

DTx Real-World Evidence in Practice: Pragmatic Clinical Trials as a Compelling Approach to Inform Healthcare Decisions

What is a pragmatic trial?

A pragmatic clinical trial is a research study that evaluates the impact of an intervention or usual care on a group of participants who are representative of those usually affected by the condition under investigation in real-world clinical settings.

What is real-world data?

Real-world data (RWD), derived from various sources like electronic health records, medical claims, disease registries, and digital health technologies (DHT), provides insights into routine healthcare delivery and patient health status.^{1,2}

What is a randomized pragmatic clinical trial (PCT)?

A randomized pragmatic clinical trial is a type of clinical trial designed to compare an intervention and a comparator (usual care) in participants who are more similar to those affected by the condition(s) under study in the real world.³

What is implementation science?

Implementation science can be described as a scientific field that focuses on methods to ensure that research findings and other evidence-based practices are systematically adopted into regular practice. This process aims to enhance the quality and efficiency of health services.⁴

What is the value of a pragmatic trial to a payor in decision making?

A pragmatic trial, as a component of implementation science, serves as a tangible piece of evidence for stakeholders. It provides scientific data on the effectiveness of a particular intervention (including usual care) and the patient's journey through it.

What does a pragmatic trial offer that an implementation pilot does not?

- Offers greater generalizability. Pragmatic trials demonstrate that the new intervention can be implemented throughout the entire ecosystem. Commercial implementation pilots typically involve smaller segments of a population versus the entire population.
- Allows a focus on patient journey outcomes, including patient activation, meaningful engagement, acceptability, patient-reported outcomes, and adherence, along with effectiveness outcomes that would not otherwise be collected in a pilot.
- Serves as a scientific resource and source of evidence for regulatory submissions and peer-reviewed scientific publications.

What is the value of a pragmatic trial for digital therapeutic (DTx) companies?

Overall, pragmatic trials help DTx companies gather real-world evidence (RWE), optimize product design and strategy, offer more flexibility to validate

1 <https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence>

2 https://www.researchgate.net/publication/363455794_The_Digital_Therapeutics_Real_World_Evidence_Framework_An_approach_for_guiding_evidence-based_DT_x_design_development_testing_and_monitoring/link/63448e7376e39959d6b34436/download

3 <https://www.fda.gov/about-fda/oncology-center-excellence/project-pragmatica>

4 <https://implementationscience.biomedcentral.com/articles/10.1186/1748-5908-1-1>

the effectiveness of their solutions, and support regulatory, payor, and clinician acceptance. Pragmatic trials offer several key advantages for DTx companies:

- **Timeline and Pipeline Considerations:** Depending on the development phase of the product, pragmatic trials can help evaluate real-world effectiveness, generate learnings around workflow optimization, and inform future development stages.
- **Evidence:** Shortens duration and cost of trials by rapid enrollment and less attrition, particularly if not randomizing to a concurrent control arm. Provides flexibility to create a robust external cohort arm (i.e., historical, concurrent) and enables easier recruitment of heterogeneous populations to the study. Also enables Health Economic Outcomes Research (HEOR).
- **Patient-Centered Approach:** DTx products are typically designed to be patient-centered, with a focus on personalized treatment (“N of 1”). Pragmatic trials enable the evaluation of these solutions in real-life settings that closely match the individual circumstances of patients.
- **Phases of Product Release:** Pragmatic trials can be particularly valuable during limited market releases (LMR) or pilot launches. These trials can provide valuable data that inform marketing strategies and reveal potential areas for clinical improvement.

