CLINICAL TRIALS TRANSFORMATION INITIATIVE

Developing & driving adoption of practices that will increase the quality and efficiency of clinical trials

CTTI Recommendations:

Use of Real-World Data to Plan Eligibility Criteria and Enhance Recruitment

October 2019

Experts and key stakeholders from across clinical trials ecosystem, including patients and caregivers, developed these recommendations and resources.

Clinical Trials Transformation Initiative. Use of Real-World Data to Plan Eligibility Criteria and Enhance Recruitment. Published October 2019. https://ctti-clinicaltrials.org/our-work/novel-clinical-trial-designs/real-world-data/

OVERVIEW

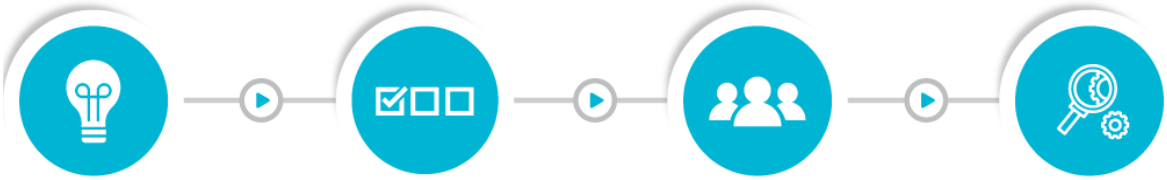
The growing availability of real-world data (RWD) creates opportunities not only for innovation in evidence generation, but also for improving the efficiency and potential success rates of more-traditional clinical trials. To varying degrees, sponsors are now regularly using RWD to make data-driven decisions about trial feasibility, based on assessment of planned eligibility criteria. And increasingly, RWD are being used to support targeted, timely, and personalized outreach that may improve the efficiency and effectiveness of the recruitment process.

The recommendations, resources, and case studies in this document provide actionable tools to support researchers in implementing emerging best practices, including resources for:

- Determining whether RWD are fit for purpose with respect to study planning and recruitment.
- Optimizing the use of RWD for study planning and recruitment by engaging cross-functional teams and building out organizational systems and processes.
- Understanding patient and site needs to develop successful and patient-centric approaches to RWD-supported recruitment.

Researchers can use this comprehensive set of work to apply RWD in a way that enhances eligibility criteria and recruitment, potentially resulting in increased efficiency, shorter timelines, and better patient access to research efforts.

SUMMARY OF RECOMMENDATIONS



GENERAL
PRINCIPLES FOR USING RWD

1. Begin seeking insights from RWD as early as possible.
2. Use RWD to complement and support collaborative study design.

RECOMMENDATIONS FOR
USING RWD TO PLAN FEASIBLE ELIGIBILITY CRITERIA

1. Evaluate available RWD sources against the particular needs of the study being planned.
2. Use RWD to identify and test important assumptions about the impact of potential eligibility criteria on trial feasibility.
3. Plan for iterative, targeted team discussions starting early in protocol design.

RECOMMENDATIONS FOR
USING RWD TO SUPPORT RECRUITMENT

1. Start by designing realistic eligibility criteria.
2. Incorporate RWD-supported recruitment strategies whenever feasible.
3. Understand and address the needs of patients and sites with respect to RWD-supported recruitment.

RECOMMENDATIONS FOR
ENHANCING RWD CAPABILITIES FOR THE RESEARCH ENTERPRISE

1. Identify opportunities and risks of enhanced data linkage.
2. Support continued development of underlying technology.
3. Evaluate RWD-supported recruitment strategies and identify best practices.
4. Explore transparency of secondary data use to the patient community and opportunities to enhance patient agency with respect to usage of their data.
5. Enhance communication channels for RWD-supported recruitment.
6. Identify opportunities to increase diversity of study participants.
7. Identify and support approaches for creating global data sets.

CONTENTS AT-A-GLANCE

Thank you to the experts and key stakeholders from across the clinical trials ecosystem who helped create this set of recommendations and resources, including all project team leaders and members, Expert Meeting members, Recommendations Advisory Committee members, and many others.

INTRODUCTION

Focusing primarily on the use of electronic health record (EHR) and insurance claims data for US-based studies of medical products, these recommendations identify considerations that are unique to, or especially important for, the use of RWD in planning eligibility criteria and recruitment. The recommendations can be used to support in-house curation and analysis of RWD sets, as well as to enhance interactions with data partners and technology providers.

