The 3Ps of Digital Endpoint Value

PATIENTS · PHARMA · PAYERS

Using evidence from digital endpoints to demonstrate the value of a new drug: Considerations and recommendations

April 2022

Great progress has been made in the development and evaluation of digital endpoints as fit-for-purpose drug development tools (DDTs), allowing us to measure a wide range of concepts of interest relevant to the patients' lived experience: we have recently seen the first qualification of a digital endpoint by a regulatory authority, and many other candidates are in various stages of maturity and acceptance by industry.

The Digital Medicine Society (DiMe) convened partners from Anthem, Biogen, Evidation, Janssen, Lilly, Merck, Savvy Coop, and Pfizer to ensure patient-centric digital endpoint evidence can be used not just for registration, but for bringing new medicines all the way to the market and to the patients who stand to benefit the most. For digital endpoints to deliver value throughout the entire drug development lifecycle, evidence generated from digital clinical measures must also be suitable for use in value and reimbursement discussions by payers and health technology assessment (HTA) agencies.

Contents

The Integrated Evidence Plan

Integrated Evidence Plans (IEPs) are processes and documents which outline a strategy to connect labeling concepts (i.e. the claims associated with a new drug) to the evidence-generating trials and studies in the drug program.

IEPs will be critical to:

1. Generating the **evidence** needed to support the use of digital endpoints to **evaluate new drugs** and other medical products
2. Assessing that evidence for **registration**, **reimbursement**, and **value**

IEPs are a conscious effort to avoid siloed thinking in drug development and ensure that all stakeholders throughout the process are focused not just on registration, but on bringing new medicines all the way to the market and to the patients who stand to benefit the most.

Building upon previously generated data, and planning for data that needs to be generated, IEPs focus on evidence that needs to be generated to advance decision-making for **multiple stakeholders**.

The IEP "defines how the evidence will be generated within each clinical trial and real-world observational study, and how this will be leveraged to satisfy **patient**, **physician**, **provider**, **payer**, and **regulatory** requirements". When evidence to support value and reimbursement discussions are generated early in development of the drug, IEPs facilitate securing a positive recommendation from HTA and regulatory authorities.

Although IEPs look slightly different from company to company, they all aim to **increase productivity** by helping pharma companies plan for and assess the likelihood of getting a product to market. In the digital era of health, they offer a path to defining and committing to opportunities for digital endpoints to move beyond "nice to have" and become "must have" because they are an agreed upon, critical part of the evidence supporting commercialization.

Accelerating the adoption of evidence from digital endpoints in reimbursement and value

Three stakeholder groups are critical to ensuring that evidence from digital endpoints is acceptable for reimbursement decisions:

1. **Pharmaceutical companies** developing new drugs and other medical products evaluated using data derived from digital endpoints.
2. **Payer organizations** making reimbursement decisions about new drugs demonstrating their efficacy using data derived from digital endpoints
3. **Patients and patient groups** who are instrumental to establishing the value of evidence derived from digital endpoints

A secondary stakeholder group is vendors developing digital clinical measures for use as digital endpoints in trials of new drugs and other medical products.

The following recommendations are intended to help those developing and deploying digital endpoints as part of an evidence generation strategy supporting value and reimbursement discussions, or those assessing such evidence.

Recommendations for pharma

These recommendations are intended to help pharma stakeholders advance the acceptability of evidence derived from digital endpoints for payers.

Best practices throughout the drug development process

1. Engage with payers alongside regulators as soon as the decision to include a digital endpoint is made
2. Prepare to bridge knowledge gaps and requirements to demonstrate acceptability and value of digital endpoints to all stakeholders
3. Build your IEP before starting your clinical trials

> Repeatedly the payer stakeholders stressed the need for engagement with the different payer bodies in trial design, even in tool ideation phases to ensure that their perspective is heard and included. “Early and repeated payer interaction is the path forward if you want to change things.”
>
> *- National Payer*

To assist stakeholders from pharmaceutical and other companies who are developing new DDTs, drugs or medical products, the project team has developed this decision guide to facilitate inclusion of relevant, acceptable and informative digital endpoints into integrated evidence plans.

Recommendations during digital endpoint selection and development

1. Validate and evaluate digital endpoints against health-related quality of life (HRQoL) and patient-centric outcomes and patient reported outcomes (PROs) as well as established clinical outcomes
2. Investigate the relationship between digital measures and endpoints with long term outcomes and events
3. Include study design elements that allow for estimation of minimal clinically important difference (MCID).
4. Engage early with national healthcare standards bodies such as the National Quality Forum (NQF) in the US, as well as payers and regulators, to advance acceptance of the digital endpoint.
5. Develop evidence of acceptability and usefulness of a new measurement outside of clinical development.

