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ISPOR Report

Improving Transparency to Build Trust in Real-World Secondary Data Studies for Hypothesis Testing—Why, What, and How: Recommendations and a Road Map from the Real-World Evidence Transparency Initiative

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ABSTRACT

Real-world data (RWD) and the derivations of these data into real-world evidence (RWE) are rapidly expanding from informing healthcare decisions at the patient and health system level to influencing major health policy decisions, including regulatory approvals and coverage. Recent examples include the approval of palbociclib in combination with endocrine therapy for male breast cancer and the inclusion of RWE in the label of paliperidone palmitate for schizophrenia. This interest has created an urgency to develop processes that promote trust in the evidence-generation process. Key stakeholders and decision-makers include patients and their healthcare providers; learning health systems; health technology assessment bodies and payers; pharmacoepidemiologists and other clinical reseachers, and policy makers interested in bioethical and regulatory issues. A key to optimal uptake of RWE is transparency of the research process to enable decision-makers to evaluate the quality of the methods used and the applicability of the evidence that results from the RWE studies.
Registration of RWE studies—particularly for hypothesis evaluating treatment effectiveness (HETE) studies—has been proposed to improve transparency, trust, and research replicability. Although registration would not guarantee better RWE studies would be conducted, it would encourage the prospective disclosure of study plans, timing, and rationale for modifications. A joint task force of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the International Society for Pharmacoepidemiology (ISPE) recommended that investigators preregister their RWE studies and post their study protocols in a publicly available forum before starting studies to reduce publication bias and improve the transparency of research methods.

Recognizing that published recommendations alone are insufficient, especially without accessible registration options and with no incentives, a group of experts gathered on February 25 and 26, 2019, in National Harbor, Maryland, to explore the structural and practical challenges to the successful implementation of the recommendations of the ISPOR/ISPE task force for preregistration. This positioning article describes a plan for making registration of HETE RWE studies routine. The plan includes specifying the rationale for registering HETE RWE studies, the studies that should be registered, where and when these studies should be registered, how and when analytic deviations from protocols should be reported, how and when to publish results, and incentives to encourage registration. Table 1 summarizes the rationale, goals, and potential solutions that increase transparency, in addition to unique concerns about secondary data studies.

Definitions of terms used throughout this report are provided in Table 2.

Keywords: real world evidence, regulatory decision-making, transparency, study registration.

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Introduction

"Trust but Verify" (-Russian Proverb)

In the government, consumer markets, and the financial sector, transparency is a critical policy tool to engender trust among stakeholders and enable these stakeholders to evaluate the quality of information used to inform decision-making. Transparency can help decision-makers set priorities and make decisions that are legitimate and fair—and that are perceived as such.[1] In evidence-based medicine, these needs are similar.

Those who make regulatory, coverage and reimbursement, and other healthcare decisions need to be able to evaluate and make informed decisions on the basis of high-quality relevant evidence.

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Interest is growing in the use of data from clinical practice, referred to as real-world data (RWD), as well as the derivations of these data into real-world evidence (RWE), to help inform these decisions.[2] This growing interest has created an urgency to develop processes that promote trust in the evidence-generation process and to enable decision-makers to evaluate the quality of the methods used in real-world studies.[3-7] The need to increase the credibility of RWE is becoming more important as RWE studies play an increasing role in healthcare decision-making.

RWE studies based on the secondary analysis of existing data are susceptible to biases, which are less of an issue for preplanned studies of prospectively collected data (eg, the primary analysis of a randomized controlled trial). For example, RWE studies are more susceptible to results-driven design modifications. Furthermore, an understanding of the totality of evidence is poor because of a bias against publishing these types of studies.

