

White Paper

# Pragmatic Trials: Clinical Evidence for the Real World

By Carolyn Gretton

October 2026



# Table of Contents

|                                      |    |
|--------------------------------------|----|
| Introduction                         | 03 |
| Not new, but adoption growing        | 03 |
| Advantages of pragmatic trial design | 05 |
| Some challenges exist                | 06 |
| Connection with RWE                  | 07 |
| Continuum rather than choice         | 08 |
| Conclusion                           | 11 |
| About the Author                     | 12 |
| References                           | 13 |
| About Citeline                       | 15 |

## Introduction

Traditional randomized clinical trials study the effectiveness of treatments delivered to carefully selected populations under ideal conditions. However, their results often are difficult to translate to the real world, and systematic reviews of these trials consistently find evidence is lacking to effectively inform care decisions providers and patients must make. Plus, patients with complex comorbidities, socially diverse patients, and those most in need often are not being reached by traditional trials.

The upshot: Results generalized under idealized conditions can be difficult to apply to the realities of clinical practice. Also, insufficiently diverse trial populations may overstate the therapeutic agent's effectiveness and fail to identify variations across subgroups. For

example, while a treatment may prove effective in relatively healthy, middle-aged trial participants, frail elderly patients with complex needs may not respond as robustly.<sup>1</sup>

Pragmatic clinical trials are designed with input from health systems, providers, and patients, producing evidence that can be used to improve care and accelerate the integration of research, policy, and practice.

Pragmatic trials include diverse populations and are constructed around the standard healthcare operations of practitioners and patients. The pragmatic study protocol is flexible, minimizing intrusion into the daily workflow of healthcare practitioners and the day-to-day activities of patients.

## Not new, but adoption growing

The concept of pragmatic trials is not new. In 1967, Daniel Schwartz and Joseph Lellouch proposed the distinction between pragmatic and explanatory trials. They described explanatory trials as measuring whether a treatment can work under ideal conditions and pragmatic trials as determining whether a treatment does work in the real-world clinical settings where it will actually be used.<sup>2,3</sup>

While this concept has been around for decades, pragmatic trial adoption has accelerated sharply over the past few years amid regulatory momentum behind real-world evidence (RWE), a maturing real-world data (RWD) infrastructure, and mounting pressure to make clinical trial populations more representative. These factors have made the pragmatic approach to trials more feasible and valuable.

Randomized pragmatic clinical trials are designed differently from traditional randomized trials by integrating prospectively collected RWD and involving participants more similar to those affected by the condition under study in routine clinical practice settings.<sup>4</sup> Some examples of these RWD include medical claims; lab tests and results, including biomarkers and genomics; electronic health records (EHRs); census data; and Centers for Medicare and Medicaid Services (CMS) data. By incorporating design elements more reflective of these settings, the study can account for how to optimize an intervention within busy, diverse clinical practice settings and come closer to illustrating how the intervention will impact a patient's condition in the real world.<sup>4,5</sup> Pragmatic trials can result in decreased burden of trial participation, more diverse trial populations, speedier enrollment, and reduced attrition.<sup>4</sup>

A pragmatic trial often results in broader eligibility criteria, ease of recruitment and follow-up, flexibility in drug delivery, and more patient-centric outcomes. Of course, the flexibility of its design elements depends on the trial context, with patient safety and trial integrity always coming first.<sup>4</sup>

