Harnessing the Potential of Real-World Evidence Master Protocols
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Disclosures

Rachele Hendricks-Sturrup is an independent executive with the National Alliance Against Disparities in Patient Health and independent director on the board of Public Responsibility in Medicine & Research (PRIM&R).

Mark B. McClellan, MD, PhD, is an independent director on the boards of Johnson & Johnson, Cigna, Alignment Healthcare, and PrognomiQ; co-chairs the Guiding Committee for the Health Care Payment Learning and Action Network; and receives fees for serving as an advisor for Arsenal Capital Partners, Blackstone Life Sciences, and MITRE.
Executive Summary

Advanced considerations of real-world data and evidence (RWD/E) within the clinical trial ecosystem have increased demand to create more efficient, systematic, and flexible ways to address multiple research questions using a single, master protocol (MP). Despite being a well-established method of testing multiple hypotheses within a single clinical trial, MPs are not fully conceptualized to support RWE studies. In this white paper, we describe key characteristics of RWE MPs and how they can support the development of critical evidentiary needs for medical products. First, we provide an overview on how innovative MP templates are emerging to support more consistent structures and processes for designing and conducting multiple RWE studies under a single research protocol, and how these templates are improving RWE study governance, transparency, and reporting. Next, we highlight four key areas in which RWE policy stakeholders could align to create and capture the value of RWE MPs:

- Shared terminology, definitions, and concepts
- Source data considerations
- Factors toward developing and leveraging RWE MPs
- Stakeholder engagement and collaboration

These proposed next steps could advance stakeholder understanding of RWE MPs and inspire opportunities to further their development and use.

How This Paper Was Developed

This white paper was informed by a series of breakout group discussions and a private workshop entitled, “Harnessing the Potential of Real-World Evidence Master Protocols: Key Challenges and Opportunities,” hosted by the Duke-Margolis Master Real-World Evidence Protocols Workstream from February 28-March 1, 2023. During the workshop, stakeholders representing industry, sponsors, research groups, data vendors, and patient advocacy groups provided insight and expert perspectives on the evolving development and implementation of master protocols with observational data to generate real-world evidence. Workstream members and workshop participants offered input regarding key characteristics of RWE MPs and how these protocols can support the development of critical evidentiary needs for medical products. The Workstream sought to build on prior, multi-stakeholder efforts to generate observational evidence, and aimed to determine how different data sources were used to answer the same research questions, improve study quality, and facilitate comparisons across studies.

Introduction

MPs have long supported traditional, randomized, controlled clinical trial operations across multiple sites and for a growing range of innovative medical product developments. MPs hold promising potential as tools to implement flexible study designs that allow multiple hypotheses to be tested on different treatments or patient populations. Realizing the greater efficiencies and research scale offered by MPs requires enhancing the usual trial coordination around both clinical trial governance and operations. Stakeholder interest grows in leveraging MPs for real-world evidence studies, with an aim to improve RWE study efficiency, scale, and consistency. The COVID-19 pandemic efforts notably demonstrated the utility of these protocols. In the absence of available evidence and given the multitudes of challenges and delays that clinical trials operations faced during the COVID-19 pandemic, stakeholders sought to leverage the real-world data captured during routine care for COVID-19 patients. RWD availability combined with efficient coordination...
mechanisms afforded by MPs helped researchers to conduct timely and effective analyses to distinguish key variables, and identify relationships between key variables, to generate actionable RWE for a broad range of diagnostics and treatments.²

Yet, specific challenges to developing and leveraging MPs for RWE studies exist. For instance, RWD sources are often broad and data collection is inherently subject to variation and confounding. Inconsistent data sourcing and curation techniques, data management practices, and applications of data quality standards also add complexity to attempts to fit real-world contexts across heterogenous care settings. Partners collaborating in the development and implementation of MPs may also experience potential difficulties in communicating data requirements, key parameters, and potential assumptions, all of which are necessary to understand when designing and conducting RWE study analyses. Overall, these inherent complexities in operationalizing MPs for RWE studies can lead to inconsistencies that may impact potential applications and integrations of RWE and affect RWE relevance and reliability among key stakeholders. Unlocking the potential of RWE MPs necessitates aligning stakeholders across technical logistics; addressing statistical, operational, and contextual challenges as appropriate for each protocol; and maintaining communication at every step. Thereby, MPs will reliably and systematically address a broad range of clinical research questions using a single protocol.