Although transparent reporting of study methodologies would help users understand how the findings from these studies were produced, a transparently reported study is not necessarily one of high quality.[8] Poorly conducted RWE studies can be fully transparent. Nevertheless, transparency improves the ability of decision-makers to assess the quality and validity of a study by giving them a deeper understanding of why and how the research was conducted and whether the results reflect preestablished questions and methods. Transparent reporting also facilitates the replication of results and an understanding of why findings of apparently similar studies differ.[9,10] Conversely, lack of study transparency makes it difficult for decision-makers to distinguish between high-quality and flawed studies.

Study registration—particularly for hypothesis-evaluating treatment effect (HETE) studies using secondary data[11]—has been proposed to improve transparency and trust in RWE. HETE studies or comparative treatment effect studies evaluate the presence or absence of a prespecified effect or its magnitude. Existing study registries (eg, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Post-Authorisation Study [EU-PAS] register and ClinicalTrials.gov) focus on studies that collect primary data or lack many of the features needed for a study registry designed to improve transparency (see Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.04.002).

This report describes an approach designed to facilitate the registration of HETE studies that analyze existing data and were collected for reasons other than research (eg, insurance claims, electronic health records, and patient registry data). The focus is on studies that test hypotheses or make causal inferences about the effects or safety of 2 or more interventions. Although other types of patient-contributed data from wearables and mobile device apps are increasingly part of the digital data landscape, the use or impact of these types of data is outside the scope of this article; however, these data will also likely benefit from these efforts.

Transparency to Ensure High-Quality RWE

Figure 1 shows the relationships among interventional and noninterventional studies as well as among primary and secondary data. This article is focused on the subset of secondary data studies that evaluate treatment effects. These RWE studies will be the ones most likely to inform decision making and, therefore, are under the most scrutiny. These HETE studies are the main focus of the following discussion.

Although the most stringent requirements for transparency might be for RWE used for regulatory assessment and health technology assessment (HTA), payers and others who use data to make evidence-based healthcare decisions for populations are increasingly seeking robust, transparent RWE studies to inform their decisions.[4]

Secondary data are used for hypothesis evaluation, most successfully in pharmacovigilance and postapproval safety studies, such as the U.S. Food and Drug Administration's Sentinel Initiative and the Canadian Network of Observational Drug Effect Studies. In addition, several efforts are underway to evaluate if the same results as clinical trials can be obtained using RWD to show the capabilities of high-quality studies that use noninterventional data sources.[12,13]

Numerous regulatory agencies, HTA agencies, and professional societies have published guidelines for designing, conducting, and analyzing the results of RWE studies.[14-25] These guidelines address such issues as ensuring the high quality of RWD collection and curation processes, making causal inferences from studies that evaluate hypotheses about treatment effectiveness or safety, adequately reporting study results, and ensuring reproducibility of study results. Nevertheless, reporting guidelines may not be enough to engender transparency of study methods in enough detail for some end users of the results.

Further complicating these issues are the differences between RWE studies based on secondary analyses and studies that collect data prospectively. RWE studies often use noninterventional secondary data that can be obtained and analyzed quickly once the researcher obtains access to the data set and has a well-developed protocol and analysis plan. Although exploratory analyses of secondary data are often necessary to understand the relevance and quality of the data for the proposed analysis, a concern is that analysts could make decisions on study design after seeing the preliminary results. Such analysts might, for example, cherry-pick selected findings that involve post-hoc changes to inclusion/exclusion criteria, specific patient subgroups, or defined study outcomes/endpoints, executing many exploratory analyses to choose the version of the study that points closest to their desired outcome. Without transparent pre-specification of hypotheses, data sources, protocols, and analysis plans, concerns about results-driven selection of study parameters and selective reporting on favorable findings can undermine confidence in the reported results of HETE studies.

Another concern that is not unique to RWE studies is publication bias. The publication of favorable results only and the decision by some journals not to publish studies with negative results dilute access to the complete evidence base for a given topic. This issue may be even more dire for RWE studies than for randomized controlled trials because journals may have less expertise in evaluating such studies,[10,26] and these studies are largely not registered, much less registered with results posted. The totality of evidence on a given topic requires that information about most studies on the topic, including from studies with negative results, be available to users. Having access to a full complement of study information in specific topic areas allows researchers and decision-makers to put a single study into context within the results of other similar studies. This information also allows for better comparisons of study results and methods for a given hypothesis as well as replications of studies. Transparency increases the credibility of study findings.