We suggest using these recommendations as part of a broader Quality by Design process that focuses effort on activities that are essential to the credibility of the study outcomes, and that involves the broad range of stakeholders in protocol development and discussions around study quality. CTTI believes that increasing use of RWD from early in study planning will not only enhance trial feasibility and recruitment, but also support enrollment of patients that better reflect the populations most likely to use medical products, in alignment with emphasis in the FDA Reauthorization Act of 2017 (FDARA)[1] and recent draft and final guidance documents.[2]

DEFINITIONS:

Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected by a variety of sources.

Real-World Evidence (RWE) is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Source: Framework for FDA's Real-World Evidence Program

[1] See section 610(a) of FDARA, 131 Stat. 1005, Public Law 115-52 (Aug. 18, 2017). Available at https://www.congress.gov/115/plaws/publ52/PLAW-115publ52.pdf

[2] See, for example, *Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs*, and *Design Considerations for Pivotal Clinical Investigations for Medical Devices*.

SECTION I: General Principles for Using RWD

The recommendations below apply both to designing eligibility criteria that enhance the feasibility of recruitment, and to supporting recruitment processes by enhancing patient and site identification. See also specific considerations for each usage in Sections II and III, respectively.

1. Begin seeking insights from RWD as early as possible.

- Ideally, research sponsors should begin seeking insights from RWD early in the product lifecycle (e.g., prior to initiating phase 1 trials or feasibility studies, to characterize relevant patient populations and subpopulations, and understand unmet need). These insights help ensure that data-driven decisions can be made at the study level without delaying start-up timelines.
- Similarly, as early insights are sought, begin identifying the range of potentially relevant RWD sources for planned studies, along with their appropriate uses and the situations for which they are not well suited. In some cases, it may be feasible to also begin developing algorithms for analysis of RWD sets that will be broadly relevant to the medical product or indication.
- Maximize the benefits of RWD by identifying all potential uses. For example, data sets acquired to support post-market safety assessments may also be useful for designing eligibility criteria and related activities such as estimating event rates for relevant outcomes.
- Establish systems and processes to support the use of RWD for planning eligibility criteria and recruitment. See Establishing Use of RWD as a Standard Process in Study Planning and Recruitment.

2. Use RWD to complement and support collaborative study design.

- Recognize that, while RWD and other data sources can provide important insights, data will never tell the whole story. Patients and (whenever relevant) sites should be engaged in study planning, alongside other internal and external stakeholders, as part of a Quality by Design process.
- Assemble a cross-functional team to interpret RWD, extract actionable insights, and plan recruitment strategies. Relevant expertise may include clinical, operations, clinical epidemiology, biostatistics, informatics and data science, and other perspectives.

"Our study needed to make fast decisions, and having the data in-house and the expertise ready to analyze it quickly was a huge time-saver."

Read the case study for more insights from this sponsor, who used RWD for determining eligibility.

Claims vs. Electronic Health Record (EHR) Data for Planning Eligibility Criteria and Recruitment

These recommendations focus on EHR and claims data, both of which have been successfully used to help plan eligibility criteria and support recruitment. The table below is a starting point, only, for understanding the advantages and disadvantages these two sources of RWD tend to have. The specific advantages and disadvantages of EHR and claims data (and their international equivalents) will vary from one data source to another.

	Typical Advantages	Typical Disadvantages
EHR	▶ Depth of data (e.g., richness of information in unstructured data) ▶ Availability of clinical information relevant to provision of medical care in structured data fields (e.g., height, weight, blood pressure) ▶ May include relevant covariates not found in claims data (e.g., smoking status) ▶ Relatively rapid availability of data ▶ Provides opportunities for care providers to discuss study eligibility and participation with patients as part of routine health care	▶ Unstructured data can be challenging to work with ▶ Data may need to be aggregated across multiple providers or disparate sources (e.g., radiographic images, genomic data, laboratory results) ▶ Data completeness and accuracy can vary for a given patient (e.g., if they see several providers), as well as across provider organizations ▶ Data from medical encounters outside the specific healthcare system or provider (e.g., prescription fills) tend not to be included
Claims	▶ Fully structured data ▶ Widespread availability and generally consistent across major claims providers ▶ Captures data across entire continuum of reimbursed medical care encounters (multiple healthcare providers and healthcare systems, including prescription fills) ▶ Covers entire insured populations, not just those who use services	▶ Limited depth/richness of data ▶ Primary purpose is billing; clinical details and accuracy may be lacking ▶ Data completeness and accuracy can vary for a given patient (e.g., due to lapses or changes in coverage) ▶ Data are subject to a time lag (30 to 90 days or more) to allow for adjudication of claims ▶ Insured population may not reflect the relevant target population