In this white paper, we first provide an overview on how innovative MP templates are emerging to support more consistent structures and processes for designing and conducting multiple RWE studies under a single research protocol and improving RWE study governance, transparency, and reporting. Next, we highlight key areas in which RWE policy stakeholders may align to create and capture the value of RWE MPs:

- Shared terminology, definitions, and concepts;
- Source data considerations;
- Factors toward developing and leveraging RWE MPs; and
- Stakeholder engagement and collaboration.

We conclude with proposed next steps to advance stakeholder understanding of RWE MPs and inspire opportunities to further their development and use.

### Overview of Master Protocol Template Design and Governance

A seminal paper by Drs. Janet Woodcock and Lisa LaVange has described the need for clinical trials to better evaluate targeted therapies as part of “precision medicine” efforts.³ MPs can address this need, given their potential to help improve patient recruitment for targeted therapies in exploratory trials (e.g., identifying the best treatment for biomarker-defined patient groups) or confirmatory trials (e.g., evaluating different therapies relative to a control for a single disease in parallel). While not all characteristics of randomized, controlled trials (RCT) may apply to RWE studies, MPs used to operationalize RCTs can be a helpful baseline for constructing RWE MPs. For instance, RWE MPs can provide a roadmap with definitions and key characteristics that help address and navigate RWE study design and implementation.

MPs have been used to flexibly design and streamline clinical trials for multiple diseases, multiple patient subgroups, and/or multiple therapies studied under a single protocol.⁴ These studies are commonly referred to as basket trials, umbrella trials, and platform trials.⁵ Research shows that MPs are inherently adaptive, allowing for trial arms to be added or removed, and are flexible in that they allow one or more design parameter(s) to become modified during a clinical trial.⁶ Given these features, innovative statistical methods such as Bayesian and frequentist approaches are potentially well-suited for MP designs.

Shared infrastructure and centralized governance are benefits to RWE MP implementation, given their purpose to improve efficiency, scale,
and ultimately consistency in study protocol implementation. Design efficiencies, such as centralized data governance and study coordination, fundamentally support these MP-driven study attributes. Through centralized governance, investigating partners can decide on key protocol components up front, such as study design and how and when to adapt trials. This helps researchers take advantage of similarities across trials and leverage shared infrastructure to realize new efficiencies. With these coordinating mechanisms in place, stakeholder confidence and interest (e.g., regulators and medical product sponsors) is more likely due to a transparent, collaborative study design and process.

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Shared Study Terminology, Definitions, and Concepts

As RWE MPs are a relatively new construct, a widely accepted definition is needed to develop a common understanding of RWE MPs. A need also exists to determine study designs and design concepts that are most appropriate for RWE MPs, given substantial variation in how stakeholders develop, use, and/or rely on MPs generally. To address both areas, in this section we propose a conceptual and definitional framework and working construct for RWE MPs.

**Conceptual and Definitional Framework**

A few key questions should be considered when developing an initial framework to describe RWE MPs. For instance, how should stakeholders define an RWE MP and its key components? Formulating a definition might depend on when it is most valuable to conduct an RWE MP, so what might be potential use cases? Crucially, how could MPs address the needs of diverse RWE policy stakeholders? Ideally, RWE MPs can be used to streamline uses of diverse RWD sources across multiple study designs that offer high versus low precision + accuracy and study efficiency to address a single research question (see Figure 1).

Components within the RWE MP may include, for example, common data elements and definitions, standardized study design and analysis plans, and data curation and analysis methods to reduce the likelihood of misinterpreting results.