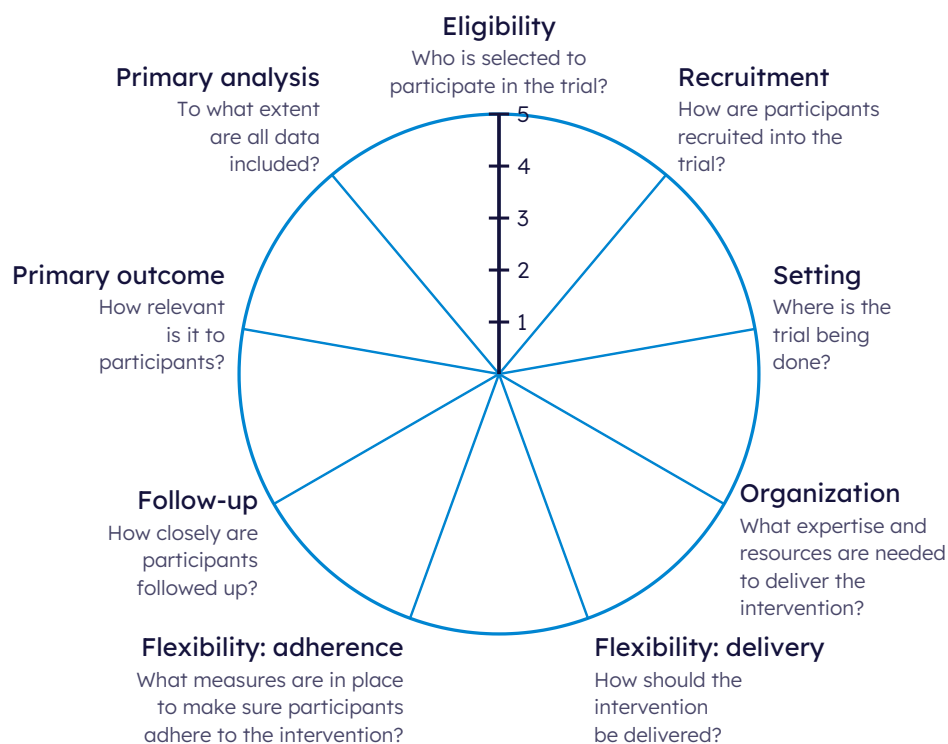
In 2009, a team of international researchers developed and published a tool called the Pragmatic-Explanatory Continuum Indicator Summary (PRECIS) to help clinical trial designers think more carefully about the impact their

design decisions would have on applicability.<sup>6</sup> A second team improved and validated the model to create PRECIS-2, a model resembling a wheel divided into nine domains based on trial design decisions.<sup>7</sup> This PRECIS-2 model can help illustrate where a trial falls on the pragmatic-to-explanatory continuum, with trials taking an explanatory approach falling nearer the hub and those with a pragmatic approach being closer to the rim (see Fig. 1).<sup>8</sup>

Novo Nordisk defines randomized pragmatic trials as “randomized designs at the point of care, such as large simple trials or those that incorporate pragmatic elements, to generate comparative effectiveness RWE in routine practice for decision-making by clinicians, payers, policymakers, and for regulatory purposes moving forward.”<sup>9</sup> The company notes that, based on the PRECIS-2 model, many clinical trials fall somewhere on a continuum, being neither fully explanatory nor fully pragmatic.<sup>9</sup>

One of the world's first pragmatic randomized controlled trials was the Salford Lung Study, a Phase III study of a combination of fluticasone furoate and vilanterol in patients with asthma. The study was conducted between 2012 and 2014 in real-world clinical practice settings using patients' linked electronic medical records (EMRs) to collect clinical endpoints. This method offered minimal disruption to patients and investigators while ensuring patient safety.<sup>10</sup>

**Figure 1. PRECIS-2 model**



Source: [PRECIS-2](#)

## Advantages of pragmatic trial design

Because pragmatic trials are conducted in routine settings with representative patient populations, they produce results that can more easily and accurately be applied across all patients who will receive the therapy once it is approved.<sup>11</sup>

Pragmatic trials help investigators gain RWD on a therapy's effectiveness that go beyond the

narrow set of endpoints generated by a randomized trial. This can better inform treatment guidelines and coverage.<sup>11,12</sup>

While many randomized trials compare the investigative therapy against a placebo alone, pragmatic trials often compare it against existing clinical alternatives, mirroring the choices clinicians face in real-world practice.<sup>12</sup>

Pragmatic trial design embeds randomization within routine care, retaining the internal validity of a randomized trial while enhancing the external validity of RWE and improving operational feasibility.<sup>13</sup>

Because pragmatic trials use inclusive eligibility criteria and recruit patients in diverse real-world settings, they can reach patients who might be excluded from randomized trials with stricter protocols. These include patients from

underrepresented races, ethnicities, genders, or social strata; older patients; and patients with comorbidities.<sup>11</sup>

When well designed and well executed, pragmatic trials can generate RWE of the treatment's value in routine clinical practice at an earlier stage than in the current paradigm of collecting RWE post-treatment launch.<sup>11</sup> This evidence increasingly underpins funding, regulatory, policy, and organizational decisions.