Origins of the Transparency Initiative

In 2017, ISPOR and ISPE created a joint task force to identify good practices for addressing the concerns described above and to

Table 1. Rationale, goals, and potential solutions to increase transparency.

Rationale	Goals	Potential solutions to increase transparency
For decision-makers, the lack of transparency in how real-world evidence is generated in hypothesis-evaluating treatment effect studies that use secondary data is a major barrier to using RWE for high-stakes decisions.	For researchers: Implement transparent study processes, such as reporting the study design and analysis plan before the study starts and post the results once they are available. For end users: Over time, increase confidence of decision makers in the evidence from these studies by elevating the evidence's credibility. For all: Provide information on all the evidence on a given topic from RWE studies so that the reproducibility of the results can be evaluated as part of the use of credible RWE.	Post each RWE study protocol, including key study parameters, in a registry so that decision makers can be confident that they understand how the study developed its findings. Use structured reporting templates to improve the readability of posted information, encourage reporting of all study findings, and increase efficiency for researchers and reviewers by making clear what to look for and where to look for it.
Concerns		
Results-driven selection of study parameters because researchers can easily conduct the same analyses using altered study parameters based on full access to the data.	Make clear the extent to which the process for selecting study parameters could have been driven by the results. Clearly report revisions to the initial plan, which are often necessary for studies that use secondary data.	Date-stamp the registered study protocol with an attestation about the nature of data exploration (eg, such as feasibility testing for numbers to support power calculation vs outcome rates by exposure). Date-stamp all revisions to the protocol and give the rationale for each change.
Selective reporting of favorable findings because a nonrandomly selected denominator of studies makes it difficult to conduct comprehensive evidence reviews.	Avoid selective reporting of study results so that decision makers and researchers aggregating evidence can prepare balanced summaries.	Establish a comprehensive registry of date-stamped protocols and results tables for all RWE studies that have been initiated on the topic to facilitate evaluation of publication bias. Create incentives to register hypothesis-evaluating RWE studies that are similar to journal requirements on randomized controlled trials and that the European Medicines Agency has imposed on post-authorization studies.

RWE indicates real-world evidence.

enhance confidence in evidence derived from HETE RWE studies. The ISPOR-ISPE Special Task Force has published recommendations for improving the transparency of HETE RWE studies.[11] The first of these recommendations was for researchers to declare at the outset whether they are conducting a HETE study (ie, a study that requires hypotheses to be tested in a defined patient population) or an exploratory, hypothesis-generating study. The second recommendation was to post the study protocol and data analysis plan in a publicly accessible registry before the study results were analyzed. The third recommendation was, when publishing the study results, to issue an attestation of conformance or deviation from the initial study protocol and analysis plan.

The ISPOR-ISPE task force recommendations to improve the transparency of research methods are not unique. Previous proposals have called for the registration of noninterventional studies,[9,10,27] but study registration remains uncommon. Recognizing that published recommendations alone are insufficient unless they are implemented, ISPOR brought 30 experts together on February 25 and 26, 2019, in National Harbor, Maryland, to explore the structural and practical challenges to successful implementing the ISPOR/ISPE task force's recommendations. Participants represented regulatory agencies, pharmaceutical companies, contract research organizations, academic institutions, HTA bodies, study registry hosts, patient organizations, and journal editors.

The meeting and the continued discussions of the named authors on this article (the steering committee) led to the creation of the RWE Transparency Initiative, initially led by a partnership among ISPOR, ISPE, the National Pharmaceutical Council, and the Duke-Margolis Center for Health Policy. This initiative is focused on establishing a culture of transparency for study analysis and the reporting of HETE studies using secondary data, particularly using study registration as a tool for encouragement.