While this document focuses on EHR and claims data, the same considerations can generally be applied to other sources of RWD (e.g., product and disease registries) that can also be highly appropriate for planning eligibility criteria and supporting recruitment. In many cases, it may be valuable to use several RWD sources side-by-side. In working with RWD, it is important to engage individuals knowledgeable about the specific data sources being used.

SECTION II: Using RWD to Plan Feasible Eligibility Criteria

This section provides specific considerations for using RWD to help plan eligibility criteria that fully consider the feasibility of successfully recruiting for the clinical trial.

1. Evaluate available RWD sources against the particular needs of the study being planned.

- Recognize that RWD can often inform eligibility criteria (and support recruitment) even when limitations are identified. In evaluating whether available RWD sources are fit for purpose, sponsors should define requirements relative to the needs for study planning. These are not necessarily the same as requirements for use of these data to generate real-world evidence for regulatory decisions.
- See detailed considerations in Evaluating Whether RWD Is Suitable for Planning Eligibility Criteria and Supporting Recruitment.

"[B]roadening eligibility criteria, when appropriate, maximizes the generalizability of trial results and the ability to understand the therapy's benefit-risk profile across the patient population likely to use the drug in clinical practice, without jeopardizing patient safety."

FDA Draft Guidance for Industry on Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs

2. Use RWD to identify and test important assumptions about the impact of potential eligibility criteria on trial feasibility.

Avoid making important decisions about eligibility criteria based only on assumptions and precedent set by prior studies. CTTI recommends using RWD alongside other sources of relevant information to inform decisions about eligibility criteria, pressure test assumptions, and explore the impact of different eligibility criteria on the feasibility of successfully recruiting for the trial. Focus analyses and decision-making on the eligibility criteria with the greatest impact on trial feasibility and generalizability.

3. Plan for iterative, targeted team discussions starting early in protocol design.

In designing eligibility criteria for a clinical trial, a range of factors must be considered, including generalizability of findings, participant safety, and recruitment feasibility. Sponsors should plan for iterative discussions of eligibility criteria, as these and interrelated considerations (e.g., potential enrichment strategies[3]) evolve over the course of planning a trial. For greatest impact on trial operational success, begin using RWD to help plan eligibility criteria early in study design, when there is still substantial flexibility in the protocol, as part of cross-functional discussions that also engage patients and other stakeholders. See Effective RWD-Supported Discussions of Eligibility Criteria.

Case Studies on Using RWD to Plan Study Eligibility Criteria

Sponsors have successfully utilized RWD to expand eligibility criteria, mitigate protocol amendments, and address mid-study recruitment challenges:

- Expanding Eligibility Criteria for Phase II Inflammation Trial
- Expanding Eligibility Criteria for Phase III Endocrinology Trial
- Solving Mid-Study Recruitment Challenges for Phase Ib/II Breast Cancer Trial

[3] See, for example, Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products.

SECTION III: Using RWD to Support Recruitment

This section provides recommendations for using RWD to support clinical trial recruitment. Though limited, evidence suggests that RWD-supported recruitment strategies—such as direct email and letter campaigns to patients identified through claims data, and EHR-supported discussions at the point of care—have the potential to increase recruitment effectiveness (number of relevant patients identified) and efficiency (faster recruitment) for many trials.

1. Start by designing realistic eligibility criteria.

See Section II for recommendations on using RWD to design eligibility criteria that will enhance the feasibility of recruitment. Sponsors should not expect the use of RWD at the recruitment stage to resolve issues with low or slow recruitment that are caused by unrealistic eligibility criteria.

2. Incorporate RWD-supported recruitment strategies whenever feasible.

In general, CTTI recommends incorporating RWD-supported recruitment, alongside traditional modes of recruitment, whenever fit-for-purpose data are available. Sponsors should especially consider using RWD-supported recruitment strategies for any trial likely to face recruitment challenges (e.g., small target population, high screen-failure rates anticipated, short timelines for meeting enrollment targets).