> "To ensure full acceptability of the new measure, digital or not, it is essential to develop the tool with a high level of consensus between the different stakeholders; patients, subject matter experts (SMEs), regulators, payers etc. Validation is of less importance if the acceptability and appropriateness of the new tool is secured."
>
> *- National Payer*

6. Select endpoint(s) that are scalable for collecting evidence in the real world and fit-for-purpose across individuals and over time to account for the progression of disease and individual experiences.
    - For example, developing a suite of measures, ideally from a single digital measurement product, that is relevant across the patient experience (e.g. pre- and post- events, or different disease phases) and across individuals, or efforts to establish core measure sets for patient relevant measures (e.g. ambulation).

Recommendations during digital endpoint deployment

1. Prioritize collection of confirmatory evidence that shows scalability of new evidence as well as the relationship to accepted endpoints in clinical development (e.g. a real world equivalent of the six minute walk test)

2. Include outcomes that matter to payers in trials (e.g. medical cost usage, hospitalization)

3. Collect more real-world evidence (RWE), in parallel with digital endpoints, earlier in clinical development

Recommendations for payers

1. Align as an industry to provide consistent guidance to pharma and their partners developing and deploying digital endpoints on topics including
    - Evidence thresholds for acceptability of a digital endpoint in a given context, digital endpoint validation, and MCID
    - Appropriate instruments to use as comparators (e.g. for HRQoL)

2. Define pathways for pharma to engage with you early in their IEP development

3. Align further with regulatory decision-makers wherever possible to streamline the evidence generation process for digital endpoints and the new drugs they are evaluating.

Recent progress and existing efforts to align payer and regulatory decision-making are extremely valuable and encouraging.

- In the EU, the HTA-EMA collaboration includes the development of a parallel consultation process
- In the US, the Payor Communication Task Force aims to accelerate patient access to medical devices.
    - While there are still challenges remaining, successes have been achieved

Examples of misalignment across regulatory and payer decisions include

- Decisions related to aducanumab (Aduhelm) for the treatment of Alzheimer's disease
- Relevance of FEV1 as a measure in COPD

4. Consider the opportunity to encourage more personalized treatment regimes, for example by providing guidance on using digital endpoints to define treatable traits and benefits for individuals

Appendix 1: Methods

The Digital Medicine Society (DiMe) led a multi-stakeholder team including experts from Anthem, Biogen, Evidation, Janssen, Lilly, Merck, Savvy Coop, and Pfizer to host a series of workshops to develop a framework to support a transparent, consistent, and patient-centered decision process for digital endpoints as value-evidence in drug development.

The team chose case studies to explore during the workshops that:

1. Embrace a range of different indications and disease types (acute, chronic, episodic, special populations (e.g. pediatric))
2. Leverage examples of digital clinical measures already in use with patients in different contexts.

The team selected the following case studies:

U.S. focused workshop	European focused workshop
Non-sedentary behavior in Heart Failure	Stride velocity in Duchenne Muscular Dystrophy
Cognitive decline in Alzheimer's Disease	Motor scores in Parkinson's Disease
Steps-per-day in COPD	Steps-per-day in COPD

Workshop attendees included clinical experts, patients, advocates, payer and HTA representatives, pharma stakeholders, and regulators from the U.S. and Europe.

The workshop series was held virtually and took place in January and February 2022.

Appendix 2: Opportunities and challenges to using digital clinical measures to inform reimbursement decisions in drug development

The value of digital endpoints for reimbursement decisions

To date, digital clinical measures have primarily been developed for evidence generation in clinical development. For example, as endpoints for decision making during drug development and in anticipation of supporting registration of new drugs and other medical products.

Digital endpoints can capture high quality, high resolution data, including information about new facets of disease that have been previously impossible to measure, with little patient burden. As such, it is critical that pharma, payers, and patients intentionally plan for including such evidence in value and reimbursement discussions.

The value that digital endpoints offer to reimbursing and pricing decisions:

1. Digital endpoints are delivering **high quality evidence** across a range of therapeutic areas:
    - Clinical - tracking symptoms and exacerbations
    - Humanistic - Health Related Quality of Life (HRQoL), independence, activities of daily living
    - Economic - hospitalizations, readmissions, preventable increase in acuity
    - Risk reduction - predictive applications and stratification

2. Digital endpoints can support a **more complete** understanding of **patients' lived experience**: This includes the capabilities to:
    - Better measure, and in turn manage, daily fluctuations or cyclical changes in symptoms
    - Improve early detection
    - Lower the burden of assessment, often through passive data collection

> "No one understands my disease until they measure me at my best and at my worst: the best is the potential, and the worst is the opportunity"
>
> *- Patient Expert*
>
> "We are not introducing new measures because we can, but rather because they capture something new and relevant"
>
> *- Pharma Exec*

Patient stakeholders underlined the opportunity for "dual-use" of evidence: evidence as an outcome and as feedback to patients to support outcome improvement. This points to a further source of value:

3. **Evidence** for all '3Ps': **Pharma**, **payers** and **patients**. Digital clinical measures can provide valuable information to patients directly in addition to sponsors and reimbursement committees. Patients recognize the opportunity for outcome improvements by using digitally generated data to:
    - Plan and manage their day
    - Understand the benefits of treatment
    - Set goals and manage expectations
    - Communicate their symptoms to clinicians and caregivers
    - Provide more relevant information

    Our findings and existing evidence informs us that patients are very open to sharing data if it returns value to them through **better**, **more affordable** care.