The participants in the February 2019 meeting defined the overarching objectives of the RWE Transparency Initiative and discussed next steps to encourage a registration of the plans for and results of hypothesis-evaluating RWE studies. The initiative's goal was to reach consensus on considerations and recommendations that could help establish a culture of transparency for analysis and the reporting of HETE RWE studies.

This positioning article describes the next steps for the initiative to encourage registration as a common practice. These next steps include specifying the rationale for registration of RWE studies, identifying the studies that should be registered and the timeframe for registration, analyzing how and when analytic deviations should be considered, posting results, and creating incentives to encourage registration.

Table 2. Definitions of terms used in this report.

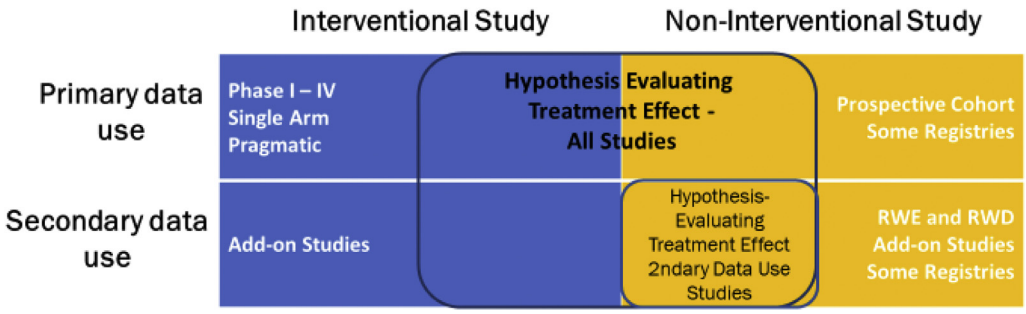
Term	Definition
Real-world data (RWD)	Data on patient health status and/or routine healthcare delivered. RWD can come, for example, from electronic health records, claims and billing databases, product and disease registries, wearable devices, and electronic applications (apps). Data can also be collected prospectively such as disease registries.
Real-world evidence (RWE)	Clinical evidence from RWD analysis on the use and potential benefits or risks of an intervention. RWE can be generated by different study designs or analyses, including randomized trials (and large simple trials), pragmatic trials, and prospective or retrospective observational studies.
Primary data studies (prospective research)	Studies, such as phase III clinical trials or prospective observational studies, that use data gathered prospectively for a specific purpose and analysis.
Secondary data studies (retrospective research)	Studies that use data collected for another purpose than that of the study of interest. Examples of secondary data used in studies include healthcare claims data, clinical trial data, and electronic medical records. "Secondary" is used in this report in place of "observational" because the latter term does not cover all types of secondary data studies.
Interventional studies	Studies in which participants are assigned to a study intervention, standard of care, or placebo to measure the impact of the intervention.
Noninterventional studies	Studies in which participants receive routine clinical care and are not assigned to a specific treatment. These data are often evaluated using epidemiological methods.
Hypothesis-generating studies	Studies that seek relationships and patterns in a specified dataset or related data sets. These relationships and patterns can be tested in a subsequent, well-designed, and perhaps controlled study. These studies can use primary or secondary data.
Hypothesis evaluating treatment effectiveness (HETE) studies (comparative effectiveness or causal inference studies)	Studies that evaluate the presence or absence of a prespecified effect and/or its magnitude. "Effect" in this usage includes both effectiveness and safety. HETE studies test a hypothesis in a specific population. When evaluated in conjunction with other evidence, the results may lead to treatment recommendations. For example, HETE studies might provide insights into whether a treatment effect observed in randomized controlled trials is the same in the real world, where low adherence rates and other factors could alter treatment effectiveness. HETE studies can use primary or secondary data.
Transparency	Openness and honesty about the study design, research questions and hypotheses, variables, endpoints, analysis plans and planned reporting in research. Transparent research "processes" should include publicly declaring these elements before the study starts and updated version control of study elements as required.
Study registration	Posting study elements including protocols and analysis plans, in a public study register prior to initiating the study
Data exploration (pre-looking)	explore existing data sets to understand availability of patients, variables, outcomes, etc, in preparation for study design. Feasibility testing or hypothesis generating studies often use data exploration. Some data exploration or pre-looking is necessary in study planning but should not 'overly inform' the design for risk of pointing the study to an artificial result.
Results driven study parameter selection (data dredging)	Secondary data studies are at risk for researchers re-running analyses multiple ways in order to see how the results change as analytic approaches change. Although sensitivity analyses are required to understand the impact of certain variables on the results, these should be prespecified and transparent. Over analysis of data for the purpose of finding the right combination of factors to produce a desired result is also known as data dredging.
Publication bias	The failure to publish the results of a study "on the basis of the direction or strength of the study findings." This nonpublication introduces a bias, which impacts the ability to accurately synthesize and describe the evidence in a given area. https://catalogofbias.org/biases/publication-bias/
Fallacy of incomplete evidence (cherry picking results)	The act of pointing to individual cases or data that seem to confirm a particular position while ignoring a significant portion of related cases or data that may contradict that position. A study researcher may report only those results that support the hypothesis.