## Some challenges exist

While pragmatic trials do have the advantage over randomized trials in achieving generalizability, they are not without their challenges. For instance, one requirement for participants entering a pragmatic trial is that they be similar to patients who would receive the therapy if it became usual care — something that can be difficult to ascertain at this stage of the trial.<sup>2</sup>

The same flexibility that gives pragmatic trials their external validity also introduces heterogeneity. While some forms of this diversity are welcome, others are undesirable because they can cause greater risk of bias and confounding. Because pragmatic trials have a

less-controlled environment, it can be more difficult to establish clear cause-and-effect relationships. In addition, careful planning is needed to ensure adequate sample size while managing real-world complexities.<sup>14</sup>

Sponsors must carefully consider each pragmatic trial design element, including the study setting and population, type of intervention, and existing treatment regimens to which the investigatory therapy is being compared. These choices must strike a balance between enabling appropriate generalizations to the target patient group and ensuring operational feasibility and optimal success in clinical practice.<sup>11</sup>

## Connection with RWE

In 2018, the US Food and Drug Administration (FDA) created a framework under its 21st Century Cures Act to evaluate the potential use of RWE in supporting the approval of a new indication for an already-approved therapeutic agent or satisfying post-approval study requirements for an investigatory therapy.<sup>15</sup> In that framework, the FDA treats pragmatic trials as a source of RWD and a potential generator of RWE. The agency says it “sees promise in the opportunities created by pragmatic clinical trials, including broader inclusion/exclusion [I/E] criteria and streamlined data collection.”<sup>16</sup>

US regulators are increasingly accepting the use of both RWD and RWE in application reviews. The FDA continues to broaden acceptable deidentified RWD sources that track patient outcomes across diverse populations and treatment settings in ways traditional trials cannot.<sup>17</sup> And federal agencies such as the FDA and National Institutes of Health (NIH) have launched programs to encourage broader use of pragmatic trial design.\*

The European Medicines Agency (EMA) mentions RWE and RWD in its scientific guidelines on patient registry-based studies, saying that pre-authorization evaluation may in

some cases be supported by registry-derived observational evidence. The guideline states: “Examples of such evidence may include information on standards or real-world practice of care for the disease, incidence, prevalence and determinants of disease outcomes in clinical practice, or the characteristics of the registry population.”<sup>18</sup>

Use of RWD in pragmatic trials can strengthen both its internal validity and external relevance. With access to high-quality RWD, pragmatic trials become more feasible, faster, and more representative of actual patient populations. In pragmatic trials, RWD supports the work of designing and executing the trial: identifying and locating eligible patients, revealing the comorbidity profiles of the target population, and selecting comparators and outcomes grounded in actual clinical practice.\*\*

For many therapies, there is insufficient clinical evidence available to fully guide physicians and policymakers in choosing the right treatment for patients. Pragmatic trials help bridge this gap by providing RWE of the treatment’s relative effectiveness in routine clinical practice within a framework that does not completely abandon randomized controlled trial elements.<sup>11</sup>



[The FDA] sees promise in the opportunities created by pragmatic clinical trials, including broader inclusion/exclusion [I/E] criteria and streamlined data collection.



US Food and Drug Administration  
Framework for FDA's Real-World Evidence Program, 2018

## Continuum rather than choice

Depending on the results sought, it may not be a question of choosing pragmatic over explanatory trial design. It is more a matter of deciding how far toward the pragmatic end of the continuum to go. At least one study found many trials that label themselves pragmatic had wide variation in how pragmatic they actually are, prompting the authors to recommend use of structured tools such as PRECIS-2 to evaluate their design.<sup>19</sup> Design choices need to balance feasibility, stakeholder acceptability, validity,

precision, and generalizability so they have the best chance of succeeding in practice.<sup>11</sup>

Ultimately, explanatory and pragmatic trials are complementary, not competing. Explanatory designs remain indispensable for establishing efficacy and safety under controlled conditions, particularly in early development, while pragmatic designs extend that knowledge into real-world usage. For a complete foundation of evidence, both are needed.<sup>20</sup>