- In evaluating whether RWD sets are fit for purpose, consider the same factors as for planning eligibility criteria, as well as additional recruitment-specific considerations. See Evaluating Feasibility of RWD-Supported Recruitment.
- Ensure that partners who will be expected to provide data and directly communicate with patients about the study (e.g., local investigators and research staff, health system, insurance company) are available, experienced, and willing to collaborate. Data sets can be most effectively used for recruitment only if there is an appropriate pathway to contact patients; and for the subset of RWD where this is possible, successful use often requires partnership with the data set owner and an understanding of privacy regulations.
- Consider the potential for both time and cost savings in evaluating feasibility. For example, RWD-supported recruitment may be worthwhile even when direct recruitment costs are higher than with traditional recruitment methods, if recruitment rates are also substantially faster.
- Recognize that there will always be situations in which database searches would add little or no value to patient and site identification processes (e.g., when a sponsor has already identified the small number of practices at which patients with a particular rare disease are treated).

3. Understand and address the needs of patients and sites with respect to RWD-supported recruitment.

RWD-supported recruitment creates unique opportunities both for massive scale (e.g., contacting tens of thousands of patients through claims databases), as well as highly individualized and timely communication (e.g., facilitated through the EHR system during routine medical appointments). Sponsors should engage with patients and sites (as well as IRBs, regulators, and other appropriate stakeholders) to plan RWD-supported recruitment strategies that are respectful of patient privacy, comply with applicable laws and regulations, achieve an appropriate level of interpersonal interaction and trust, integrate with provider and site workflows, and account for potential impacts on participant retention and overall trial experience. See Planning RWD-Supported Recruitment Strategies.

SECTION IV: Enhancing RWD Capabilities for the Research Enterprise

To maximize the opportunities afforded by RWD to improve the efficiency and potential success rates of clinical trials, CTTI recommends continued, multi-stakeholder discussion, research, and identification of best practices. Specifically, we recommend addressing the following:

1. Identify opportunities and risks of enhanced data linkage.

The use of RWD becomes more powerful as data are increasingly linked, allowing researchers to build a more complete picture of patient health. To support this, more tools and resources should be developed to help establish common data models and terminology (e.g., PCORnet Common Data Model, Sentinel Common Data Model, Observational Medical Outcomes Partnership (OMOP) Common Data Model, Minimal Common Oncology Data Elements (mCODE)), build appropriate infrastructure within EHR systems, and enhance data recency. At the same time, it is important to understand and address the implications of increased data linkage for patients and the public, including potential risks to privacy, as well as any regulatory guidelines on how data can be linked and used. Note that linking data sets may require conformance with governance structures.

2. Support continued development of underlying technology.

Currently, operationalizing eligibility criteria, as they are written in protocols, into structured queries of RWD sources is a highly manual process. Stakeholder collaboration can facilitate development of technology that makes this process substantially more automated and therefore scalable.

3. Evaluate RWD-supported recruitment strategies and identify best practices.

CTTI encourages sponsors to assess RWD-supported recruitment approaches, and share the results to contribute to the development of best practices; this may include comparing efficiency and effectiveness of different recruitment approaches and communication channels across a range of trial designs, therapeutic areas, disease severities, etc. Frameworks and best practices should also be put in place for building relationships with patients, clinicians, health systems, payers and other stakeholders, engaging them in research, and fostering a culture of data sharing.

4. Explore transparency of secondary data use to the patient community and opportunities to enhance patient agency with respect to usage of their data.

The patient community may not be generally aware of how their data are being used. To help facilitate greater acceptance of the use of RWD for a variety of research-related purposes, all stakeholders should work together to understand current perceptions, increase transparency and awareness, and identify best practices to ensure that patients are able to make informed decisions regarding use of their data. Such discussions should be considered in the evolving context of global privacy considerations.

5. Enhance communication channels for RWD-supported recruitment.

Collaboration between sponsors, providers, patients, IRBs, payers and other data partners can support development of communications channels that better meet the needs of all stakeholders and facilitate innovative recruitment approaches, such as identifying potential participants in real time at the point of care in clinical practice settings. Consider, for example, that many providers may find pop-up messages in a patient's EHR during patient visits annoying and burdensome; and that providers are often protective of their patients being approached directly by external parties even where permitted by privacy regulations.

