HPR173

Regulatory Landscape, Challenges and Trends in the Adoption of Digital Endpoints in Clinical Trials

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Introduction

- The integration of digital health technologies (DHTs) into clinical research has facilitated the emergence of novel digital endpoints.[1-2]
- These endpoints can be collected outside conventional clinical settings, allowing for high-frequency and sensitive measurement of health outcomes.[1-2]
- Regulatory authorities and Health Technology Assessment (HTA) bodies are progressively recognising the value of digital endpoints, with several issuing guidance to support their development; however, significant variation exists in the acceptability and adoption of digital endpoints across different markets.[3-5]
- The objective of this research was to synthesise current knowledge on digital endpoints and assess the implications for regulatory approval and reimbursement decision-making.

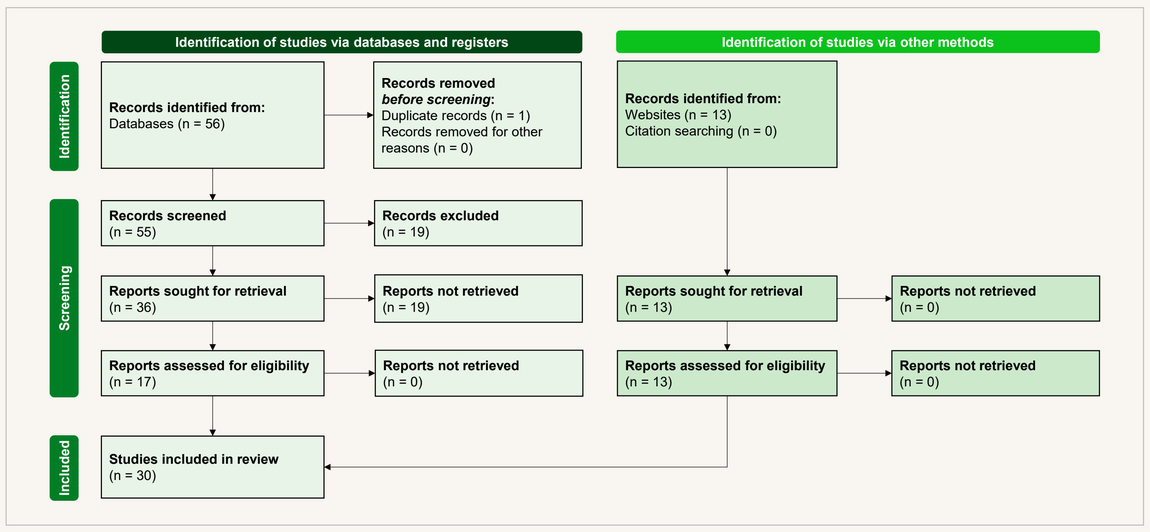
Methods

- A comprehensive scoping review of the published literature was conducted.
- Sources included peer-reviewed journals and grey literature from industry bodies, payer organisations, and relevant regulatory and HTA authorities.
- Publications were eligible for inclusion if they addressed: i) regulatory considerations relevant to digital endpoints, or ii) the appraisal of digital endpoint data for product value assessment within HTA processes.
- Verbatim extracts from relevant discussions of digital endpoints were captured using a standardised charting form and coded by a single reviewer.
- Coded data were analysed to identify descriptive and overarching analytic themes reflecting the current landscape for digital endpoints.[6]

Results

- Bibliographic database searches identified 55 unique records for title and abstract screening.
- Of these, 36 publications were selected for full-text assessment, with 17 ultimately included in the review.
- Grey literature searches yielded 13 records, all of which were included.
- In total, 30 articles were incorporated into the final review; a combined PRISMA flow diagram is presented in **Figure 1**.
- Descriptive themes were consolidated into four analytical categories, highlighting key challenges and trends in the use of digital endpoints: relevance and impact; regulatory aspects and barriers; qualification for product approval; and reimbursement.
- Key insights from each analytical category are summarised in **Figure 2**.

Figure 1. PRISMA diagram of the literature search and inclusion of publications in the review



Conclusions

- Digital endpoints present promising opportunities to capture a more authentic assessment of the patient's experience and enhance the sensitivity of clinical trials.
- While the foundational principles for developing digital endpoints are broadly aligned with those for traditional endpoints, uncertainties persist regarding validation and qualification processes and evidentiary standards for establishing clinical relevance.
- Addressing these gaps is essential to fully realise the potential of digital endpoints in supporting regulatory and HTA decision-making.

