to powering dynamic systems.

Augmented data management products can examine large samples of operational data, including actual queries, performance data and schemas. Using the existing usage and workload data, an augmented engine can tune operations and optimize configuration, security, and performance.

Data and analytics leaders should look for augmented data management enabling active metadata to simplify and consolidate their architectures and increase automation in their redundant data management tasks.

In coming years, it is predicted the manual efforts in data management will be reduced to a level of 45%.

5. Blockchain in data and analytics

The trend in using Block Chain technology is increasing day by day. Blockchain technologies will provide full lineage of assets and transactions and transparency for complex networks of participants.

Ledger database management systems (DBMSs) will provide a more attractive option for single-enterprise auditing of data sources. Data and analytics should position blockchain technologies as supplementary to their existing data management infrastructure by highlighting the capabilities mismatch between data management infrastructure and blockchain technologies.

6. Interoperability

A traditional problem in data management segment has been a lack of seamless interoperability systems on assimilation and reconciliation of clinical data from EHR/EMR records, external academic, foundational and registries data in corporate clinical databases. Hospitals and other healthcare institutions have not always been able to easily exchange data, making care more cumbersome. But this has been changing fast. By 2015, over 80% of hospitals in the US proved

capable of data sharing with other organizations, improving the convenience of both healthcare professionals and patients.

Interoperability is more than just convenient, however; it helps us move closer to a fully integrated, seamless healthcare experience where patients and their medical providers have the information they need to make informed decisions at the touch of a button.
However, this shift comes with security concerns that need to be addressed. How can the industry make the most out of data sharing without creating bottlenecks for end-users or compromising the security and privacy of patients? That question has yet to be settled.

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