Next Steps for the RWE Transparency Initiative

A culture of transparency for noninterventional RWE studies used to evaluate treatment effects takes time to build and requires commitment at the user, organizational, and research team levels. This transparency should encompass all aspects of research, from initial RWD sourcing and curation through study protocol development, analysis, and reporting of results.

The recommendations discussed in the following sections and summarized in Table 2 focus on the role of registration of the study protocol and analysis plan before study execution to improve study replicability, facilitate evaluation of validity, and limit the potential for results-driven selections of study parameters and selective reporting of positive results. Discussions of data sourcing and curation are beyond the scope of this article but are being addressed elsewhere, such as by the Duke Margolis Center for Health Policy.[28] The intention is to start small by encouraging researchers to post their studies in existing study registers, such as the EU-PAS. The ultimate goal, however, is to evaluate these study registries and work with the

Figure 1. Data use and study type relationship schematic.



RWD indicates real-world data; RWE, real-world evidence.

study registry hosts to optimize these resources for HETE RWE studies.

Short Term

Do not let the perfect be the enemy of the good

In the short term, the RWE Transparency Initiative (hereafter referred to as "the initiative") is working to identify the most suitable study registration site for HETE RWE studies, which can accommodate noninterventional secondary data research (Table 3). Several existing platforms can be used for RWE study registration (see Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.04.002). The ease of registering RWE studies in these registration sites differs, as does the ability of users to report and track details on study design and results, track changes to a study's design, and make external audiences aware of the registry. Using one of the existing study registries is the most expeditious path forward because this approach takes advantage of the experience, expertise, and resources allocated. Nevertheless, the initiative should evaluate all options, including the creation of a new registry, possibly with support from the Center for Open Sciences, which encourages and hosts online study registration with a mission of increasing openness, integrity, and reproducibility of research.

The initiative, in collaboration with our stakeholders, must evaluate, test, and potentially modify current registration procedures to make these registries suitable for HETE studies. Criteria for evaluating whether an existing registry is suitable for HETE studies include:

- The level of interest and constraints of current register-holders in modifying the registry's study registration procedures
- Current and future registry criteria
- The resource burden involved in implementing changes to the registry portal or creating a new study register
- The resource burden of a new registration process from the research team perspectives
- The ability to gain buy-in for using this resource as the central registry from all stakeholders or coordinating use in addition to current study registers

Use of an existing study registration site requires support from the study registry's owners. Discussions with these owners, including the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance for the EU-PAS and the National Library of Medicine of the National Institutes of Health for ClinicalTrials.gov, are underway.

