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Operational Tools and Best Practices to Support Electronic Health Record-Sourced Data Quality, Relevance, and Reliability at the Data Accrual Phase

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Disclosures

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EXECUTIVE SUMMARY

Electronic health records (EHRs) are an often reliable source of in-depth information about health care events, seeking behavior, and interactions throughout the course of a patient's life. Data that can be sourced from an EHR often includes structured and unstructured information within data fields, including but not limited to demographic details, clinical encounter details, diagnoses, symptoms, treatments, laboratory test results, prescriptions, imaging, charts, patient experience insights, and clinical narratives. Ongoing advancements and technological developments in EHR platforms, coupled with sophisticated data accrual methods used to obtain data or analytical insights from EHR records, have rendered EHR-sourced data useful to support critical decisions made within the health system, including regulatory decisions.

EHR-sourced data used to support regulatory decision-making falls within the scope of real-world data (RWD) and real-world evidence (RWE), rendering EHR-sourced data as subject to regulatory agency scrutiny. In this white paper, we discuss complex operational workflows that exist at the EHR-sourced data accrual phase; review current initiatives and use cases that provide insights into best practices for EHR-sourced data accrual management; and outline tools and best practices that can be useful among trial sponsors and data collaborators seeking to support EHR-sourced data relevance, reliability, and quality, and communicate those aspects to regulators and others.

HOW THIS PAPER WAS DEVELOPED

This paper draws upon insights gleaned from engagement within the 2024 Duke-Margolis RWE Collaborative workstream, entitled "Operationalizing Electronic Health Record Data Relevance, Reliability, and Quality for RWE Policy Stakeholders." The workstream met monthly between March-August, 2024 and conducted a private workshop entitled, "Operationalizing Electronic Health Record-Sourced Data for Quality, Relevance, and Reliability," on September 24, 2024. Workstream and 2024 RWE Collaborative Advisory Group members, all of whom contributed towards the development of and engagement in the workstream, are listed and named in **Appendices A and B.**

BACKGROUND

This white paper builds on our prior related work within Duke-Margolis to understand practical applications for RWD and RWE development using EHR-sourced data and ensure data relevance, reliability, and quality.[1, 2, 3, 4, 5, 6] In prior work, we explain that EHR-sourced data must be evaluated for systematic biases that skew representativeness and thus, hinder data relevance.[7] EHR-sourced data can be irrelevant for regulatory decisions for the public if it does not reflect patients with representative demographics, is overly influenced by individual physician practices, or includes inconsistent coding. Furthermore, an EHR-based study may have inclusion/exclusion criteria that render a single EHR dataset too small to be relevant in regulatory contexts.

Also, creating learning health care systems that are capable of creating and sharing relevant, reliable, and high-quality EHR-sourced data to meet both prospective and retrospective research and regulatory goals is an immediate and long-term aspiration that requires multi-system collaboration as well as standardization at multiple data management levels, including data accrual. EHR-sourced data comes in many forms as they can contain native data elements (e.g., patient demographics, health information collected from clinical encounters, etc.) and peripheral documents (e.g., imaging data and pathology reports). EHR platform features, including data fields, can be customized based on health system goals and standards, clinician information needs and documentation practices, patient preferences and information sharing behaviors, clinical guidelines, standard operating procedures, and more. The reliability of EHR-sourced data for research also is affected by the EHR system's primary role in supporting clinical workflow and electronic billing. As a result, data documented or captured within customizable and/or other types of EHR platforms may differ across health systems and clinical practices even for a single patient or patient population, leading to inconsistencies in data that becomes documented or provided within the EHR. As mentioned in our prior work from one health system representative, "The EHR records can be useful, but it's a pretty heavy lift. And that is the result of issues around trying to develop data standards, then implementing data standards within the EHR."[8]

