



Digital Health Technology in Clinical Trials: Opportunities, Challenges and Biometrics Future Re-imagined



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ABSTRACT

There has been significant increase in clinical trials using digital health technologies (DHT). It is estimated that by 2025, 70% of clinical trials will incorporate DHT in one form or another[1,2,3]. While COVID-19 pandemic severely impacted clinical trials affecting patient participation, recruitment, supply chain disruptions [6]; it has also accelerated adoption of DHT to protect patient safety and enable clinical trials continuity with minimal disruptions. Food and Drug Administration (FDA) has created the Digital Health Center of Excellence within the Center for Devices and Radiological Health (CDRH) [4]. CDRH provides technological advice and oversight for use of DHT in clinical trials.[5] With accumulating evidence that DHT will immensely benefit clinical trials with decentralized and hybrid trials that with patient-centric focus. There are potential proportionate benefits for society, healthcare systems, health care providers, insurance companies, and Pharmaceutical industry with site-less trials, availability of more follow-up data, patient retention, generation and supplementation of real-world evidence. Operational efficiency in the conduct of clinical trials will also accelerate drug development process. The rapid evolution of DHT also presents challenges to keep-up the pace, with changing landscape and evaluation of these technologies in time to be of use in clinical trials. The digital access divide also poses the challenge of access of these trials to disadvantaged groups who may not have access to internet or older population unable to use the DHT. This proposed paper/poster, examines the trends, benefits, challenges of use of DHT in clinical trials. We also present case-study from recently conducted clinical trials in AstraZeneca Late-Stage Development Cardiovascular, Renal and Metabolism (Late-CVRM)) to highlight the benefits and challenges in using DHT especially from programming perspective.

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INTRODUCTION

The utilization of DHT in clinical trials has been in practice since the early 2000's [1]. It is estimated that by 2025, 70% of clinical trials will be employing DHT [2,3]. This expansion has only been fueled further by COVID-19 pandemic[6]. Adoption of DHT has been seen enhance subjects' participation, recruitment, reduce supply chain disruptions; ensure and protect patients' safety; enable contactless and remote monitoring; accelerate adjudications and decision making; deliver correct therapies in a timely fashion. Food and Drug Administration (FDA) has also formed the Digital Health Center of Excellence within the Center for Devices and Radiological Health (CDRH)[4] to provide technological advice and oversight for use of DHT [5] in clinical trials. CDRH proposed its guidelines for "Providing Regulatory Submissions for Medical Devices in Electronic Format" (2020). CDISC and CDASH collaborate and now frequently release the medical device based medical trials the SDTMIG-MD v1.1 (2019) [9], ADAMIG-MD v1.1 (2021) with updates. While the benefits are plenty to be accounted for and cannot be taken away, there are certain challenges that happen from a Biometrics standpoint. Here we outline the benefits and challenges from Biometrics standpoint, via a case study employing a DHT, and outline potential areas which can be looked upon early for DHT generated data reconciliations.

Benefits: Employing DHT(Wearable Devices, Health Care Apps).

- Reduced Patient and Health Care Systems burden
- Potential to reduce over all clinical trials costs and enabling cheaper medicines with acceleration in completion and lowering health care costs for all the stake holders
- Accelerates screening and recruitment of automated electronic based health records.
- Enhances patient participation and participant engagement.
- Promotes, via wearable devices, remote health round the clock monitoring (vitals, labs, results) at patient's convenience, and enables continuous patient monitoring for key parameters.
- Reduces adjudication/decision response time for adjudicators, physicians and investigators in collecting patient-reported outcomes (e-PROs) and Clinical Reported Outcomes (e-COAs), Adverse Events (AEs). [4]
- Augments missing data issues and promotes reliability on improving data accrued.



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Potential Challenges - Biometrics

Potential Challenges:

- ❑ Rapid evolution of DHT presents challenges in evaluation of technology and appropriateness for clinical trial and at-risk of being redundant before the completion of clinical trials especially in long-term outcome trials.[8]
- ❑ Need for recruitment of automation and collaboration of SMEs in AI, Big Data, Computing and Machine Learning with Biometrics. [10]
- ❑ Access issues in economically disadvantaged populations across the globe may result in inequitable distribution of benefits.[7]
- ❑ The DHT based clinical trials, calls for the imposition of stringent security and automation measures to be imposed to maintain data integrity, to avoid duplicate data, mismatches, and error prone data. Or Ensuring Data Integrity and data traceability due to potential errors in DHT or loss of data.
- ❑ Availability of skilled workforce to be able to leverage data in changing landscape including change in infrastructure, computing platforms and skill-upliftment of existing workforce. New Technology and innovation calls for the additional training to be provided to data managers, programmers, statisticians, physicians and other healthcare professionals.[10]
- ❑ Cyber security risks in maintaining data confidentiality and data privacy and risk of potential data breach while transferring data through different ecosystems.
- ❑ The Digital Health and devices that are being utilized for administering Digital Health interventions or DHT testing in the patients, must be calibrated and validated regularly for safety reasons. Also The testing needs to be done against known standards which sometimes are not yet in place, due to novelty nature of the DHT clinical trials.
- ❑ Verification, validation and interpretation of data acquired from digital health applications. Risks involved in missing data due to non-functional data, changes in devices due to upgrade to the devices or replacements of the devices or calibration errors.