Medium Term

Determine what registration should involve and when studies should be registered

The initiative will collaborate with groups doing related work, such as the U.S. Food and Drug Administration who is creating a structured protocol and reporting template, to avoid duplication and create synergies when possible. Determining the appropriate balance between the amount of detail needed on each study, the level of transparency of the information in the registry, and the level of confidentiality required is critical for ensuring appropriate usage of the registry (Table 3). Accomplishing this balance requires understanding not only the information that the registry will capture but also how and when to capture that information. The registration process will begin, at first, with the submission of a protocol and answering a small set of questions about study characteristics; these questions on study characteristics might evolve as the technology advances and support for the registry increases.

The initiative will also consider how the registration template should incorporate a description of exploratory analyses conducted before the study protocol was developed, along with some type of attestation that the research team has not tested the proposed study hypothesis with the study data before designing and registering the study. If attestation is required, definitions of various levels of data exploration will need to be developed so that the researchers do not provide their own definitions of data prelooking.

The initiative will need to address concerns about intellectual property that might, for example, prevent sponsors seeking regulatory reviews of their drugs from disclosing proprietary information that is part of the study hypothesis and analytic plans because it would be available on a publicly accessible registry. Therefore mechanisms must be investigated for supporting study registration so that parts of the registered data are not publicly accessible by, for example, using a temporary lock-box approach in which some users, such as regulatory authorities, would have access by invitation only and members of the public would not have access.

Before rolling out the full system, the study registration process must be tested using actual studies. Impact metrics could be defined for registering studies on: searchable study parameters, the transparency of the study process, and the ability to upload and reproduce study findings to demonstrate the registry's value. For example, registry use reports could provide information on the completeness and reliability of information on each study and the utility of each core element. In addition, a user interface survey on whether the site is user friendly for researchers who enter data on

Table 3. Recommendations for the RWE Transparency Initiative.

	Recommendation	Timeframe	Action	Considerations
1	Identify site to register HETE studies that use secondary data	Short term	• Actively encourage registration on existing sites (eg, EU-PAS, Clintrials.gov, and COS.io) • Initiate discussion with current study registry hosts (eg, NLM, ENCePP, and EMA)* • Consider hosting a test site with the Center for Open Science	• Current sites are "good enough" for some form of registration • Focus on HETE RWE studies whose purpose is to support decision-making (eg, about regulations or coverage).
2	Determine the characteristics of a "good" registration process to fit the purpose (starts in parallel with short term recommendations)	Medium term	Create multijurisdictional taskforces to do the following: 1. Survey potential users (investigators who register their studies and users of the results) about their needs for feasibility, transparency, and confidentiality 2. Design core requirements for registration and for study protocols based on those developed for other initiatives 3. Determine timing for release of study information 4. Pilot-test updates to registry and use the results to update partner registry or new registry, if required	• Feasibility of registering studies based on researcher and reviewer workload • Core elements to report in study registry, including fields and associated documents (eg, protocol, statistical methods, results) to upload • Balance between transparency and confidentiality (e.g., might establish a "lock box" that provides different access levels to different users) • Time-stamping of all data submitted to registry, including data looks and audit trail of changes made to any of this information
3	Provide incentives for routine registration of HETE studies	Long term	• Collaborate with key stakeholders to encourage implementation of registration requirements. • Encourage publication of findings from registered studies in peer-reviewed journals, just as the investigators of registered clinical trials are encouraged to publish their findings • Issue registry use reports (eg, quarterly reports with key information on registered studies) on the registry website; from time to time published	• Encouragement of registration of HETE RWE studies by funders, journals, regulators, payers, and those who assess health technologies

EMA indicates European Medicines Agency; ENCePP, European Network of Centers for Pharmacoepidemiology and Pharmacovigilance; HETE, hypothesis evaluating treatment effect; NIH, National Institutes of Health; NLM, National Library of Medicine.
*In progress.

their studies should be administered. This process will be iterative, purposeful, and flexible once it is implemented to align with advances in digital or web-based technology that could ease the ability to address some of the issues raised here.