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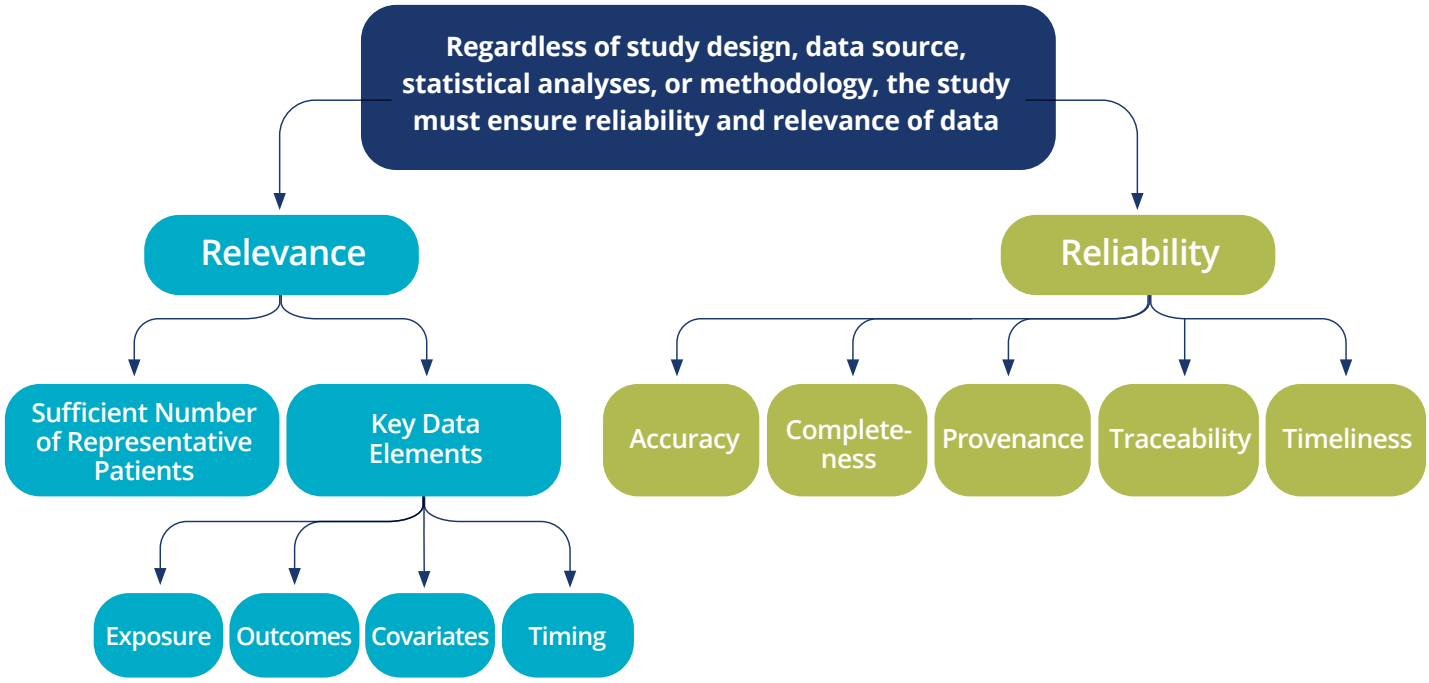
EHR-sourced data use is accompanied by limitations that have been and should be noted. EHR-sourced data can be arguably biased based on the context in which data were accrued (e.g., emergency, inpatient, or outpatient care). Also, the primary purpose of an EHR is to collect information needed to facilitate clinical care, documentation, and billing, whereas EHR-sourced data use and sharing often becomes a secondary purpose or endeavor. Last but not least, since not all individuals have continuity of care across different, disconnected health care systems, additional concerns over EHR data completeness and accuracy remain relevant. While these complexities alone can make RWD standardization during data accrual phases uniquely challenging even within a single health system, certain practices like conformance checks to assess data structure, can characterize a source's completeness, missingness, and plausibility. Moreover, transparency and collaboration among those who work with health systems for data management and use purposes continues to be helpful in identifying best practices and tools. These tools can be leveraged to achieve these best practices and facilitate communication with regulators and collaborators in RWE generation, management, use, and consideration.

Overview of Regulatory Fit-For-Purpose Considerations for EHR-Sourced Data

The U.S. Food and Drug Administration (FDA) has provided guidance to sponsors concerning EHR-sourced data relevance and reliability at the data accrual phase (outlined in **Figure 1**). Reliability is determined by the accuracy, completeness, and traceability of a dataset as well as data integrity and quality. Data relevance is determined by the number of representative patients available for a study and by key data elements related to exposure, outcomes, covariates, and timing.[9] In cases where RWE is derived from multiple RWD sources, each source will be evaluated as standalone and aggregated data to determine its relevance and reliability. If data is not accrued in a relevant and reliable manner, then it will be unfit for any downstream uses.

Figure 1 | Regulatory Fit-for-Use Considerations for EHR-Sourced Data at the Accrual Phase



Use Cases of Fit-For-Purpose EHR-Sourced Data

RWE can play a critical role when traditional randomized clinical trials (RCTs) are unable to generate sufficient evidence for regulatory consideration for logistical, ethical, or other reasons. Before sponsors are allowed to market a new drug, they are required to demonstrate substantial evidence that a new treatment safely and effectively works as intended, and that evidence may include RWE. FDA has generally interpreted substantial evidence to include "two adequate and well-controlled clinical investigations."

