Paper ET14

Recasting Trial Designs with Digital Endpoints

Key Considerations from Design to Reporting

Kishore Shyamala, Algorics, India

Sugumaran Muthuraj, Algorics, India

ABSTRACT

The use of digital endpoints has become a topic of interest in recent times, given its ability to maximize efficiency and enhance patient centricity in clinical trials. While digital endpoints have several advantages, Complex Innovative Trial Design (the CIDs) program has recommended the use of scientifically driven methods to determine trial designs for digital or novel endpoints. Thus, digital trial designs must be evaluated for their suitability, selection of patient populations, treatment arms, complex therapies, and safety concerns.

This paper discussed various adaptive trial designs suitable for digital endpoints and a roadmap to achieve standardization of digital endpoints design, collection, and reporting.

INTRODUCTION

The adoption of Digital Health Technology (DHTs) has increased in the past few years, specifically in the post-pandemic world. One of the breakthroughs of using DHTs is using Digital Endpoints (DEs) offers advantages such as reducing the patient burden and wide use of Internet of Medical Things (IoMT) as an alternative to traditional endpoint assessment, Fig. 1 shows the key areas of digital data sources used widely across digital trials and decentralized Trials. Using these digital data sources in digital trials / hybrid trials helps in patient recruitment, digitalizing the existing endpoints, novel endpoints, patient outreach and diversity, and patient monitoring outside of the clinical setting for increased surveillance.

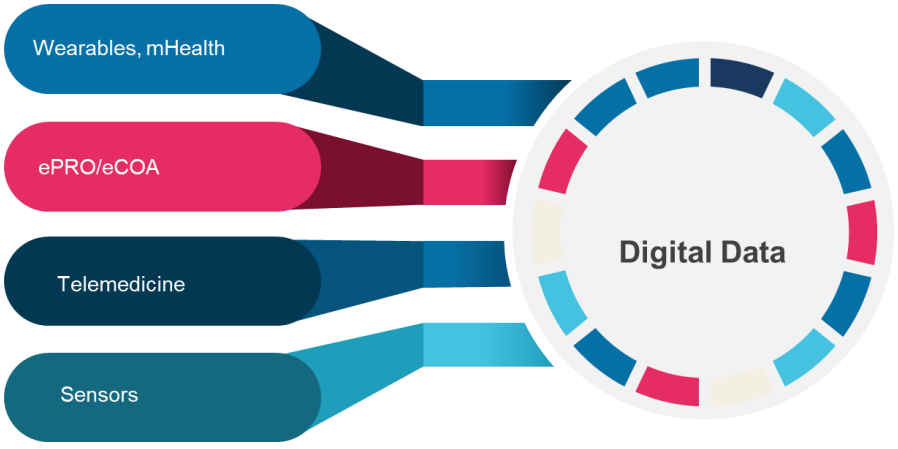
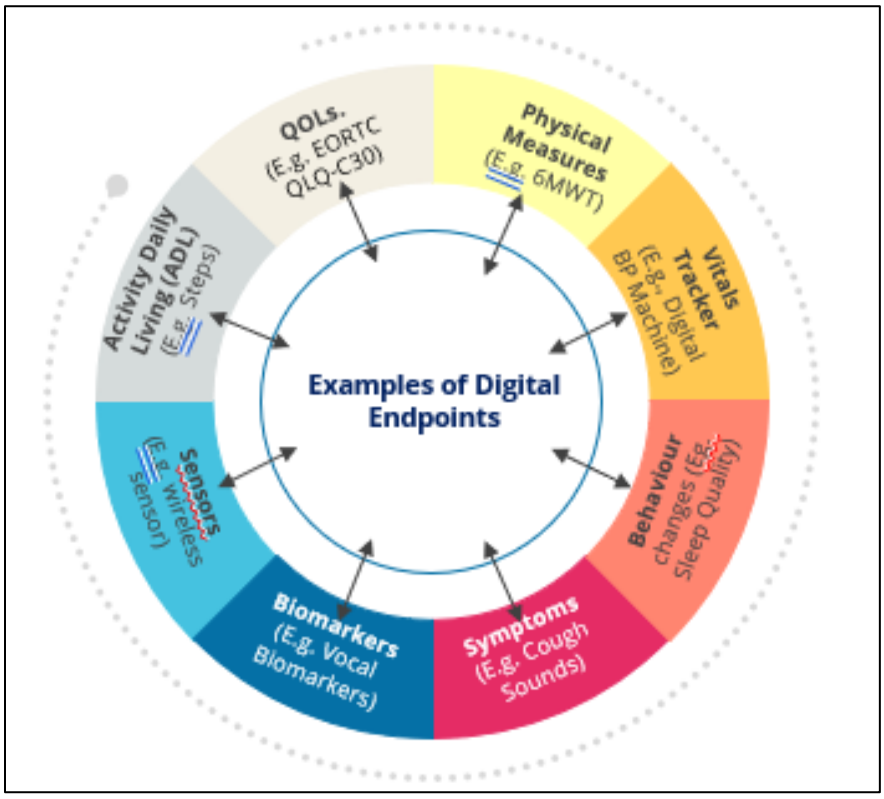