**Figure 1** Characterizing Precision + Accuracy and Study Efficiency Across Various Study/Trial Designs

<table>
<thead>
<tr>
<th>Precision + Accuracy</th>
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<td>High Precision + Accuracy</td>
<td>High Study Efficiency</td>
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<td>Low Study Efficiency</td>
<td>• Trials with pragmatic elements in clinical practice settings</td>
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<td>Low Precision + Accuracy</td>
<td>Low Study Efficiency</td>
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<td>• Cohort study</td>
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<td>• Case-crossover study</td>
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Study Design Concepts

In 2022, Concato and Corrigan-Curay illustrated a spectrum of study types with increasing RWE reliance. Traditional, randomized, interventional studies rely on RWD the least, and conversely, non-randomized, non-interventional, observational studies largely rely on RWD. In theory and to some degree, an RWE MP could be useful for and applicable to each of these study designs. Although, given that study designs with the greatest reliance on RWD are inherently subject to greater variation and confounding, MPs should include control measures for documenting and addressing instances and/or sources of bias and confounding. Figure 1 visualizes minimizing statistical noise while retaining efficiency (blue quadrant), and trade-offs associated with chosen methodology and available source data.

In addition, MPs should distinguish unwanted versus wanted variation, or variation of analytical importance within and across RWD sources. Unwanted variation can impede consistent implementation of RWE studies and an RWE MP by extension. Specifically, if RWD sources are not sufficiently comparable due to a lack of standardization within an MP, then researchers may have limited capabilities to build accurate representations of medical concepts for analysis. Therefore, when studying population and subpopulation effects, broad inclusion criteria would be important to monitor specific outcomes across multiple studies operating under an RWE MP and ensure diversity among a study cohort (desired variation). Inclusion criteria can help mitigate unwanted sources of variation in addition to the aforementioned features inherent to RWE MPs: streamlined operations and coordination, common data and protocol design elements, operational definitions and data models, analytic tools and platforms, and centralized governance.

Source Data Considerations

When considering source data used within an MP, a minimum necessary standard could provide clarity to ensure stakeholders are adequately informed and equipped to run the study under an RWE MP. By identifying and clearly communicating key data requirements to appropriately run an RWE MP, a minimum necessary standard would enable greater study efficiency and scalability. To apply a minimum necessary standard within an RWE MP, it will be important to define or describe the following:

- Common protocol designs and data models;
- Programming specifications and considerations; and
- Bias control, data validation, and analysis parameters.

Common Protocol Designs and Data Models

Scaling the potential of RWE MPs requires optimizing efficiency and consistency, which hinges upon determining fit-for-purpose source data (i.e., RWD that are relevant and reliable) that are suitable for analysis under an MP as well as accessing data infrastructure needed to conduct specific analyses. Scientific discussions have emerged around common RWE study protocol designs, all of which directly inform the development of key features and characteristics of RWE MPs. One recent example is the HARmonized Protocol Template to Enhance Reproducibility (HARPER). Common design protocols like HARPER can help establish or strengthen communication around key study parameters to improve implementation, reproducibility, transparency, communication, and assessment of sources of bias and confounding to judge RWD relevance and reliability.
assessment of sources of bias and confounding to judge RWD relevance and reliability. Potential opportunities under the HARPER template specifically include exploring detailed study summaries that concisely describe elements of the protocol and clear operational definitions for exposures, outcomes, confounders, and effect modifiers.\textsuperscript{10} In addition, the updated Structured Process to Identify Fit-For-Purpose Data (SPIFID2) and similar tools are intended to harmonize how RWE studies are structured, provide guidance for reporting and transparency, and offer key criteria for assessing data requirements.\textsuperscript{11} However, even with these tools, details at the program specification level remain less standardized and are often not systematically communicated. Lack of standardization and communication impacts protocol implementation and subsequent study results.