Although, alternative approaches to RWE as substantial evidence within a total evidence package warrant consideration based on lessons learned in prior use cases concerning several drugs and one medical device. We highlight them below in **Table 1.** Further use cases highlighting clinical trials and FDA Demonstration Projects are in **Appendix C.**

Table 1 | Use Case Description: Drug/Medical Device

	Avapritinib[10, 11]	Capmatinib[12, 13, 14]	Alpelisib[12]	Tazemetostat[15]	MSK-IMPACT[16, 17] (Integrated Mutation Profiling of Actionable Cancer Targets)
Indication/ Device Purpose	Adults with unresectable or metastatic GIST harboring a PDGFRa exon 18 mutation, including PDGFRa D842V mutations	Treatment of adult patients with metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping as detected by an FDA-approved test	Indication: Adult and pediatric patients two years of age and older with severe manifestations of PIK3CA-related overgrowth spectrum who require systemic therapy	Adult patients with relapsed or refractory follicular lymphoma	Device: Qualitative in vitro diagnostic test that uses targeted next generation sequencing of formalin-fixed paraffin-embedded tumor tissue matched with normal specimens from patients with solid malignant neoplasms to detect tumor gene alterations in a broad multi-gene panel
FDA Decision	Full Approval in 2020	2020 Accelerated Approval, converted to Full Approval in 2022 after additional trial data to verify clinical benefit	Accelerated Approval in 2022	Accelerated Approval in 2020	Granted device approval in 2017
RWE Source	Chart review from Retrospective, multicenter chart review to characterize natural history of patients with PDGFRa D842V driven GIST previously treated with TKI	The initial application included RWE retrospective chart collection data (Study X2401) to describe the natural history of advanced MET dysregulated NSCLC	EPIK-P1, a single-arm chart review study in patients two years of age and older with PIK3CA-related overgrowth spectrum who received alpelisib as part of an expanded access program (EAP) for compassionate use	EHR data; Molecular data on EZH2 mutation status and clinical information were collected through patients' medical records and institute database from four major cancer centers	EHR data from advanced cancer patients; database included patient-matched controls
RWE used in regulatory decision	**Yes**	**Yes**	**Yes**	**No,** study only used as descriptive	**Yes**
FDA Comments	Patient data were collected over a relevant time period; data analysis was done routinely to minimize potential confounding	Incomplete data submitted. However, FDA considered data from Study X2401 to be supportive	The acceptability of EPIK-P1 data was supported by the following attributes: use of a prospectively defined protocol for data collection and statistical analysis plan; use of blinded, independent, central review to assess patient imaging; and broad eligibility of patients participating in the EAP to reduce selection bias	The study did not report missing data elements, including the study period and inclusion and exclusion criteria. The FDA had concerns about generalizability, potential selection bias, and confounding bias	RWE extracted from a retrospective review of medical records was used to estimate somatic mutation prevalence, validate a cut-off, and support evaluation of a claim for the sponsor's De Novo classification request

Related Initiatives

A joint initiative between the FDA's Oncology Center for Excellence (FDA OCE) and Reagan-Udall Foundation for the FDA created the Oncology Quality, Characterization and Assessment of Real-World Data (QCARD) Initiative that provides key RWD and study design elements needed for an initial oncology proposal to FDA.[18] This Initiative was developed with the intent to help streamline the FDA's assessment of RWD appropriateness and feasibility. Through a landscape analysis and stakeholder engagement with domain experts, an executive committee developed an Initial Proposal Characterization (IPC) with six domains:

- **Data temporality:** the availability of original source data, study period, extraction date(s), and an initial study design diagram.
- **Study population:** the therapeutic area, indication statement, biomarker data, eligibility criteria, anticipated study size, and demonstration of external validity.
- **Medical product exposure, comparator, and covariates:** exposure type and description, comparator of interest and description, and covariates of interest beyond the exposure of interest.
- **Clinical endpoint measurement:** definitions of both the primary and secondary endpoints (potentially including associated operational definitions).
- **Statistical analysis plans:** planned analysis methods for the primary endpoint(s) along with bias and confounding variable controls (as needed).
- **Data quality:** individual quality plans for data auditing, data provenance documentation, data quality control, and missing data strategies.

These domains help medical product developers, sponsors, narrow in on key areas that are necessary to address for and with regulators. Importantly, the Oncology QCARD-IPC only represents a first step in the review process and provides the minimum essential data expectations. Sponsors should expect expanded documentation and demonstration requirements as the regulatory process proceeds. Although oncology focused, the Oncology QCARD-IPC can be potentially useful as a general mechanism to support FDA filings and submission outside the scope of oncology that incorporates RWD elements for regulatory consideration. We discuss in more detail below how the Oncology QCARD-IPC can be useful in practice to ensure EHR-sourced data is fit-for-use in regulatory settings.