Fig 1: Key areas of Digital data sources

DIGITAL ENDPOINT ADOPTION

The use of digital endpoints and their existence were discussed in various industry forums. One such forum where a survey was conducted among sponsors on the use of digital endpoints (reference provided). Based on the results, it was evident that digital endpoints are being used as primary or secondary endpoints and are largely used in early phase studies (specifically Phase 2). Further, a detailed analysis of the type and indication where Digital endpoints are used, Fig. 2 shows the various type of digital endpoints such as physical measures, monitoring, behavioral, biomarkers, and Activity Daily Living (ADL).



Indications:

- Rheumatoid Arthritis
- COVID-19
- Axial Spondylarthrosis
- Asthma
- Congestive Heart Failure
- ADHD
- Parkinson's Disease
- Alzheimer's disease

Fig 2: Type of Digital Endpoints

QUALIFIED DIGITAL ENDPOINT-END-TO-END STRATEGY

Though Digital Endpoints are being used widely, qualifying the digital endpoints is a demanding zone for Clinical Research, considering the limited knowledge of the outcome measures. Therefore, detailed planning is required, and Fig. 3 shows our proposed end-end strategy for qualifying digital endpoints, which includes design, collection, and reporting considerations.

Further, to make a data-driven decision, leveraging the retrospective data collection and using prospective trials for effective digital endpoint trials.