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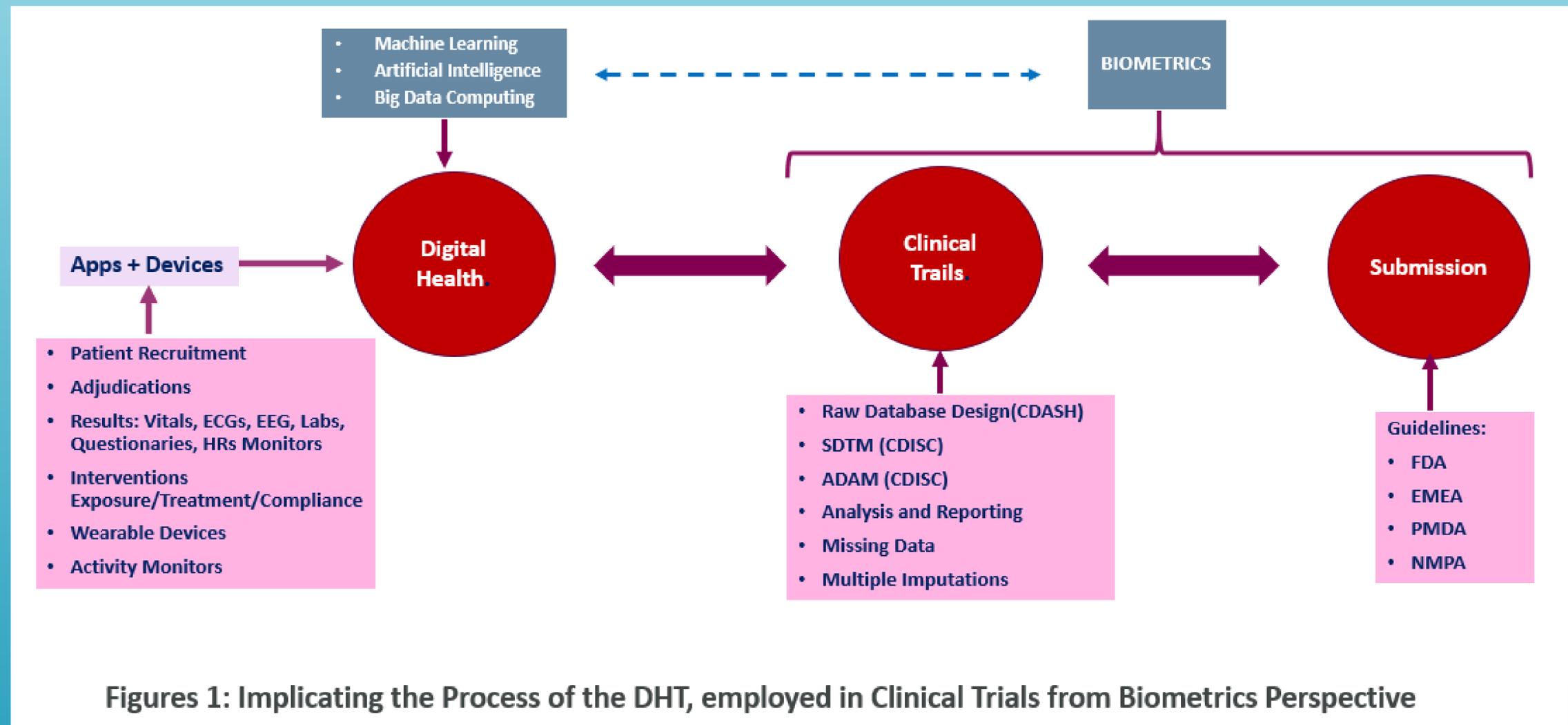
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Potential Challenges-Biometrics

❑ The Regulatory framework is still evolving and lagging the DHT that can be used in robust decentralized clinical trials.