6. Identify opportunities to increase diversity of study participants.

It is likely that appropriate use of RWD can help address challenges with lack of diversity in clinical research and poor generalizability of findings. For example, RWD approaches may facilitate recruitment from more demographically diverse community providers. Such opportunities should be systematically identified and assessed.

7. Identify and support approaches for creating global data sets.

One of the primary barriers to wider use of RWD for planning trials and recruiting participants (as well as for other purposes) is the lack of global data sets. As a long-term goal, stakeholders should explore opportunities to develop global data sets that can be made appropriately available to all researchers. Though extremely challenging to develop, such data sets have potential to provide tremendous value to the research enterprise and improve public health.

RELATED CTTI RECOMMENDATIONS

The recommendations in this document should be used in conjunction with the following related CTTI recommendations:

Quality by Design in Clinical Trials

- When using real-world data to help design eligibility criteria and enhance recruitment, it is important to do so within the broader context of overall study design and conduct. CTTI recommends following a Quality by Design (QbD) approach that engages the broad range of stakeholders and focuses resources on the errors that matter to decision-making.
- See recommendations and resources available at https://ctti-clinicaltrials.org/our-work/quality/quality-by-design/

Recruitment Planning for Clinical Trials

- CTTI's Recruitment recommendations outline a general framework for enhancing recruitment within which insights and approaches afforded by real-world data should be understood and implemented.
- See recommendations and resources available at https://ctti-clinicaltrials.org/our-work/quality/recruitment-2/

Other CTTI Projects and Recommendations of Interest

- Effective Engagement with Patient Groups Around Clinical Trials
- Conducting Clinical Trials Using Clinical Observational Registries
- Using Mobile Technologies to Improve Clinical Trials

ADDITIONAL RESOURCES

Draft and final guidance documents that may be of interest include, but are not limited to:

1. Framework for FDA's Real-World Evidence Program. Available at https://www.fda.gov/media/120060/download
2. Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices. Available at https://www.fda.gov/media/99447/download
3. Use of Electronic Health Record Data in Clinical Investigations. Available at https://www.fda.gov/media/97567/download
4. Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs. Available at https://www.fda.gov/media/127712/download
5. Design Considerations for Pivotal Clinical Investigations for Medical Devices. Available at https://www.fda.gov/media/87363/download
6. Cancer Clinical Trial Eligibility Criteria: Minimum Age for Pediatric Patients. Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cancer-clinical-trial-eligibility-criteria-minimum-age-pediatric-patients
7. Cancer Clinical Trial Eligibility Criteria: Patients with HIV, Hepatitis B Virus, or Hepatitis C Virus Infections. Available at https://www.fda.gov/regulatory-information/search-fda-

guidance-documents/cancer-clinical-trial-eligibility-criteria-patients-hiv-hepatitis-b-virus-or-hepatitis-c-virus

8. Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies. Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cancer-clinical-trial-eligibility-criteria-patients-organ-dysfunction-or-prior-or-concurrent
9. Cancer Clinical Trial Eligibility Criteria: Brain Metastases. Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cancer-clinical-trial-eligibility-criteria-brain-metastases
10. Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials. Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-inclusion-adolescent-patients-adult-oncology-clinical-trials

ABOUT THE RECOMMENDATIONS

These recommendations are based on results from CTTI's RWD for Eligibility and Recruitment Project.

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All of CTTI's official recommendations are publicly available. Use of the recommendations is encouraged with appropriate citation.

ABOUT CTTI

The Clinical Trials Transformation Initiative (CTTI), a public-private partnership co-founded by Duke University and the U.S. Food and Drug Administration, seeks to develop and drive adoption of practices that will increase the quality and efficiency of clinical trials. Bringing together organizations and individuals from across the enterprise—representing academia, clinical investigators, government and regulatory agencies, industry, institutional review boards, patient advocacy groups, and other groups—CTTI is transforming the clinical trials landscape by developing evidence-based solutions to clinical research challenges. Many regulatory agencies and organizations have applied CTTI's more than 20 existing recommendations, and associated resources, to make better clinical trials a reality. Learn more about CTTI projects, recommendations, and resources at www.ctti-clinicaltrials.org.