The Professional Society for Health Economics and Outcomes Research (ISPOR) has described common concerns and limitations of EHR-sourced data and presents ISPOR's Suitability of EHR Data (SUITABILITY) Checklist as a helpful tool for health technology assessments (HTAs).[19] Because most EHR data is unstructured and formerly not widely analyzed, it is capable of providing previously unavailable information on clinical rationale for treatment or care decisions. Given the purpose of HTAs—measuring health technologies' value throughout their lifecycle—that information can greatly enhance the organizational decision-making processes. On the other hand, EHR data requires resource- and labor-intensive processing, commonly referred to as extraction, transformation, and loading (ETL). In their article, ISPOR acknowledged the risk of bias, errors, and information loss during ETL. Thorough, transparent "gold standard" protocols, where specialized staff follow validated protocols, are needed to mitigate this risk. The ISPOR taskforce recommends HTA organizations follow their SUITABILITY Checklist, which attempts to fill the gap of similar frameworks that treat EHRs inconsistently and non-specifically. It provides guidance for both data delineation (characterizing data, establishing data provenance, and confirming proper governance) as well as data fitness-for-purpose (establishing data reliability and relevance) determinations.

Both the Oncology QCARD-IPC and SUITABILITY Checklist represent critical and generalizable steps toward consensus building for organizational EHR-sourced data standards and expectations, despite being field- or non-regulatory end-user specific.

Operationalizing Relevance, Reliability, and Quality

The fundamental goal of using EHRs is to support clinical care and documentation.[20] They are, therefore, optimized to help clinicians carry out patient care and document those interactions for later referral and other administrative actions.[21] Secondary research activities and needs, however, may or may not align with EHR systems' designs and operational features. The seeming disconnect between EHR system design and research goals creates an opportunity to bridge informational gaps through the use of existing tools and best practices.

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Four broad challenges with data accrual from EHR systems exist, with the first challenge dealing with concerns about harmonizing various data sources within and across EHR systems. Depending on the research question of interest and subsequent study design, investigators may accrue data across multiple EHR systems and subsequently, pool the data together.[22] Systems are likely to vary in underlying data models, leading to different data representations and storage formats.[23] Even within a single health system, coding between clinical units (e.g., outpatient, hospital, laboratory, etc.) may diverge.[24] Consequently, harmonizing these data is a prerequisite for teams to be able to run further analyses and draw conclusions. Doing so necessitates data interoperability and standardization. Researchers' ability to harmonize their data, as well as their capacity to demonstrate the validity of harmonization efforts, can significantly impact fitness-for-use determinations. This aspect additionally extends to more fundamental considerations of trial sites' IT resources and infrastructure for accruing data from their EHR systems. Their ability to do so, and the extent to which sites are capable of developing needed infrastructure, may impact their capacity to participate in EHR-based trials.

As mentioned above, a second challenge is that EHR data can present in structured or unstructured formats. While EHR architecture for structured data may introduce possible bias, the second broad challenge considers difficulties related to unstructured data abstraction within EHRs. Unstructured data has the capacity to richly contextualize clinical rationale for treatment decisions.[25] Sufficiently excavating decision-making processes, however, requires text abstraction and coding. Manual free text review and abstraction introduce the possibility for differences in EHR documentation among individuals (i.e., low inter-related reliability) and thus bias in resulting EHR data.[26] To mitigate this risk, extensive training of individual coders according to well-validated and transparent abstraction protocols is suggested.[27] While beneficial, doing so can be resource- and labor-intensive, burdening the research process and limiting teams' overall capacity for data accrual. Assisting mechanisms, like artificial intelligence and machine learning (AI/ML) algorithms capable of identifying themes and patterns within unstructured data, are considered as an alternative to manual abstraction.[28] Although, AI/ML performance varies and should be validated through transparent reporting mechanisms.[29] Examples of validation demonstrations include iterative benchmark tests throughout a study, federated, multi-site training with standardized algorithms, or performance comparison to gold standard approaches.[30] In fact, a "gold standard" approach may need to be reconsidered based on context. In especially labor-intensive and time-sensitive surveillance, optimal performance may call for ML to compliment manual abstraction of unstructured notes.[31] Additionally, more general governance considerations for AI use within health systems, as explored in other Duke-Margolis work, should be considered.[32]

The third challenge deals with missing data within EHR datasets. Patient movement, referral, and navigation between health systems, due to a variety of factors, can cause incomplete data capture and fragmentation.[33] Even