Figures 1: Implicating the Process of the DHT, employed in Clinical Trials from Biometrics Perspective



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Case Study:

DETERMINE-Preserved and DETERMINE-Reduced were international, multi-centre, parallel-group, randomized, double-blind, placebo controlled, phase III studies in patients with HFpEF and HFrEF respectively evaluating the effect of dapagliflozin 10 mg versus placebo (given once daily in addition to background local standard of care therapy, including treatments to control co-morbidities) on change in HF symptoms.

Both the studies used commercially available accelerometer to measure one of the component of composite endpoint measuring improvement in exercise measured by change in baseline in 6-minute walk test (6MWD). In addition, accelerometer measured secondary endpoint measuring increase in non-sedentary measured by total time spent in light to vigorous physical activity, and exploratory outcomes of increase in exercise capacity by measuring movement intensity during walking, effect on physical activity in amount, duration, and intensity.

Two different accelerometers were used; Move Test Accelerometer was used at clinic and was used to evaluate primary endpoint of 6MWD, while Move Monitor accelerometer was used by patients at home as wearable device to assess physical ability during day-to-day activities. Data collected from Move Monitor spanned a period of 7 days at each time-point.

Studies were completed successfully and with very high quality. Nevertheless, there were few challenges that required innovative approaches, flexibility, and paradigm shift in evaluating the core competencies required for the successful evolution of statistical programming group with DHTs becoming increasingly common in clinical trials.



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Case Study:

Electronic Patient Reported Outcomes (ePROs) were used to assess health status of subjects by EQ-5D-DL, Quality of Life, Social Limitations, symptom burden and system stability by following KCCQ domains. Patients performed assessments by using site based tablets during clinical visits. e-PRO protocol was followed in both studies to ensure high quality data along with positive patient experience with focus on patient centricity. This was reflected in availability of very high-quality data; KCCQ data were available for most of the subjects in both studies at final visit. The mapping of ePROs and Censor based data are illustrated in figure 2.

From programming perspective, The accelerometer data presented all the elements and challenges of managing big data across all the 5 elements of Big data: a) Volume: Large amount of data from move monitor; b) velocity as for each time-point data spanned a period of 7 -days; c) variety- due to diversity of data, number of observations, and number of variables recorded, and associated metadata; d) veracity- ensuring quality and accuracy of data, and e) value- the value these data provided. In addition, complexity of analyses combined with huge volume was additional challenge.

While there was very small proportion of missing data generated by e-PRO instruments, there were differences in proportion of missing data from devices used at home versus at clinic. Data generated by accelerometer at clinic was more complete than data generated by move monitor used by patients at home.





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Case Study:

In addition, meta data, and data generated from accelerometers did not conform to AZ raw data standards and required additional effort in mapping to CDISC compliant data. At present, there are no standards for data generated from digital health devices that would enable uniform guidance to enable standardization to create submission ready datasets. FHIR and CDISC joint guidelines is positive indication of changing landscape and efficient use of clinical information for clinical research and were released after the completion of these two trials.

Despite all the challenges, the data from these studies provided unique opportunity for programming team to innovate, build capacity, and gap analyses to identify the areas of innovation to continue to maintain and sustain delivery of high-quality clinical trials



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Case Study-Lessons Learnt:

- ❑ Advances in computing, multifold increase in storage and transmission capabilities, and e-PROs (Electronic Patient Reported Outcomes), e-COAs (Electronic Clinical Outcome Assessments), and sensor-based data requires statistical programming groups to integrate big data computing environment and skills to leverage the changes for efficient clinical trials. It will require IT infrastructural changes at organizational level, and acquiring additional skills and use of programming languages along with SAS (R, python, etc.)
- ❑ Metadata based repositories, standardization of Digital Health meta data that is compatible with CDISC standards are going to be evolving areas for future. HL7 (Health Level Seven International). (FHIR= Fast Healthcare Interoperability Resources) and CDISC mapping initiative is significant step in incorporating remotely captured clinical data from health systems into clinical research by mapping these data to CDISC standards.
- ❑ Interoperability of Digital health data and ability to run on general computing forms, and transmission along with user-friendly APIs will enable programming groups to leverage and utilize the data efficiently and unlocking the value. It will also require the shift in the way databases are designed at maintained at present.
- ❑ Missing data due to complexity of Digital Health Device, device failure, transmission failure, or insufficient training to patients can affect quality of data in significant way. Close coordination of Biostatics, programming, and data management group in defining Risk Management Plan to minimize missing data due to non-compliance, software upgrades, interoperability of systems, or due to trial participant errors is going to be essential component of future clinical trials.