## \* US federal support for pragmatic trials

In 2022, the FDA Oncology Center of Excellence launched Project Pragmatica with the goal of exploring how to appropriately incorporate pragmatic design elements in clinical trials for approved oncology therapies. The project is part of a broader effort to modernize evidence generation in oncology research.<sup>4</sup>

### Project Pragmatica's objectives:

- Explore the feasible and appropriate range of pragmatic elements to incorporate in regulatory and clinical aspects of cancer trials while maintaining patient safety and data integrity.
- Work with patients, trial investigators, pharmaceutical companies, government agencies, and international healthcare policy stakeholders to assess opportunities and challenges for including pragmatic elements in multiregional cancer trials.
- Evaluate potential benefits of pragmatic trial elements to patients, investigators, and trial sponsors (e.g., more rapid recruitment, more diverse population, less attrition, lower costs, decreased time).<sup>4</sup>

The first Project Pragmatica-generated effort, Pragmatica-Lung, is an ongoing Phase III clinical trial comparing pembrolizumab plus ramucirumab to

standard of care chemotherapy for second-line treatment of advanced or metastatic non-small cell lung cancer (NSCLC).

Pragmatic design features employed in Pragmatica-Lung include broad eligibility criteria, minimal changes to clinical delivery, and streamlined follow-up data collection.<sup>21</sup>

The NIH also is seeking to advance the use of pragmatic trials through its NIH Pragmatic Trials Collaboratory, operating since 2012.<sup>22</sup> Its mission is to “strengthen the national capacity to implement cost-effective, large-scale research studies that engage healthcare delivery organizations as research partners.”<sup>23</sup>

To fulfill that mission, the collaboratory supports the design and rapid execution of large-scale pragmatic NIH collaboratory trials conducted in partnership with healthcare systems. These trials address questions of major public health importance covering a range of clinical areas and have a wide variety of interventions and study designs.<sup>23</sup>

The collaboratory also has seven core working groups that provide technical support and pragmatic trial expertise for collaboratory trials. Each core working group is focused on a specific topic:<sup>23</sup>

- Biostatistics and Study Design

- Community Health Improvement
- Electronic Health Records
- Ethics and Regulatory
- Health Care Systems Interactions
- Implementation Science
- Patient-Centered Outcomes

The collaboratory works to ground its research in real-world patient outcomes through its efforts to promote data collection from clinical care environments. Its emphasis on gathering data from underrepresented communities makes its research findings more relevant and addresses disparities in healthcare delivery and outcomes.<sup>24</sup>

In addition to its own trials, the collaboratory helps establish best practices and provide proof of concept for innovative designs in pragmatic clinical research, and trains a new generation of investigators in

pragmatic trial methods. It produces data, tools, and resources for the greater research community to promote healthcare system partnerships and drive transformation in the conduct of clinical research. And it contributes to the work of stakeholder organizations engaged in related efforts, including [PCORnet®, the National Patient-Centered Clinical Research Network](#).<sup>23</sup>

PCORnet® is a free, US-based resource providing a fully integrated network that gives access to built-in broad, highly representative health data, research expertise, and patient insights.<sup>25</sup> Users include potential investigators, patient groups, healthcare organizations, clinicians and clinician groups, government, industry scientists, sponsors, and stakeholders who want to leverage the PCORnet® infrastructure and collaborate on patient-centered research.<sup>26</sup>

## \*\* Pragmatic real-world data usage in practice

As the data infrastructure matures, RWD is becoming increasingly indispensable for supporting pragmatic trials. A 2025 review of clinical trials with pragmatic elements found among the 22 use cases of clinical trials with pragmatic elements, half incorporated RWD, with the remainder conducted at the point of care or in a real-world practice setting.

Breaking down which RWD sources were employed, the researchers identified four studies as utilizing electronic health records (EHRs) and claims data to enrich patient-level data. Seven studies leveraged RWD infrastructure to embed clinical trials within the existing healthcare database and

systems, with three out of those seven using EHR data to streamline processes from initial screening to data collection. Other RWD sources used included pharmacy dispensing information, lab results, national registries, and National Death Index records.

According to the review, RWD was used across these trials to enhance patient-level data, facilitate patient recruitment, simplify follow-up procedures, and streamline collection of baseline and/or outcome data. The review also found a few trials that employed RWD in the extension phases of the original trials, primarily to collect long-term follow-up evidence.