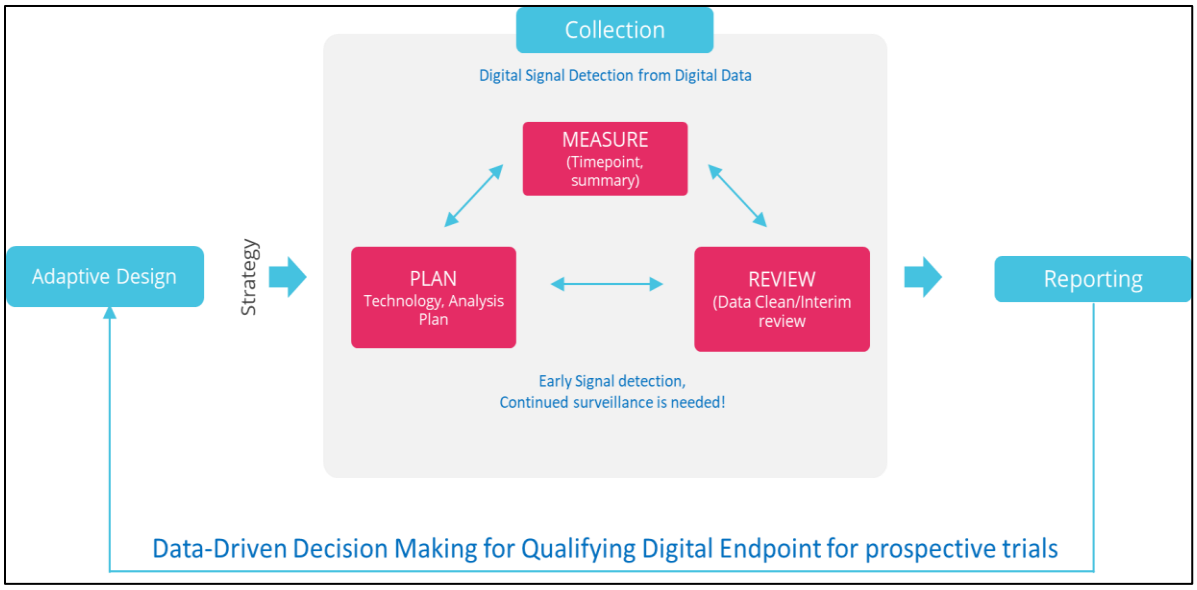


Fig 3: End-End Strategy for Qualifying Digital Endpoints

DESIGN CONSIDERATIONS

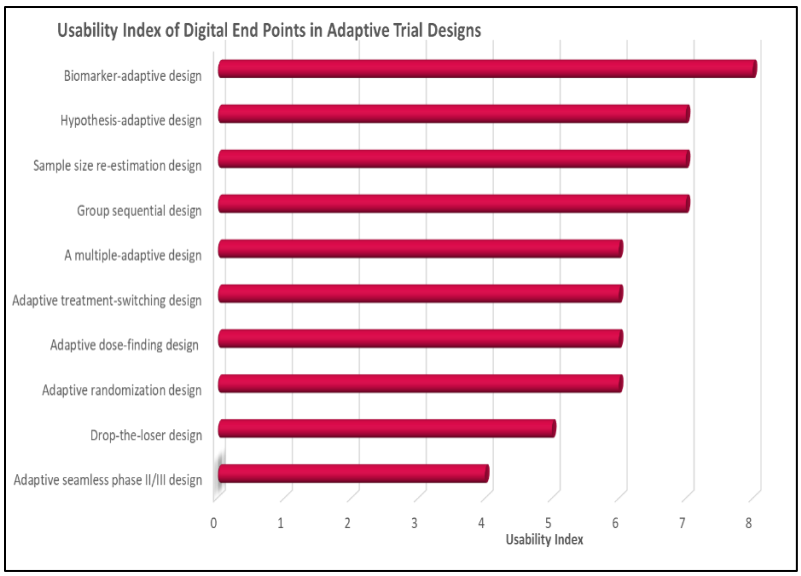
Using an adaptive design alternative to traditional design needs various considerations. Starting from the disease landscape (only for those diseases under study where potentially digital data sources or In-Home procedures could be used), the trial is for new indications/therapeutic areas, protocol optimization (specifically tailoring the visit schedules if it is a hybrid model), any previous trial simulations which have a proven result of usage of existing endpoints and using in synthetic control arms. The other important element of using the adaptive design is the choice of digital data sources, such as the most widely used data sources such as EHR/EMR, validated ePRO/eCOA, Wearables/mHealth, Digital Biomarkers, and sensors.

Based on our assessment and experience, we have looked at various adaptive designs used for digital endpoint evaluation. Each adaptive trial design was scored on the likelihood of usage depending on the digital data sources.

Based on the expertise, the Usability Index scale from 0 to 6 (or more than 6) was rated among each trial design to determine the consideration of DEs in Adaptive Trial Design. The scale has been rated as follows:

0 – 2	Less Likely
2 – 4	Moderate Likely
4 – 6	Likely
>6	Most Likely

Fig. 4 shows that Biomarker-adaptive designs, Hypothesis-adaptive designs, and Sample size re-estimation designs are more likely to be used for digital endpoints.