Abbreviations

DEEP=Digital Evidence Ecosystem and Protocols; DHT=digital health technology; DiGAs=digital health applications; DMD=Duchenne muscular dystrophy; EDiHTA=European Digital Health Technology Assessment; EMA=European Medicines Agency; HTA=Health Technology Assessment; IHI=Innovative Health Initiative; Q&A=questions and answers; QoNM=Qualification of Novel Methodologies; ROI=return on investment; SV95C=Stride Velocity 95 Centile.

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Figure 2. Overview of the key takeaways from the identified literature for each analytical category

Challenges & opportunities

Impact

- Digital technologies enable high-frequency data collection and promote clinical trial decentralisation.
- Highly sensitive digital measures of disease can reduce the sample size required to show significant benefit of intervention.
- Deploying digital measures in clinical trials offers substantial value by reducing uncertainty, thereby enabling more robust and confident go/no-go decision-making.
- Digital medication adherence systems offer a promising opportunity to improve patient adherence, enhance clinical outcomes, and achieve cost efficiencies in care delivery.

Regulation

- Definitions of ‘digital endpoint’ and ‘digital health technology’ differ between regulatory bodies and global markets.
- DHTs that also meet the definition of a medical device are subject to medical device regulatory oversight.
- Regulatory acceptance of digital endpoints must balance potential benefit with potential harm e.g., worsening of health inequality due to access to digital technology.

Qualification

- The European Medicines Agency (EMA) expectations for digital endpoints have been established in guidance documents.
- Transition of digital endpoints from exploratory to capable of supporting label claims requires the existence of population-specific reference values.
- Clinical validation stands as a significant challenge, as there are no specific guidelines orienting the validation of digital endpoints.

Reimbursement

- Digital endpoints create an opportunity to generate continuous and objective evidence, which better reflects the burden of disease and the value of interventions.
- Developers of digital endpoints need to demonstrate how these endpoints relate to patient quality of life.

Trends & Milestones

2005

- Digital endpoints registered in a clinical trial (restless leg syndrome)

2019

- The Digital Evidence Ecosystem and Protocols (DEEP) platform is founded to facilitate the collaborative development of novel clinical endpoints for clinical trials
- EMA defines “digital technology-based methodology” as “the specific use of a methodology in the development, use, or monitoring of medicinal products pre- or post-authorization”
- EMA qualifies the digital outcome measure Stride Velocity 95 Centile (SV95C) as a secondary outcome for trials in Duchenne muscular dystrophy (DMD)
- NICE develops the first draft guidance for the evidence standards framework for DHTs, to promote more consistency in the evaluation of digital health technologies;
  The German government establishes a new evaluation procedure for digital health applications (DiGAs) to facilitate their reimbursement by statutory health insurance

2020

- EMA creates several pathways for sponsors to receive feedback on digital technologies that are intended to measure novel endpoints:
  - Sponsors can seek advice through the scientific advice procedure, whereas the qualification of novel methodologies for drug development procedure can be followed if the technology has been developed independent of a specific product
- EMA publishes Questions and Answers (Q&A) guidance:
  - “Qualification of digital technology-based methodologies to support approval of medicinal products”

  The alternative assessment pathway is established using the EMA's Qualification of Novel Methodologies (QoNM) platform

2021

- The Innovative Health Initiative (IHI) is created, supporting projects working on health-related mobile and digital technologies such as MOBILISE-D and IDEA FAST
- EMA issues guidance:
  - “Computerised Systems and Electronic Data in Clinical Trials”
- The European Digital Health Technology Assessment (EDiHTA) consortium commences developing the first framework for evaluating digital health technologies across Europe

2023

- EMA qualifies SV95C as a primary outcome for trials in DMD

2024

- 18 interventional trials register at least one digital endpoint (1700% increase compared with 2005)

  Therapy areas include:
  - Women’s health
  - Cardiovascular disease
  - Diabetes
  - Musculoskeletal disease
  - Respiratory disease
  - Cancer

2025

- Early evidence suggests that, for Phase III trials, return on investment for digital endpoint development may be up to six times development costs