within a single health system, data may not be captured across clinical subunits. For example, ambulatory or specialty EHR data may not be accessible or visible within inpatient datasets.[34] Additionally, time-lags due to awaiting laboratory test results, differing clinical practices, and non- or inconsistent adherence to clinical guidelines can impact how and whether clinical data are captured.[35] Consequently, investigators must work to assess the completeness of their acquired datasets and, when possible, what options they have to address missingness. Carrying out subgroup analyses to assess gaps within the data or linking EHR data with other sources (like claims or patient-generated data) are possible strategies to address this problem.[36] Implementing these solutions carries further considerations that could limit the overall utility of an EHR dataset. Linking data sources, for instance, would likely necessitate removing unlinked patient data from an analysis, reducing the total sample size, and can possibly introduce selection bias into the resulting linked sample.[37, 38] This challenge underscores the importance of data provenance across all stages of the data lifecycle, including any transformations that take place. If research teams are relying on retrospective "research-ready" datasets, they are drawing from third-party vendors that may have varying degrees of transparency into their data accrual techniques. Regulatory authorities require in-depth knowledge of research data and metadata provenance in order to determine its relevance, reliability, and quality. Proprietary limitations on the level of access provided to researchers and/or regulatory authorities about vendors' accrual and transformation practices can impede fitness assessments.[39] Operationally, teams must consider how they can provide adequate information surrounding provenance as they design their study.

The fourth challenge recognizes that investigators should consider how research can impact clinicians and care flows. Given that EHRs are geared towards clinical care and administrative needs of health systems, secondary research (when done prospectively) often requires additional actions from clinicians that might conflict with their scope of training and care.[40] These actions may include carrying out extra tests and exams (which may or may not involve insurer authorization) as well as inputting supplementary information into the EHR, either as free text or in specialized research fields. Though researchers are encouraged to minimize these additional activities to the extent possible, clinicians are already operating at high-capacity, whereby added responsibilities may increase documentation burden and negatively impact clinician well-being and burnout.[41, 42] Research protocols that do not sufficiently address these considerations could diminish clinicians' willingness to participate in studies, as seen in the ICAREdata demonstration project.[43]

Tools and Best Practices

Both general and context-dependent tools as well as best practices to support goals to operationalize relevance, reliability, and quality at the EHR data accrual phase can offer standardized approaches to readily communicate research methods and findings with collaborators, including regulators. We highlight these tools below in **Tables 2 and 3** and best practices in the next two sections (see **Appendix D: Glossary of Tools**).

Table 2 | Useful Tools to Assess the Relevance, Reliability, and Quality of EHR-Sourced Data

Tool	Relevance	Reliability	Quality
SPIFD	X	X	
SPACE		X	
SPIFD2	X	X	
STaRT-RWE	X		X
NIST AI Risk Management Framework		X	
FDA QCard Initiative	X	X	X
TransCelerate Audit and Inspection Readiness Considerations	X	X	
HARPER	X	X	X
ATRAcTR	X	X	X

Table 3 | Features, Limitations, and Applications Associated with Useful Tools to Address the Relevance, Reliability, and Quality of EHR-Sourced Data

Tool	Features	Limitations	Application
SPIFD	Provides systematic process to conduct feasibility assessments; Identifies relevant, fit RWD for research that informs decision-making; Openly available templates; Visual structure that compares databases across domains so investigators can select data sources	Not all of the variables that it evaluates may be pertinent during any given research question; Time-intensive to use; Limited scalability; Has already been updated as SPIFD2	Contemplating study design and defining variables for target trial emulation
SPACE	Identifies design elements and minimal criteria for feasibility, validity, and transparency; Helps investigators lay out all assumptions and variables to ensure valid study design	Heavily relies on directed acyclic graphs; Has been updated and integrated into SPIFD2	Documenting decision-making to ensure sufficient transparency for regulatory purposes
SPIFD2	Updated SPIFD by incorporating lessons from SPACE	Has yet to become widely adopted among the research community, warranting further work demonstrating the utility of SPIFD2	Combined utility of SPIFD and SPACE
STaRT-RWE	Provides a detailed template to design and report on study implementation using RWD to create reproducibility and clear communication	Not a definitive checklist for unbiased decisions	Quickly finding and sharing information to evaluate and compare RWE-based studies
NIST AI Risk Management Framework	Comprehensive white paper on artificial intelligence developed through extensive, public-partner deliberation	Not inherently health care or RWD/E focused	Evaluating, understanding, and mitigating any risks accompanying artificial intelligence use at the data accrual stage
FDA Qcard Initiative	Easy to disseminate and publicize as US FDA tool; Informative for oncology-focused reviews; High level lessons could be applicable beyond oncology	High level; Designed specifically for oncology use cases	Evaluating data reliability prior to FDA review of an oncology product
TransCelerate Audit and Readiness Considerations	Comprehensive white paper directed to medical product sponsors, data curators, and regulators to demonstrate RWD source reliability and relevance for product effectiveness; Extensive terminology definitions	Does not specifically address safety or overall fitness-for-purpose	Communicating standards and tailoring management systems for a regulatory decision about effectiveness
HARPER	Intends to improve reproducibility, replicability, and assessment of potential bias sources in a study using RWD; Communicates data provenance, design, analysis, and RWE study implementation	May not be useful for communicating transparency at every stage of the study/data life cycle	Assisting investigators and reviewers in decision-making about study parameters, biases, and study reproducibility
ATRAcTR	Provides user-friendly screening criteria to evaluate RWD source quality and fitness-for-purpose to create RWE	Does not directly address the RWE study design issues that regulators consider when evaluating safety/effectiveness	Training researchers with less RWD management experience and evaluating existing RWD sources for new RWE generation