Source: [Clinical Pharmacology & Therapeutics](#)

## Conclusion

Sponsors continue to adopt pragmatic trial design elements because they help definitively answer the most important question in pharma research: Does this treatment work for real patients in real practice? Pragmatic trials also address the increasing recognition of RWE by regulatory frameworks and expectations of diversity in clinical trial populations.

By enrolling more representative populations,

delivering interventions in routine settings, and measuring decision-relevant outcomes, pragmatic trials bridge an evidence gap that strictly explanatory trials do not address. Sponsors that employ these designs are better able to identify the right patients, understand real-world patient journeys, and design trials that balance rigor with relevance, ultimately generating evidence that translates smoothly to the real world, not just the trial site.

## About the Author

### Carolyn Gretton

Senior Writer, Citeline

---

Carolyn Gretton is a content writer for Citeline with an extensive background in writing for the life sciences industry. A former journalist, she has written for online and print publications such as *PharmaVOICE*, *Med Ad News*, *Dow Jones Newswires*, and *The Philadelphia Inquirer*.

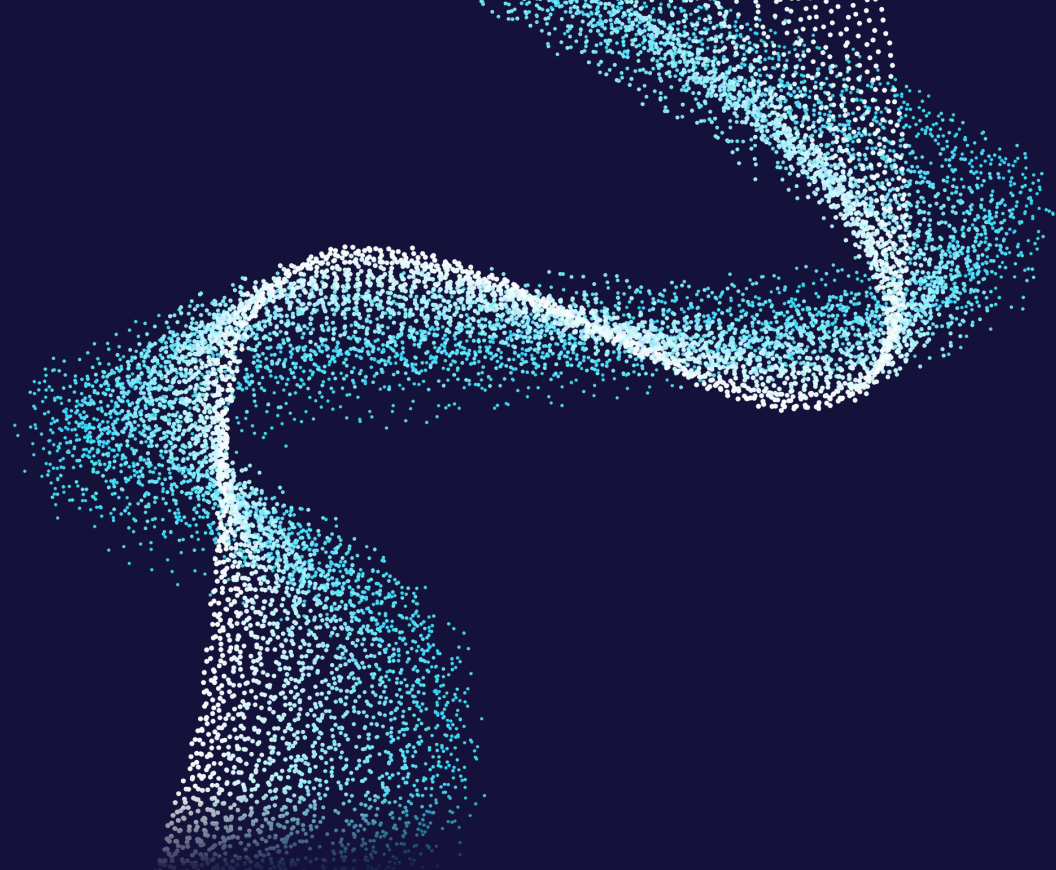


## References

- <sup>1</sup>Jensen J-U, Johansen ND, Mathioudakis AG, et al. (2025) The silent exclusion: rethinking eligibility and generalizability in clinical trials. *The Lancet Regional Health - Western Pacific*, 61, 101605. Available from <https://www.sciencedirect.com/science/article/pii/S2666606525001427> [Accessed July 7, 2026]
- <sup>2</sup>Ford I and Norrie J (2016) Pragmatic Trials. *The New England Journal of Medicine*, 375, 454–463. Available from <https://www.nejm.org/doi/full/10.1056/nejmra1510059> [Accessed June 29, 2026]
- <sup>3</sup>Schwartz D and Lellouch J (1967) Explanatory and pragmatic attitudes in therapeutical trials. *Journal of Chronic Diseases*, 20(8), 637–648. Available from <https://www.sciencedirect.com/science/article/abs/pii/0021968167900410> [Accessed July 2, 2026]
- <sup>4</sup>US Food and Drug Administration (2025) Project Pragmatica: Advancing evidence generation for approved oncology medical products. Available from <https://www.fda.gov/about-fda/oncology-center-excellence/project-pragmatica> [Accessed June 10, 2026]
- <sup>5</sup>Le-Rademacher J, Gunn H, Yao X, et al. (2023) Clinical Trials Overview: From Explanatory to Pragmatic Clinical Trials. *Mayo Clinic Proceedings*, 98(8), 1241–1253. Available from <https://www.mayoclinicproceedings.org/article/S0025-6196%2823%2900186-6/fulltext> [Accessed June 10, 2026]
- <sup>6</sup>Thorpe KE, Zwarenstein M, Oxman AD, et al. (2009) A pragmatic–explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *Journal of Clinical Epidemiology*, 62(5), 464–475. Available from [https://www.jclinepi.com/article/S0895-4356\(09\)00048-1/fulltext](https://www.jclinepi.com/article/S0895-4356(09)00048-1/fulltext) [Accessed June 29, 2026]