Top 3 Designs

Biomarker Adaptive Design: Digital biomarkers are being used widely. If clinical outcome assessment is a biomarker, the biomarker-adaptive design is preferred.

Hypothesis Adaptive Design: Digital Data such as EHR, Patient-reported outcomes (e.g., Symptom severity and QoL) are suitable for hypothesis adaptive designs based on the treatment responses/effects.

Sample Size Re-estimation: For the time-to-event endpoints, such as time to disease progression/modifications, allows to update of the sample size needed to detect a treatment effect.

Fig 4: Digital Endpoint vs Adaptive Trial Designs

COLLECTION CONSIDERATIONS

Digital Data collection and processing is another challenging area due to its abundance and data type. Fig. 5 shows the 4-way process roadmap for effectively managing digital data for endpoint evaluation. A clear data acquisition strategy, including a data flow map and integration, helps consolidate the data collected from different sources. Next is recruitment and engagement, ensuring the patient's accessibility, training, and ease of use. After these steps and once the data starts collecting, data surveillance capabilities must be implemented to manage the data through the clinical trial period.

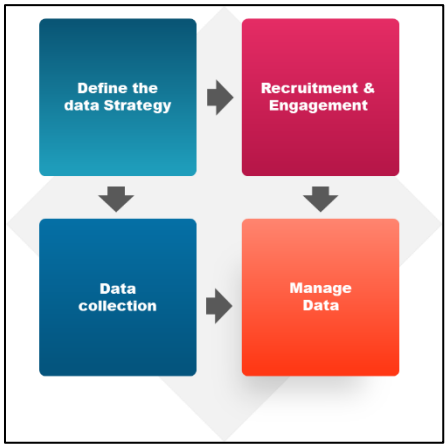


Fig 5: Roadmap for managing Digital Data

In addition, using analytics for real-time patient monitoring allows the data reviewers to review the patients and address any data quality issues centrally. Fig. 6 shows the various types of metrics that were collected from activity and sleep tracker.

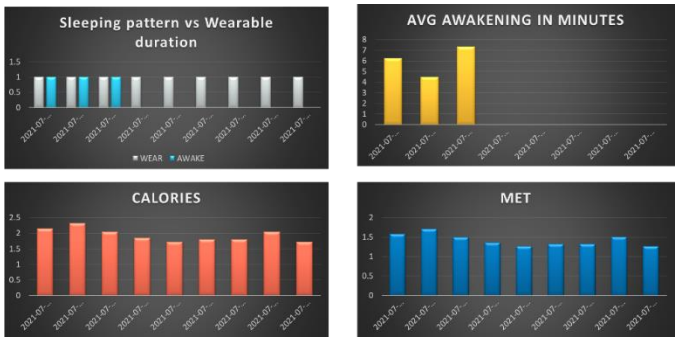


Fig 6: Metrics derived from Digital Device

REPORTING CONSIDERATIONS

The process roadmap for reporting of digital endpoint has a 4-way approach outlined in Fig. 7 It starts from reporting strategies such as a tailored Statistical Analysis Plan, selection of reporting/target variables, and mock or template reporting specifications. Further, for analysis, creating mapping data based on CDISC standards (SDTM/SDTM-like) with a specific focus on the target variables. Finally, the data will be analyzed, and reports, including TFL, will be generated for regulatory submissions.