Data quality is a paramount consideration for RWE studies, whether or not they involve the use of CDMs within an MP.\textsuperscript{18,19,20} Regardless, applying data standards can be a multi-step process as investigators find additionally necessary considerations when developing datasets. To achieve a quality standard, though, it is important to emphasize that not every RWE MP needs to utilize a CDM. The use of a CDM depends on the study question but may generally require higher levels of certainty when executing analyses intended to inform decision-making.\textsuperscript{21} A quintessential example is regulatory decision-making. The infrastructure and governance underpinning the data model make CDMs useful for reducing potential bias and confounding. They ensure data are checked for quality, are transformed and mapped properly from source data, and are routinely updated. Nonetheless, CDMs have weaknesses as well. CDMs only accommodate predefined variables, so they are typically broad and not tailored to specific therapeutic areas.\textsuperscript{22} If the study question requires more granular information, then CDMs may not offer the best approach. In the absence of a CDM, it is important to understand and vet data sources used in the analysis, including how the data are curated and quality checked. While it may not be
possible to provide granular information on every curation step or quality check performed on a dataset (e.g., audit trails), expectations should be communicated, even at a high level, regarding how underlying data sources should be organized and managed to determine if they are fit-for-purpose for the intended analysis.

Maintaining a high standard of data quality is always essential, regardless of CDM utilization, but data missingness and other biasing factors are more pressing when making decisions with RWE.\textsuperscript{23} To minimize these factors, stakeholders should leverage existing tools and build new ones to scrutinize for data accuracy, completeness, provenance, and transparency of data processing, all of which is particularly important for creating a fit-for-purpose real-world dataset.\textsuperscript{24}

\textbf{Programming Specifications and Considerations}

With RWE MPs, stakeholders have an opportunity to align around source data requirements for programming specifications. A clear understanding of time horizons, windows of exposure, and follow-ups are all fundamental to designing and conducting analysis. Defining time windows for the analysis requires understanding the intent of the RWD source and information system. When studying the time duration for a particular treatment, researchers should understand the context in which the secondary RWD were collected (i.e., how, when, and why). For example, pharmacy claims data could supplement electronic health record (EHR) data to fill gaps in a patient’s medication history. Meanwhile, insurance claims data could be used to learn the patient’s treatment outcomes to support payment. In a scenario where multiple data sources are used to contextualize or define treatment exposure windows, defined time horizons may typically be tighter in some data sources, like closed claims data sources versus EHRs, to support a longitudinal analysis or assessment. In such cases, data linkages, as well as data linkage requirements, across multiple data sources could be useful.

Data latency is another key aspect of source data requirements, as it often contributes to data missingness. Data latency is common in claims data and EHRs, and it is often an important consideration when determining whether a dataset is fit-for-purpose. When time or longitudinal gaps are observed in datasets, which indicates possible data latency, it is important to quickly rule out whether the gap is caused by lags in data refreshing within the system. For instance, two questions can help determine types of data latency. First, how much time has passed since patient record was most recently updated? Second, how far back in the record does one need to search to find a complete data picture? Periods of latency can be specific to the data source or even variables within the data source. For example, there can be a two week- to months-long lag in claims data for procedure billing for hospitalizations.\textsuperscript{25} EHR data can experience similar lags, but latency varies across different health systems. Meanwhile, in lab data, labs may be current within a day of the test. Upon understanding and minimizing possible data latency, investigators implementing the RWE MP should explore and identify other possible reasons for time or longitudinal gaps, or discrepancies in the dataset.