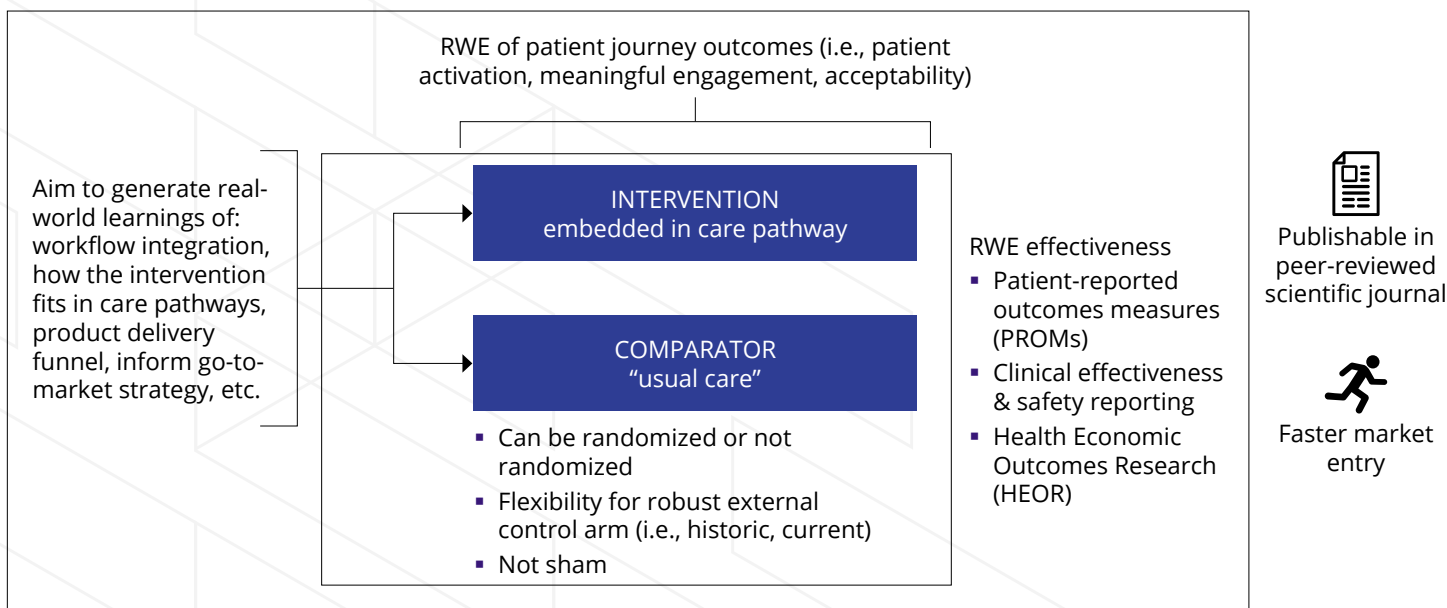
- **Limited Launch:** During the initial product release, pragmatic trials can help assess product effectiveness and identify any unforeseen issues in a controlled setting.
- **Limited Market Releases (LMR):** In this phase, pragmatic trials can support more marketing than clinical objectives by demonstrating the product’s performance in diverse real-world settings (patient journeys) and showcasing its adaptability and utility for potential users.

What are the most effective applications of pragmatic trials, and in which areas do they make the most significant impact or difference?

Pragmatic trials have a significant impact on healthcare and the medical industry. Their value is multifaceted, with critical aspects as follows:

- **Scientific Resource:** Pragmatic trials function as a rich scientific resource due to their design closely mirroring real-world conditions. This makes the data gathered during such trials valuable for studying the effectiveness of interventions in a real-world setting beyond the controlled environment of traditional clinical trials.
- **Regulatory Submissions:** The data from pragmatic trials can serve as robust evidence in

Figure 1. Schematic of a pragmatic clinical trial, highlighting key aspects of study design and additional outcomes that generate value compared to a non-pragmatic clinical trial.



regulatory submissions. Since these trials reflect the performance of interventions under typical clinical circumstances, they provide the kind of data that regulatory agencies value when considering approval.

- **Scientific Publications:** Pragmatic trial outcomes form the basis of substantial, peer-reviewed scientific publications. They contribute to the body of scientific literature and foster the development and enhancement of medical knowledge.
- **Go-To-Market Strategy:** Pragmatic trials can significantly influence the go-to-market strategy for new interventions. The evidence from such trials can be used to make compelling claims about the

intervention's effectiveness and cost-effectiveness in real-world settings, enhancing its appeal to healthcare providers and patients.

- **Faster Market Entry:** With the evidence generated from a pragmatic trial, medical companies can streamline their marketing and adoption strategies, leading to quicker market penetration. This results in faster returns on investment and potentially broader patient access to the intervention.

Overall, pragmatic trials play an instrumental role in improving healthcare delivery by contributing valuable real-world data, fostering regulatory approval, and promoting the adoption of new treatments and interventions.

Meaning of "Usual Care"

"Usual care" is an important consideration in a control arm design.

Usual care can be a control arm in real-world evidence (RWE) and pragmatic studies involving DTx products. Defining "usual care" as a control arm design in pragmatic studies is crucial, as it enables more accurate decision-making by reflecting the real-world advantages, challenges, and risks of health interventions, thereby enhancing the relevance and applicability of study results.

Why is "usual care" the most suitable term as a comparator in pragmatic real-world studies?

"Usual care" reflects real-world practices rather than an ideal "standard of care" and is a more realistic and applicable comparator in a multi-site study context. It is informative and suggests a practical approach towards healthcare research. It also provides flexibility to create a robust external cohort arm (i.e., historical, concurrent).

Why is Usual Care preferred to Standard of Care?

1. Usual care takes into consideration the variability in real-world healthcare delivery across a multi-site and geographically diverse study.

2. **Reflects real-world practices:** Usual care aligns with authentic treatment practices observed in everyday healthcare scenarios, offering a more grounded point of reference.
3. **Accounts for variability:** It considers the variations in healthcare delivery across different sites or health systems, unlike an idealized "standard of care."
4. **Avoids specificity:** It allows for a degree of flexibility, avoiding overly specific definitions that may not apply universally across different health systems or settings.
5. **Applicability:** Usual care is typically what is administered in a given health system, making it more applicable and relatable for the study participants.
6. **Practicality:** It represents the treatment that patients are most likely to receive, thus enhancing the practicality and relevance of the study results.

DTx products with "Usual Care" as the comparator show an incremental value over existing treatment options.

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