- <sup>7</sup>Loudon K, Zwarenstein M, Sullivan F, et al. (2013) PRECIS-2: a tool to improve the applicability of randomized controlled trials. *Trials*, 14(Suppl 1), O28. Available from <https://pmc.ncbi.nlm.nih.gov/articles/PMC3980948/> [Accessed June 29, 2026]
- <sup>8</sup>PRECIS-2, What is PRECIS-2? Available from <https://www.precis-2.org/Help/Documentation/Help> [Accessed June 29, 2026]
- <sup>9</sup>Novo Nordisk, Guide to Pragmatic Trials. Available from <https://www.novonordiskmedical.com/content/dam/medical/scientific-exchange/ta/x-ta/resource-documents/pragmatic-trial-guide.pdf> [Accessed June 29, 2026]
- <sup>10</sup>Woodcock A, Bakerly ND, New JP, et al. (2015) The Salford Lung Study protocol: a pragmatic, randomized phase III real-world effectiveness trial in asthma. *BMC Pulmonary Medicine*, 15, 160. Available from <https://pmc.ncbi.nlm.nih.gov/articles/PMC4676141/> [Accessed July 8, 2026]
- <sup>11</sup>Zuidgeest MGP, Goetz I, Groenwold RHH, et al. (2017) Series: Pragmatic trials and real world evidence: Paper 1. Introduction. *Journal of Clinical Epidemiology*, 88, 7–13. Available from <https://www.sciencedirect.com/science/article/pii/S0895435617305401> [Accessed July 9, 2026]
- <sup>12</sup>Jeong N-Y, Kim S-H, Lim E, et al. (2020) Pragmatic Clinical Trials for Real-World Evidence: Concept and Implementation. *Cardiovascular Prevention and Pharmacotherapy*, 2(3), 85–98. Available from <https://e-icpp.org/journal/view.php?doi=10.36011/cpp.2020.2.e12> [Accessed July 9, 2026]
- <sup>13</sup>Sagkriotis A (2026) Bridging evidence worlds: policy and practice pathways for integrating clinical trials and real-world data in drug development and HTA. *Frontiers in Pharmacology*, 17, 1786017. Available from <https://pmc.ncbi.nlm.nih.gov/articles/PMC13003634/> [Accessed July 9, 2026]
- <sup>14</sup>Giraudeau B, Caille A, Eldridge SM, et al. (2022) Heterogeneity in pragmatic randomized trials: sources and management. *BMC Medicine*, 20, 372. Available from <https://pmc.ncbi.nlm.nih.gov/articles/PMC9615398/> [Accessed July 16, 2026]
- <sup>15</sup>US Food and Drug Administration, Real-World Evidence. Available from <https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence> [Accessed July 14, 2026]
- <sup>16</sup>US Food and Drug Administration (2018) Framework for FDA's Real-World Evidence Program. Available from <https://www.fda.gov/media/120060/download?attachment> [Accessed July 14, 2026]
- <sup>17</sup>US Food and Drug Administration (2025) FDA Eliminates Major Barrier to Using Real-World Evidence in Drug and Device Application Reviews. Available from <https://www.fda.gov/news-events/press-announcements/fda-eliminates-major-barrier-using-real-world-evidence-drug-and-device-application-reviews> [Accessed July 16, 2026]
- <sup>18</sup>European Medicines Agency (2021) Guideline on registry-based studies. Available from [https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies_en.pdf) [Accessed July 21, 2026]