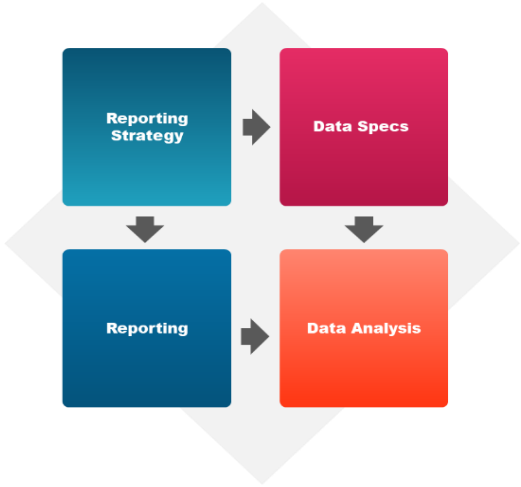


Fig 7: Considerations for Reporting DEs

CASE STUDY: USING WEARABLE DEVICE AS A DIGITAL ENDPOINT

A recent study used wearable device (activity tracking) data as an endpoint. The iterative steps outlined in the previous sections of this paper were followed and delivered efficiently. The steps followed include:

- Proposed hypothesis-adaptive design was used as a trial design.
- Statistical Analysis Plan & Data Management Plan were tailored specifically to the wearable device data.
- Determined what's a digital signal (Alerts)
- Time-point assessment of wearables largely decided based on ADL (Activity Daily Living)
- Data collected and integrated into a centralized location for the analytics (patient monitoring)
- Data Review and Cleaning.
- Standardized Data Mapping specifications as per CDISC Standards

SWOT ANALYSIS

Based on our assessment, the below table provides a high-level SWOT analysis that could be considered when we are assessing and qualifying the digital endpoints.

STRENGTHS • High Enrollment Rate • Beyond the boundaries (Simple wearables to sensors). • Innovative Designs	**OPPORTUNITIES** • Wide use of IoMT- leading to wide Patient reach out. • Could help in Precision/Personalized Medicines.
WEAKNESSES • Lack of Harmonization guidelines. • Transition from traditional to Digital CTs could be time-taking. • Digital Endpoints need to be qualified. • Data Collection Errors, Loss of Data.	**THREATS** • Data Privacy and Security • Moving away from Scientific intervention • Patients might be overwhelmed by using devices (elderly population)

CONCLUSION

Digital endpoints have numerous advantages in today's clinical digitalization world. However, meticulous planning and an unambiguous strategy are required for design, collection, and reporting. During the planning stage, the application of adaptive trial designs depending on the category of digital data sources is a critical decision. Further, the use of a robust technology platform would help to seamless ingestion and integration of digital data into a centralized location. A centralized review of the review would enable faster clinical decision-making.

Finally, creating a standard framework for reporting digital endpoints based on CDISCs structure (SDTM/SDTM-like) would support the regulatory submission. Consequently, a constant evolution of this topic is much needed for fine-tuning the approach and effective usage of qualified digital endpoints for prospective clinical trials.

REFERENCES

- *https://pharmrev.aspetjournals.org/content/72/4/899*
- *https://www.healthxl.com/blog/healthxl-report-clinical-trials-optimization-with-digital-health*
- *https://medcitynews.com/2022/05/digital-endpoints-global-opportunities-and-clinical-data-protection-and-other-challenges/*
- *https://altoida.com/blog/digital-endpoints-in-clinical-trials-for-neurology-benefits-and-impediments-to-adoption/*
- *https://www.nature.com/articles/s41746-019-0090-4/tables/1*
- *https://www.nature.com/articles/s41746-020-0227-5*
- *https://www.clinicalleader.com/doc/digitally-enabled-clinical-trials-a-practical-guide-0001*
- *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8894614/*
- *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9641516/*
- *https://www.karger.com/Article/Fulltext/525255*
- *Solving the Data Management Challenge in Digital Clinical Trials (appliedclinicaltrialsonline.com)*

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the authors at:

Kishore Shyamala

Algorics

#1-1-37, CP Chambers, 1st Floor,

Street No: 5, Habsiguda,

Hyderabad / 5400007

Email: kishore.shyamala@algorics.com

Web: www.algorics.com

Sugumaran Muthuraj,

Algorics,

SanHasa Square,

3rd Floor A-Wing, #17, Bharathi Park 3rd Cross,

Saibaba Colony,

Coimbatore / 641043.

Email: sugumaran.muthuraj@algorics.com

Web: www.algorics.com