Digital clinical measures can support value-based care models

Value based care require hard outcomes data, which can be more readily captured using digital clinical measures. Further opportunities for capturing evidence of value are possible when it is possible to treatment benefit for each individual patient.

1. **Early signals** captured with **high resolution** and **low patient** and **provider burden**.
    - Digital clinical measures can enable high resolution, predictive or prognostic measures that provide high quality indicators of hard clinical outcomes such as hospitalization.

With traditional tools, measuring outcomes that are predictive of future clinical state is often extremely burdensome to patients, often requiring a high degree of repetition and unclear value for the patient.

"Why keep asking me to come to the clinic to draw a circle when I couldn't do it the last time?"

- Patient Expert

2. More **complete** insights into the **patient experience**.
    - Currently, most measures are captured only sporadically, reflecting little of the daily lived experience of patients and missing short term symptom fluctuations.

The Integrated Alzheimer's Disease Rating Scale (iADRS) combines digital tools and long term clinical outcomes into a single outcome assessment. This adapted scale also includes long term changes relevant to patients with Alzheimer's disease and to payers.

3. **Personalized** definitions of **value** and **benefit**
    - Digital clinical measures can demonstrate benefit on an individual patient basis.

Enabled by profiling ability, personalized treatment regimes already exist in oncology. These personalized approaches have helped inform reimbursement decisions, but have required time and investment.

Technical and systematic challenges are inhibiting the use of digital endpoint data in value and reimbursement discussions

1. Data heterogeneity.
    - **Interpreting** the data generated by digital endpoints is **more challenging** when data is captured in the **real-world**, outside of the highly controlled clinical trials environment and with less information on possible confounders.

2. Confusion and knowledge gaps.
    - Currently, there is **widespread confusion** about what digital clinical measures are and what **value** they bring. For example, digital clinical measures that generate evidence in support of the performance of traditional medical products are often confused and/or conflated with digital medical products
    - Key stakeholders in reimbursement decisions, such as members reimbursement committees and actuaries, must be supported in **learning** and **active engagement** with this important topic.

3. Data availability.
    - Even when a digital endpoint is acceptable to payers, it may not yet be feasible to collect this evidence at scale in a general population.
    - Translation of digital clinical measures from use as endpoints in clinical trials to use as screening, monitoring, and diagnostic tools in routine clinical care is critical to generating high-quality digital data in real-world settings.

4. Generalizability of knowledge.
    - Currently, there is insufficient knowledge about how culture, socioeconomic status or language barriers impact acceptance and use of digital clinical measures.
    - Measuring the value of a treatment for every patient means that digital clinical measures requires must be used by every patient. More research is needed to establish best practices to ensure that digital clinical measurement is acceptable to everyone.

5. Scaling digital data collection.
    - Digital clinical measures offer a low-burden, cost effective way to capture baseline and population-level data to use as comparator data. However, widespread monitoring requires broad trust and consent, which must first be earned through robust advances in privacy, security and infrastructure.

Appendix 3: Organizations Involved In The Workshop Series

Organizations on the DiMe project team

- Anthem
- Biogen
- Evidation
- Janssen
- Eli Lilly and company
- Merck
- Pfizer
- Savvy Coop

Organizations represented at U.S. workshop

- Patient experts and advocates, including The COPD Foundation and Savvy Cooperative
- U.S. Food and Drug Administration Health and Human Services (FDA HHS)
- Anthem
- Bind
- Current Health
- Cambridge Cognition
- Evidation Health
- Abbvie
- Biogen
- Eli Lilly and company
- Janssen
- Merck
- Pfizer
- Roche
- American College of Cardiology
- UC Irvine
- University of Pittsburgh

Orgs represented at Europe workshop

- Patient experts and advocates including Parent Project Muscular Dystrophy, The Parkinson's Foundation and Savvy Cooperative
- European Medicines Agency (EMA)
- Norwegian Medicines Agency (NoMA)
- Anthem
- GKV-Spitzenverband
- Health Innovation and Technology Transfer Foundation
- Biogen
- Eli Lilly and company
- Evidation
- Janssen
- Merck
- Pfizer
- Roche
- University of Oxford