# Pragmatic Trials: Clinical Evidence for the Real World

- <sup>19</sup>Dal-Ré R, Janiaud P, and Ioannidis JPA (2018) Real-world evidence: How pragmatic are randomized controlled trials labeled as pragmatic? *BMC Medicine*, 16, 49. Available from <https://link.springer.com/article/10.1186/s12916-018-1038-2> [Accessed July 16, 2026]
- <sup>20</sup>Das S (2025) Real-World Evidence Studies and Pragmatic Clinical Trials. In: Arivazhahan A, Shah N, Sandhiya S, et al. (eds) *Introduction to Basics of Pharmacology and Toxicology*, 359–366. Springer, Singapore. Available from [https://link.springer.com/chapter/10.1007/978-981-95-1920-0\\_20](https://link.springer.com/chapter/10.1007/978-981-95-1920-0_20) [Accessed July 16, 2026]
- <sup>21</sup>Su L, Chen L, Betigeri S, et al. (2025) Clinical Trials With Pragmatic Elements: A Review of Use Cases and Real-World Data Utilization. *Clinical Pharmacology & Therapeutics*, 118(6), 1350–1365. Available from <https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.70033> [Accessed July 17, 2026]
- <sup>22</sup>NIH Pragmatic Trials Collaboratory (2026) What Are Embedded Pragmatic Clinical Trials? Available from <https://dcricollab.dcri.duke.edu/sites/NIH/KR/NIH%20Collaboratory%20Program%20Overview%20Handout.pdf> [Accessed June 16, 2026]
- <sup>23</sup>NIH Pragmatic Trials Collaboratory, About NIH Collaboratory. Available from <https://rethinkingclinicaltrials.org/about-nih-collaboratory/> [Accessed June 10, 2026]
- <sup>24</sup>NIH Pragmatic Trials Collaboratory (2024) FDA Commissioner and NIH Director Share Thoughts on the Future of Pragmatic Clinical Trials. Available from <https://rethinkingclinicaltrials.org/news/august-8-2024-fda-commissioner-and-nih-director-share-thoughts-on-the-future-of-pragmatic-clinical-trials/> [Accessed June 15, 2026]
- <sup>25</sup>PCORnet®, the National Patient-Centered Clinical Research Network, About PCORnet®. Available from <https://pcornet.org/about/> [Accessed June 15, 2026]
- <sup>26</sup>PCORnet®, the National Patient-Centered Clinical Research Network, PCORnet® Front Door. Available from <https://pcornet.org/front-door/> [Accessed June 16, 2026]



Citeline, a [Norstella](#) company, powers a full suite of complementary business intelligence offerings to meet the evolving needs of life science professionals to accelerate the connection of treatments to patients and patients to treatments. These patient-focused solutions and services deliver and analyze data used to drive clinical, commercial and regulatory-related decisions and create real-world opportunities for growth.

Citeline's global teams of analysts, journalists, and consultants keep their fingers on the pulse of the pharmaceutical, biomedical and medtech industries, covering all with expert insights: key diseases, clinical trials, drug R&D and approvals, market forecasts and more. For more information on one of the world's most trusted health science partners, visit [Citeline](#) and follow on [LinkedIn](#) and [X](#).