Certain limitations to the use of these tools should be noted along with opportunities to address them. The practical application and relevance of any given tool can be very siloed and limited to a specific number and type of use cases. Furthermore, tools may not be widely applicable across the data life cycle and usable among those encountering or managing EHR-sourced data. Even if researchers hold both relevant expertise and research needs that fit a specific tool, it will be helpful to also prioritize EHR system interoperability using Fast Healthcare Interoperability Resources application programming interface (FHIR API) along with necessary data standard formats (i.e., Clinical Data Interchange Standards Consortium or CDISC standards required by the FDA)

and/or the Observational Medical Outcomes Partnership (OMOP) common data model (CDM).[44, 45, 46] An important qualifier for CDMs is that the normalization process potentially can lead to information errors or loss among superficially similar data that are functionally distinct between health systems.[47] Continually evolving CDMs, APIs, and federated analyses—analyses performed on multiple, separated datasets rather than a single, centralized dataset—may be more sustainable for the rapid pace of current and future data management.

Prospective EHR Data Accrual Best Practices

EHRs are integral to capture data within RCTs through point-of-care (POC) and pragmatic trials, efforts to combine EHR data with RCT data, and single-arm trials or non-interventional studies (i.e., observational studies).[48] Further, EHR system designs can support trial design and the generation of supplemental evidence. EHRs are particularly useful when sponsors are able to curate templates within the EHR to collect specific trial data more routinely and seamlessly through prospectively designed RWE studies. Informed consent documents can also become embedded within EHRs.[49]

The FDA's Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice Draft Guidance acknowledges the UK RECOVERY Trial as a successful example of using clinical EHR infrastructure and health care providers in hospitals in a trial setting.[50] A pragmatic trial, the UK RECOVERY Trial evaluated randomized COVID-19 interventions using an adaptive trial platform. Data collection was optimized through integration with national health care datasets, enabling simple enrollment and follow-up of acutely ill patients. The point-of-care trial operational approach used in the UK RECOVERY Trial helped researchers and clinicians decipher treatments more readily to optimize treatment selection and thus, patient care.

While the UK's national health care system facilitates the implementation of large-scale, point-of-care, and pragmatic trials using EHR data, the fragmented structure of the U.S. health care system presents greater challenges.

While the UK's national health care system facilitates the implementation of large-scale, point-of-care, and pragmatic trials using EHR data, the fragmented structure of the U.S. health care system presents greater challenges. One such challenge is that EHR system integration can increase training time and place additional burdens on clinicians. Although, EHR system integration is key for facilitating POC and pragmatic trials, sponsors must acknowledge any increased burdens associated with integration that are placed on health care providers. For example, sponsors can collaborate with health systems to develop systems and protocols that integrate trial operations into standard clinical care workflows (i.e., collection of patient vitals, patient-reported outcomes surveys, routine laboratory testing, etc.).

General best practices can be considered within the scope of prospectively collecting or accruing EHR data to address clinical research questions of regulatory concern. Best practices prioritize data completeness, integrity, and provenance throughout the data lifecycle. These checks should be pre-defined before initiation of the study protocol and carried out repeatedly in order to ensure continued data reliability, relevance, and quality. Additionally, cross-team communication and collaboration is key for robust, comprehensive data accrual. Further, it is necessary to ensure the study team collectively possesses all the required expertise and knowledge for the project, including expertise about the data source(s), including but not limited to EHR-sourced data, and content area expertise. Lastly, if study teams rely on AI/ML algorithms, these should be validated against "gold standard" processes at several points during the study period. Documentation of these checks should be thorough and transparent.

Prospective EHR-Sourced Data Accrual Best Practices

- ✔ Carefully document data linkage, tokenization, and other data manipulations/transformations throughout the study process to evaluate exclusion patterns and/or selection bias (e.g., linking claims and EHR data can limit population to insured patients). This linkage is key for maintaining data provenance throughout the study.
- ✔ Review and validate impactful study processes before implementation. Possible examples include 1) data quality teams' data checks and queries being validated by the clinical team or 2) the RWD team provides input on the clinical team's review of data, mapping rules, and relevant documentation maintenance expectations.
- ✔ Develop feasibility evaluations and templates (pre-specified in the study protocol) to assess sufficient data completeness and detail in EHR datasets.
- ✔ When relying on algorithms (e.g., AI/ML), validate those through transparent mechanisms. This validation should be done against "gold standard" processes. An example would be developing a set of "benchmark tests" for the AI to complete repeatedly throughout the study to observe any changes or algorithmic/model drift.
- ✔ Specify how patient follow-up, data time-stratification, and data latency are assessed within an EHR data sources given porous patient data and changes over time.