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RWE MPs also should communicate how/if prior specifications are or are intended to be reused or updated under a controlled governance protocol. For example, when RWE MPs are used as part of a research network, such as the Sentinel System, RWE MPs can be either archived or updated through versioning mechanisms to embed and facilitate the implementation of the latest advancements in RWD. To start these processes, research collaborators and stakeholders can visit a library of tested and validated MPs to build upon and further deliberate resources needed for the next round of protocol developments, specifications, updates, and final implementation to address a research question.
Establishing operational definitions for key study variables (e.g., cohorts, exposures, covariates, and outcomes) also is critical. How these variables are defined and characterized using RWD can determine whether a study question may be better suited for one particular RWD source over another. Additionally, when defining and characterizing study variables (e.g., outcomes, exposures, etc.) for a RWE MP, there may be multiple methods. In some cases, multiple representations of medical concepts may exist and implementing study partners may perceive some of the study variables as subjectively defined in the master protocol. COVID-19 mechanical ventilation is one such example, as it could be based on billing codes, flowsheets, and/or any information derived from respiratory therapy notes. Yet, if multiple study definitions are used across multiple partners implementing a master protocol, then investigators must take greater care to ensure measurement of the same concept if the data are to be combined.

Bias Control, Data Validation, and Analysis Parameters

Given the multitude of source data factors to consider when developing an MP, RWE policy stakeholders should determine how to communicate these requirements with one another. Despite tools like HARPER and frameworks intended to support more consistent and replicable RWE studies, it is possible that some details may not be communicated clearly even when they are essential for study implementation. Therefore, part of RWE MPs achieving their full potential will be understanding data requirements, biases and assumptions, and parameters for implementing analyses.

Within this topic, we consider approaches for bias control and validation, using secondary data as an example. Inherent biases exist when utilizing secondary data, including data missingness, practice variance in coding, and whether a given outcome under assessment occurred. For this reason, stakeholders that include, but are not limited to, the FDA are often interested in how issues of bias and confounding are corrected and how approaches for outcome validation are implemented, all of which should be clearly communicated within an RWE MP.

In cases where it may not be possible to include exhaustively detailed context and analysis parameters, there should be opportunities to determine and disseminate high priority data requirements and parameters that are fundamental for the study. This could be accomplished in various ways. First, investigators can establish minimum necessary requirements for translating RWD into study questions, including operational definitions for key variables. Additionally, investigators can specify assumptions around time horizons, clearly document approaches for bias control and validation, and provide requirements for leveraging data sources. Such requirements would include CDM usage and identifying considerations for data curation, transformation, mapping, and latency.

Factors Toward Developing and Leveraging Real-World Evidence Master Protocols

Challenges to implementing RWE studies generally involve substantial variation in the capture, curation, and transformation of RWD for analytic datasets used across data systems and models of research. This challenge is therefore inherent to implementing RWE MPs, meaning stakeholders need a general understanding of data requirements to appropriately replicate the protocol in a way that provides credible and reliable evidence. Given the range of study questions, and context surrounding studies, a set of comprehensive data requirements is likely impractical.

Therefore, certain limitations should be considered with respect to developing and leveraging RWE MPs. First, it is unlikely that RWE MPs can
eliminate all sources of undesired variability despite being in a networked environment (i.e., competing interpretations of the same study within a given study design). For example, given that investigators may interpret protocols differently and make diverging and subjective, albeit often reasonable, decisions during a research study, uncertainty due to variation in RWE interpretation may arise. More plainly, variations in how researchers interpret programming specifications for tuning the analytic tool and executing the analysis may cause small variations in the interpretation of RWE study results. Nonetheless, although significant time and resource investments would be required up front to implement RWE studies within a networked environment governed by an MP, RWE MPs would create greater consistency and certainty around the evidence generated.

In addition, study alignment under an RWE MP may often depend on the intent behind generating RWE to address a specific research question. For instance, if the evidence generated from the master protocol is intended to address a regulatory question, then stakeholders must demonstrate and validate whether the data is fit-for-purpose (i.e., relevant and reliable). On the other hand, if the intended use of an RWE MP is to inform clinical treatment guidelines or conduct natural history studies for specific diseases, then less investment may be required to execute studies under a RWE MP that could produce general insights from multiple sources of observational data. Considering this, RWE stakeholders should contemplate real-world contexts that might warrant various tiers of streamlining under an RWE MP (e.g., informing clinical guidelines, substantiating health care payments, conducting natural history studies for diseases, informing regulatory decisions, etc.).