Long Term

Routine registration for HETE RWE studies and incentivizing use

The long-term goal of this initiative is to make registration of HETE RWE studies routine in the way that the registration of clinical trials has become routine (Table 3). The studies that need to be registered are those whose findings are intended to support decisions by regulatory agencies, payers, or other healthcare decision-makers, including clinicians and editors of peer-reviewed journals who must decide whether or not to publish a HETE study. Other RWE studies could also be registered on these sites; however, that would not be the initial focus of these efforts.

Ideally, this vision will produce a coherent understanding of the available RWE on a given topic for regulatory or other healthcare decision-makers. Nevertheless, the aspirational goal of registration of all HETE studies is probably not achievable. Even if a fully incentivized system is in place, no approach could ensure registration of all HETE studies or require that all information (including results) is available, even on studies that are registered. Still, a cultural shift toward increasing the registration of studies—even if the recommended approach is not perfect—would help users of HETE findings determine the number of attempts made to compare the results of different studies on a given topic and decide whether a given result is representative or an outlier.

Considerations

Transparency Does Not Ensure that a Study is of High Quality or Applicability

Over time, the increasing transparency of HETE RWE studies through registration could lead to the development of higher-quality evidence and its use in healthcare decision-making.

Informed interpretation and the fit for purpose application of RWE are a requirement for appropriate application of this research. Registration before a study starts requires researchers to think critically and specify a priori all the details in their analysis plan. These details might include how they will evaluate their hypothesis; the objectives and rationale; how they will define and measure exposures and outcomes; their inclusion and exclusion criteria; how they will account for confounders; and how they will analyze the data. Decision makers who use RWE HETE studies can consult good practice documents that describe elements to consider when evaluating a study's quality.[29,30] Nevertheless, such evaluations can only be completed if the users have access to information on the study's research questions, methods, and analysis plan. The ability to make an informed decision about whether a study is applicable to the question at hand will also require the end user to have enough information about the study, usually the same data points that are required to assess quality.

The initiative recognizes that transparency is necessary but not enough for acceptance of RWE by decision-makers. First, making public information on how the RWD were curated, transformed, and linked with data from other sources to make them research-ready is an important step, although this step is not described in this report as other efforts are ongoing in this area.[28] Second, RWE study registration might not have the same impact as registration of clinical trials. Study registries have been useful for randomized clinical trials in part because of the natural limits (in the form of time and money) on the ability of a different research team to quickly conduct an alternative trial to answer the same study question. In contrast, the data used to produce RWE are often already collected, so a different research group might more easily conduct an alternative study to use the same data to answer the same study question, "scooping" the original research idea and perhaps producing results before the original research study. Moreover, the potential exists to analyze the data in many ways to find the right combination of covariates or methods to yield results supporting the hypothesis. Nevertheless, transparency complemented by strong methods and deterrents to results-driven selection of study parameters will help move the RWE research field in the right direction by providing a richer opportunity to contextualize study findings, and public study registration can be an important mechanism to support these goals.[31]

Spectrum of Studies, Data-Exploration, and Protocol Revisions

The types of RWE studies range from hypothesis-generating studies to HETE studies, depending on the study aims. Public transparency is critical for certain types of RWE. The recommendations in this report are only for HETE RWE studies, particularly those that use existing, secondary data (Fig. 1). Hypothesis-generating studies are critical for understanding treatment use and safety. Nevertheless, these studies are exploratory, so prespecifying analyses for treatment effect evaluation is usually not feasible. The initiative does, however, encourage transparency of these studies to the extent possible.

Exploratory hypothesis-generating studies can be distinguished from HETE studies based on a priori hypotheses and analysis planning, as described in the ISPOR and ISPE Special Task Force report.[11] In the transition from using RWD for hypothesis generation to hypothesis evaluation, the results might need to be refined or replicated using different methods, alternative secondary research questions and sensitivity analyses, or independent data.[32,33] Earlier exploratory studies may be used to inform analysis planning for HETE studies and are not the subject of these recommendations. Nevertheless, those exploratory studies should not be constructed in such a way as to serve as a full data-exploration for the HETE study.