Retrospective EHR Data Collection Considerations

Retrospective EHR-sourced data evaluation can assist researchers with study endpoints selection (time to treatment discontinuation, time to treatment effect, overall survival, etc.), type (single measure, composite, multi-component, etc.), and positioning (primary, secondary, exploratory). For example, retrospective EHR-sourced data was considered by the FDA in the case of STRENSIQ, a treatment for perinatal/infantile-, and juvenile-onset hypophosphatasia (HPP), which is a rare, genetic, progressive, metabolic disease in which patients experience devastating effects on multiple systems in the body, leading to severe disability and life-threatening complications. The study used external RWD controls (direct matching) to collect efficacy and effectiveness data and identify a primary real-world endpoint (overall survival). Patients with juvenile-onset HPP treated with STRENSIQ showed improvements in growth and bone health compared to a natural history control group.

As seen in the case of STRENSIQ, when fit-for-use, retrospective EHR-sourced data can serve as an external control arm (e.g., direct matching) in pivotal trials evaluating the safety and efficacy of a given treatment within a patient cohort. When considering the use of retrospective EHR-sourced data, sponsors and data collaborators should ensure EHR-sourced data is complete, as missing data can interfere with regulators' ability to determine prognostic factors and compare outcomes among real-world versus trial populations. Sponsors and data collaborators also should ensure that external control arm data sourced from EHRs can be appropriately matched with trial data; reflect current standards of primary, secondary, and tertiary care to ensure generalizability; and are accompanied by protocols outlining methods used to address missing data.

In addition to the best practices for prospective EHR data accrual and considerations above, general best practices can be considered within the scope of retrospectively

collecting or accruing EHR data to address clinical research questions of regulatory concern. These practices include transparency from data vendors and other third parties on how data are obtained and manipulated, which is critical for the study team to be able to adequately contextualize the data source, identify inherent limitations, and draw meaningful conclusions from the data alongside regulators. Investigators also should understand certain legal restrictions or protections that affect data vendors' ability to disclose data sources to third-parties, including regulators. Teams should anticipate and discuss how or whether any transparency restrictions could impact the regulatory acceptability of submitted RWE.

Retrospective EHR-Sourced Data Accrual Best Practices

- ✔ Ensure external control arm data sourced from EHRs can be appropriately matched with trial data.
- ✔ Ensure EHR data reflects current standards of primary, secondary, and tertiary care to ensure generalizability.
- ✔ Provide data management protocols that outline methods used to address missing data.
- ✔ Establish the highest possible level of transparency in adherence with proprietary laws and policies applicable to third-party data vendors.
- ✔ Obtain transparent documentation around data lineage, manipulations, and curation processes, etc.
- ✔ Develop and deploy data quality controls and assurance processes to identify limitations and biases within the RWD source and results.

CONCLUSION

EHR-sourced data is vast in nature (structured and unstructured information within data fields, and more) and thus, hold equally vast potential to address research questions of regulatory concern regarding medical product safety and efficacy. EHR systems and EHR-sourced data alike, as they are used in both pragmatic and pivotal trial settings, come with unique challenges and opportunities that warrant a close consideration of best practices and data management tools to support EHR-sourced data accrual operations embedded in research. The tools and best practices outlined herein can be a useful starting point among trial sponsors and data collaborators seeking to support EHR-sourced data relevance, reliability, and quality and communicate those aspects to regulators and others.

Appendix A | RWE Collaborative Advisory Group Roster

This paper was informed by the expert collaborators in the Duke-Margolis 2024 Real-World Evidence Collaborative Advisory Group. The following list reflects the 2024 Advisory Group roster, which advised on the initial development of this workstream. Listed member affiliations may not reflect current affiliations. For a current roster of the Duke-Margolis RWE Collaborative's Advisory Group, please visit the RWE Collaborative webpage.

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Appendix B | Operationalizing Electronic Health Record-Sourced Data for Quality, Relevance, and Reliability Workstream Roster

This paper was informed by monthly meetings of the 2024 RWE Collaborative workstream on operationalizing EHR-sourced data. The following list represents workstream participants and their affiliations as of December 2024.