**Stakeholder Engagement and Collaboration**

RWE policy stakeholders derive from a diverse range of professional and personal backgrounds, functions, and lived experiences within the health system (e.g., regulators, study sponsors, patients, health systems, payors, and data curators). As RWE MPs are developed with the intent to serve the needs of these stakeholders, it will be important to collect and draw on their unique perspectives regarding the real-world value and benefits of RWE MPs, from protocol design through implementation. As described above, there are broadly applicable benefits as well as challenges to RWE MP development, implementation, and participation, exposing new frontiers and opportunities for future stakeholder engagement and collaboration.

**Patient Engagement with Study Sponsors and Regulators**

Lack of engagement among a broad and diverse range RWE policy stakeholders, especially patients who are historically and/or presently under-engaged in health care, creates missed opportunities for conducting research with potentially broad impact. For instance, patient-generated health data (PGHD), a core source of RWE, can rapidly enable RWE MPs that directly leverage electronic patient surveillance mechanisms and patient-reported outcomes data for studies seeking to develop innovative treatments with promising value. In this development process, study sponsors and their collaborators gain efficiencies in communicating patient-generated outcomes data to regulators and, when applicable, other key policy stakeholders.

**Sponsor Engagement with Health Systems and Regulators**

Sponsors benefit from MPs that embed existing health system and regulatory policies and processes; streamline trial activities to ensure local compliance across multiple regions, countries, and continents; and sustain multi-site study coordination and dissemination of findings. Sponsors may, therefore,
find the standardized processes and scientific rigor embedded within RWE MPs useful for similar reasons to coordinate multi-site RWE studies across various regions, countries, and continents and produce trial evidence that is sufficient for regulatory review. FDA has released an early RWE framework followed by several draft guidance documents for industry that will help drive these discussions.\textsuperscript{32,33}

**Health System Engagement with Providers, Patients, and Sponsors**

RWE MPs hold potential to influence care delivery processes, treatment guidelines, and payor coverage decisions. As health systems strive to integrate RWE and real-time learning into their internal quality improvement mechanisms, participation in RWE MPs creates opportunities to promote more reliable and consistent evidence streams and transparent information that may otherwise become siloed across multiple health systems. In addition, health system participation in RWE MPs can help improve provider and sponsor understanding of organizational data assets and, subsequently, access to potentially innovative data analytics. Providers employed by health systems may become incentivized and motivated to participate as key investigators for and coauthors of RWE MP-driven research. Payors also stand benefit from RWE MP implementation and evidence generated therein, given the goal to produce high-quality evidence that aligns with evidentiary needs among regulators with less upfront time and resource investment.

Therefore, RWE MPs can help inspire all RWE policy stakeholders to coordinate efforts with one another and remain engaged in driving biomedical innovation forward and promoting the credibility of RWE.

**RWE Policy Stakeholder Engagement At Large**

Finally, there are considerations for RWE policy stakeholders at large. Ultimately, the development and use of RWE MPs is premised on advancing replicable science that is transparent and effective at creating reliable and actionable evidence. Therefore, RWE MPs can help inspire all RWE policy stakeholders to coordinate efforts with one another and remain engaged in driving biomedical innovation forward and promoting the credibility of RWE. This will ultimately require coordination around shared resources as well as evidentiary needs and standards across the stakeholder ecosystem, developing use cases that highlight how initiatives address evidentiary gaps and motivate practical collaborations, and planning for multistakeholder-led legislation and regulatory action.

**Conclusion**

Given the overarching goal of RWE MPs to improve consistency in RWE study results interpretation, RWE policy stakeholders stand to benefit from this intentional design. Standardization mechanisms inherently offered by RWE MPs may reduce variation to foster the production of more reliable and directly comparable evidence, and more consistent interpretation of results. RWE MPs aim to provide minimum necessary standards for multisite RWE studies, promote effective communication across study sites, and other benefits, which translate into less redundant protocol development and more efficient uses of resources.
Appendix A: Duke-Margolis RWE Collaborative 2022 Advisory Group Members

This paper was informed by the expert collaborators in the Duke-Margolis Real-World Evidence Collaborative Advisory Group. We thank the members of the Advisory Group, especially those from the 2022 cohort, for informing the development of this paper. The following list reflects the 2022 Advisory Group roster, which advised on the initial development of this work stream.