Although some examination of the data to be analyzed before designing the study is a prerequisite for understanding the data set's appropriateness and to inform components of the research design (eg, feasibility counts, patterns of care, size of patient populations, endpoints of interest), such reviews could inform study hypotheses or study protocols in a way that could bias the final analysis plan. Examinations of the data before designing the study are difficult to control or audit, but some data owners actively monitor the kind of data exploration and amount of analysis by researchers before they start a study. In addition to such monitoring, the study team, as part of study registration, can be asked to describe and attest to the nature of any data exploration before the study is registered. This is an imperfect solution, but if definitions of data exploration are clear and study teams must attest, they can be held accountable in the court of public opinion if any untoward activity is uncovered. When a third party (eg, a government agency) controls data access, that agency adds to transparency by documenting the data access and registration dates of the study protocol and analysis plan.

Finally, investigators conducting a study using RWD not originally collected for research purposes often have good reasons (eg, discovery of a data-quality or measurement problem) to make changes to the initially registered analysis plan. Remediation of unanticipated issues might require changes in analytic methods or the use of supplemental data. Therefore some amendments from the initially planned analyses of RWD are to be expected. Nevertheless, as part of a transparent research process, the rationale and timing of amendments should be documented. Unambiguous descriptions of the planned study population (and how that population is defined) at the time of study registration as well as documentation of reasons for amendments to the initial plan during the study can address concerns about the results-driven selection of study parameters while responding to the need for flexibility in the research process. Providing clarity on the steps taken to create the final analytic study population on which the reported results are based is critical to the reproducibility of findings and the ability of reviewers and decision-makers to assess the validity of decisions about the study's design, implementation, and analysis.

Encouragement Versus Enforcement of Study Registration

Clearly defining the studies that *require* registration and those for which registration should be *encouraged* will be key to avoiding confusion. The momentum gained through the midterm survey and collaboration with stakeholders in the assessment and pilot testing processes (as described in Table 2) could motivate researchers to register their studies in a central study registry. Nevertheless, increasing uptake will probably require some incentives. Some of those incentives could come from data owners as part of their data use agreements to ensure that their data assets are used appropriately. Alternatively, journal editors could make registration a prerequisite for publication (just as many journals do with ClinicalTrial.gov registration or institutional review board certification). Journals could also offer incentives for submission of study information to a public registry, such as faster reviews of manuscripts based on registered HETE studies, seals of approval, or a discounted fee for open source designation. Researchers would also be more likely to register their studies if funders, such as the National Institutes of Health, required registration of funded studies. Finally, payer and regulatory users of RWE could require registration before considering that evidence for market authorization or reimbursement decisions.

The main objective of the Transparency Initiative is to promote the notion that appropriate transparency of data, methods, analyses, and results will increase confidence in the credibility of HETE RWE studies. A culture of transparent good practices may be best encouraged rather than required. Over the long term, sustainability of the data registration information will be critical for the credibility of not only the registered studies but also the study registry.

Conclusions

The RWE Transparency Initiative has identified practical steps to building on the foundation of existing study registries, identified issues that affect the practicality of the registration process, and considered how to facilitate routine registration of HETE RWE studies. The recommendations for next steps and considerations in this positioning article address the unique characteristics of the studies that use secondary RWD to generate hypothesis-evaluating RWE on treatment effects. Other sectors have used transparency to engender stakeholder trust in data and findings and to enable users of the information to judge its quality. As the potential use of RWE to support decision-making for market authorization, reimbursement, and clinical guideline development grows, the need to trust that evidence grows correspondingly. Improving the culture of transparency can help shed light on HETE RWE study practices so that users of the results can better determine study quality for themselves.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2020.04.002.

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