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Appendix C | Additional Use Cases

Use Case Description: Clinical Trial

Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness (ADAPTABLE Trial)[54, 55]

- Study design: open-label, randomized, pragmatically designed, comparative effectiveness study that compared two commonly used aspirin doses—81 mg and 325 mg.
- RWE source: Over 15,000 atherosclerotic cardiovascular disease (ASCVD) patients were evaluated through primary and secondary National Patient-Centered Clinical Research Network (PCORnet).
- Endpoints and positioning:
  - Primary effectiveness outcomes: time to a first occurrence of any event in the composite of death from any cause, hospitalization for myocardial infarction, or hospitalization for stroke.
  - Secondary outcomes: coronary revascularization (percutaneous coronary intervention or coronary-artery bypass grafting), the individual components of the primary outcome, and hospitalization for transient ischemic attack.
  - Primary safety outcome: hospitalization for major bleeding with an associated blood-product transfusion.
  - Patient-reported outcomes: PCORI Patient-Reported Outcomes Common Measures is a short survey form administered through a patient portal (or call center) at baseline and every six months.

Use Case Description: Demonstration Project

VESALIUS-CV EHR Demonstration Project[56]

- FDA RWD/E Demonstration project with three goals: 1) develop recommendations for evaluating RWD within large trials, 2) assess EHR data accuracy for clinical characteristics during longitudinal trial participant follow-up, and 3) understand operational considerations for EHR-sourced multi-center trial organization, site-level characteristics, and existing trial site infrastructure.
- Researchers employed a multi-modal approach with three data extraction strategies applied according to site experience and IT capabilities:
  - Network Consortium: applicable to sites with existing participation in the PCORnet distributed research network and past common data model (CDM) data mapping work. Coordinating center provided data requirements; sites supplied requested data.
  - Map-to-CDM: applicable to sites with prior, but no current, participation in a distributed research network that wanted to develop an in-house datamart for future projects. After a site's datamart was built, the site followed the Network Consortium procedure.
  - Central Transformation: applicable to sites with limited IT resources. Trial sites sent standardized reports (for individual EHR data domains) to the coordinating center for centralized transformation.
- Major lessons learned include variability in site performance for participant enrollment; data ownership and trial operations varied from site-to-site and impacted efficiency; and regardless of site experience, broad data policies required iterative, site-specific adaptation.

Integrating Clinical Trials Data and Real-World Endpoints Data (ICAREdata) Project[57]

- FDA RWD/E Demonstration Project working across 15 clinical trials and 10 trial sites to streamline clinical trial data acquisition from EHRs and eliminate redundancies by developing structured endpoint measures to capture traditionally unstructured data.
  - Developed two EHR data elements—*cancer disease status* and *treatment plan change*—through standardized questions answered by clinicians during routine workflow in added fields within the EHR.
  - Study data elements were captured by the minimal Common Oncology Data Elements (mCODE) data model, transported via FHIR API, and compared to trials' existing electronic data capture (EDC) system through a concordance analysis
- Operational lessons covered data capture, extraction and transmission, concordance, and workflow.
  - Data capture in real-world settings can occur irregularly.
- Data elements deviated from routine clinical workflow and sites experienced some difficulty in clinician participation due to increased reporting burden.
  - Data extraction and transmission was hindered due to IT resource limitations, security reviews, and contract delays. These could have been mitigated with earlier contract negotiations and clinician-IT team connection.

Appendix D | Glossary of Tools

Below are the full names of each data tool described in **Table 2 and Table 3.**

SPIFD
The Structured Process to Identify Fit-For-Purpose Data: A Data Feasibility Assessment Framework
Peer-Reviewed Article | October 30, 2021[58]

SPACE
A Structured Preapproval and Postapproval Comparative Study Design Framework to Generate Valid and Transparent Real-World Evidence for Regulatory Decisions
Peer-Reviewed Article | July 2019[59]

SPIFD2
A Structured Process to Identify Fit-For-Purpose Study Design and Data to Generate Valid and Transparent Real-World Evidence for Regulatory Uses
Peer-Reviewed Article | March 17, 2023[60]

STaRT-RWE
Structured Template for Planning and Reporting on the Implementation of Real-World Evidence Studies
Peer-Reviewed Article | January 12, 2021[61]

NIST AI Risk Management Framework
National Institute of Standards and Technology – Artificial Intelligence Risk Management Framework
White Paper | January 2023[62]

FDA QCard Initiative
United States Food and Drug Administration—Oncology Quality, Characterization and Assessment of Real-World Data Initiative
Webpage | Updated October 2024[63]

TransCelerate Audit and Inspection Readiness Considerations
Assuring Audit and Inspection Readiness – Considerations for The Use of RWD and RWE in Regulatory Decision-Making
White Paper | December 2023[64]

HARPER
Harmonized Protocol Template to Enhance Reproducibility of Hypothesis Evaluating Real-World Evidence Studies on Treatment Effects: A Good Practices Report of a Joint ISPE/ISPOR Task Force
Peer-Reviewed Article | October 10, 2022[65]

ATRAcTR
Authentic Transparent Relevant Accurate Track-Record: A Screening Tool to Assess the Potential for Real-World Data Sources to Support Creation of Credible Real-World Evidence for Regulatory Decision-Making
Peer-Reviewed Article | November 29. 2023[66]

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