Listed 2022 member affiliations may not reflect current affiliations. For a current roster of the Duke Margolis Real-World Evidence Collaborative's Advisory Group, please visit the RWE Collaborative page on the Duke-Margolis Center for Health Policy [website](http://healthpolicy.duke.edu).

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Appendix B: Appendix B: 2022 RWE Master Protocols Workstream Members

In 2022, The Duke-Margolis RWE Collaborative regularly convened select experts for the RWE Master Protocols Workstream. Monthly workstream discussions and breakout meetings culminated in hosting a 2023 private workshop on RWE MPs. Workstream member contributions at the workshop and throughout 2022 informed this paper’s development.

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Elise Berliner
Mac Bonafede
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Amanda Bruno
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Stella Chang
Noelle Cocoros
Gracy Crane
Liz Garry

Tom Haskell
Xiaolong “Jay” Jiao
Kristiyana Kaneva
Nicole Liaw
Jay Lin
Qing Liu
Nirosha Mahendraratnam Lederer

Khaled Sarsour
Debra Schaumberg
Jenny Stephens
Neal Storm
Bob Zambon
Lei Zhou

David Thompson
Open Health
Richard Willke
ISPOR
Marcus Wilson
Healthcore
Bob Zambon
Syneos Health
Appendix C: Participants at the “Harnessing the Potential of Real-World Evidence Master Protocols” Workshop

On February 28-March 1, 2023, the Duke-Margolis RWE Collaborative’s RWE Master Protocols Workstream hosted a private workshop including external, expert stakeholders.

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<tr>
<th>Adebola Ajao</th>
<th>Josh Fessel</th>
<th>Emily Rubinstein</th>
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<td>Ayad Ali</td>
<td>Henry (Joe) Henk</td>
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<td>Xiaolong “Jay” Jiao</td>
<td>Adam Shiell</td>
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<td>Marc Berger</td>
<td>Lisa Lavange</td>
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<td>William (Bill) Crown</td>
<td>Donna Rivera</td>
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<td>Joy Eckert</td>
<td>Carla Rodriguez-Watson</td>
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Appendix D: Glossary

**Common data model (CDM):** A comprehensive framework that includes definition, specifications, and operational rules for data to be presented and used in a common manner.

**Common protocols:** Separate protocols designed to align and coordinate across multiple studies in pursuit of achieving the appropriate level of master that is feasible and useful for the research context.

**Data element/value:** A piece of data corresponding to one patient within a data field.

**Data latency:** The time elapsed between when collected data is entered into a platform and when it has been incorporated into an available, updated dataset.

**Data source:** A collection of singular or mixed data types whose origin and method of collection are similar (e.g., electronic health records, claims, registries, etc.).

**Fit-for-purpose data:** An assessment of whether a meaningful, valid, and transparent data set can answer the question of interest given data quality, data relevancy, and the current body of evidence.

**Master protocol:** A single trial protocol designed to contain multiple substudies, each of which may have different objectives and involve coordinated efforts to evaluate one or more investigational questions across one or more outcome (e.g., different treatments and different disease subtypes).

**Minimum necessary standard:** An agreed upon level of data provenance transparency, quality, relevancy, reliability, and fitness-for-use.

**Real-World Data (RWD):** Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources (e.g., a patient’s electronic health record, hospital and insurance company administrative and claims data, patient-generated information outside of clinical settings, etc.).

**Real-World Evidence (RWE):** Evidence derived from real-world data through the application of research methods. For regulatory applications, RWE can further be defined as clinical evidence regarding the use and potential benefits or risks of a medical product derived from analysis of real-world data.
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