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Case Study-Lessons Learnt:

- Amount of missing data from digital health devices potentially can impact quality of data or due to intercurrent events. Mapping the MI imputed data into ADAM CDISC compliant dataset requires additional discussions.[9] There should be discussion with CDISC for guidance to map MI based data to BDS structure in future.
- High volume of data that will require change in infrastructure to transform and process the data at programming level, it will require discussions with regulatory agencies due to restrictions on data-size in e-CTD (Electronic Common Technical Document) transmission. The interim options currently in use are to split the data into multiple CDISC datasets and provide only essential data generated from digital health devices as prespecified in protocol with traceability in place along with standardized metadata for additional data. The other data generated in Digital Health or device employing trials although not a crucial part of the analysis, needs to be retained in SDTM for device data retention and traceability, purposes in case of future questions and response letters, queries from Regulatory agencies during submissions.



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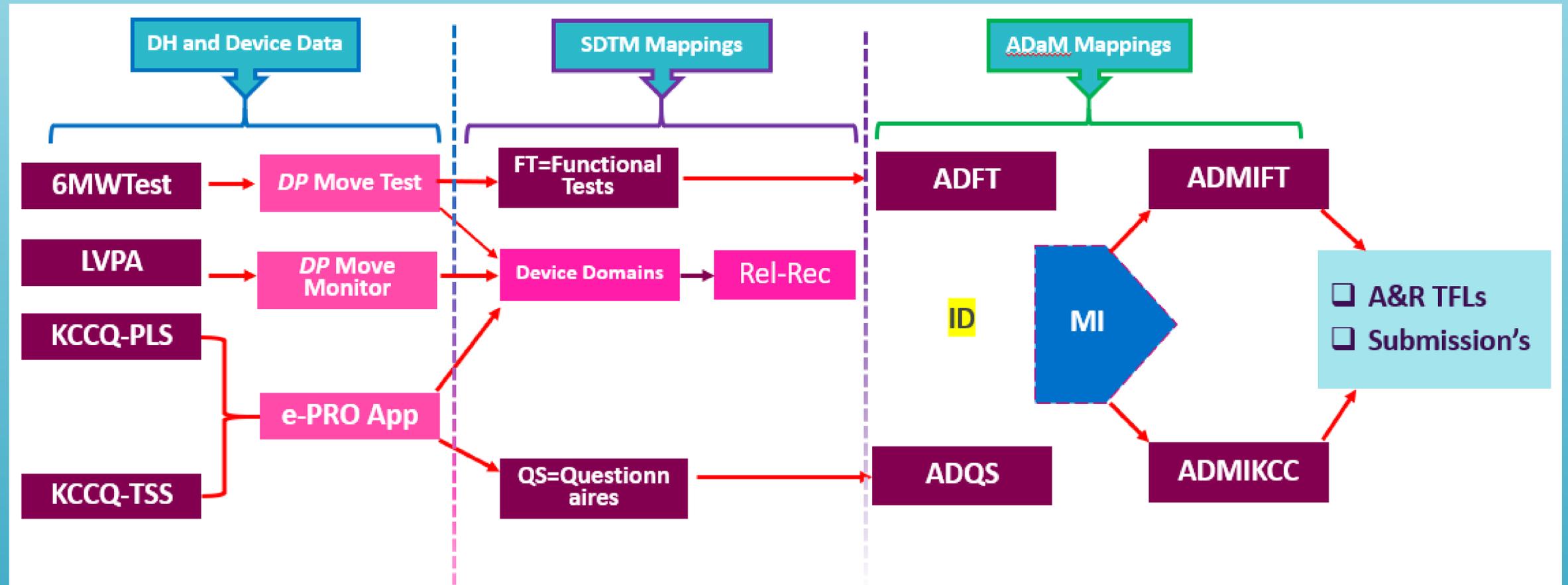
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Case Study-Lessons Learnt: Data Mapping Process Employed



Figures 2: Implicating the Mapping process for the Device and DHT Data from Raw Data Collection to Submission, 6MWTTest= Six Min Walk Test, LVPA= Light to Vigorous Physical Activity, PLS= Physical Limitation Score, TSS=Total Symptom Score, ID=Intermediate Datasets, MI=Multiple Imputation, AD=ADaM, A&R=Analysis and Reporting.





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This poster outlines the integration and increasing importance of digital health technology in clinical trials in capturing PROs, COAs, and censor-based data and accompanying changes required (and underway) in clinical trials operations, methodology, regulatory landscape. It also requires enhancement of IT infrastructure and analytical capabilities and evolution of biometrics groups to leverage the benefits and minimize the risks by implementing Risk Management Plans. Biometrics groups will continue to evolve to incorporate technology, computing environments, and skill uplifting. With decentralized trials becoming more common, programming groups are redefining the organizational set-up, job descriptions, skill requirements/enhancements to manage the clinical trials of future with efficiency, reduced costs, with increased likelihood of improved outcomes.

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