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Improving Transparency in Non-Interventional Research for Hypothesis Testing—WHY, WHAT, and HOW: Considerations from The Real-World Evidence Transparency Initiative

Draft White Paper

September 18, 2019

The Real-World Evidence Transparency Initiative Partnership

This White Paper was authored by the Steering Committee of the Real-World Evidence Transparency Initiative Partnership. The Initiative is led by ISPOR, the International Society for Pharmacoepidemiology, Duke-Margolis Center for Health Policy, and the National Pharmaceutical Council, with involvement of a number of other organizations and stakeholders. A list of all authors can be found in the appendix.

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EXECUTIVE SUMMARY

The growing interest in the use of 'real-world' data (RWD) and the derivations of these data into real-world evidence (RWE) to help inform healthcare decisions creates urgency to develop processes that promote trust in the evidence generation process and enable decision-makers to evaluate the quality of the methods and resulting evidence from 'real-world' studies. Study registration—particularly for hypothesis evaluating treatment effectiveness (HETE) studies—has been proposed as an important mechanism for improving transparency and trust. However, existing study registries such as ENCePP/EU-PAS and ClinicalTrials.gov are either oriented toward studies involving primary data collection such as (randomized) controlled trials, or they lack many of the features that should be incorporated in a study registry system designed to improve transparency and trust for studies performed on existing data, often referred to as secondary data use. This paper outlines an approach designed to facilitate the registration of HETE studies based upon secondary data use such as insurance claims and electronic health records, particularly those testing hypotheses regarding effectiveness and/or safety of two or more interventions. The summary table below outlines the rationale, goals, and some potential solutions as well as specific concerns that are unique to real-word evidence studies performed on secondary data.

Summary Table: Rationale, Goals, and Potential Solutions

	Rationale –	Goals –	Potential solutions –
	Decision makers see **lack of transparency regarding how evidence is generated in hypothesis evaluating treatment studies using secondary data as a major barrier** to using RWE for high-stakes decisions.	Researcher: First encourage transparency of study processes, including reporting on study design and implementation prior to study start, including posting of results when available Recipient: Over time - increase confidence of decisions makers in these studies, elevating the credibility All: Provide insight into the totality of evidence so reviewers can gauge reproducibility and replicability as part of the credible use of RWE	Post a study protocol reporting key study parameters so that a decision-maker can be confident that they understand how the study arrived at its findings. Use structured reporting templates to improve readability, encourage completeness of reporting, and increase efficiency for researchers and reviewers by making it clear what to look for and where to look for it.
	Specific concerns include:		
1	**Results-driven selection of study parameters** Ease of rerunning analyses with altered study parameters.	Provide clarity about the degree to which study parameter selection could have been driven by results. Revisions to the initial plan are often necessary when working with secondary data and need to be clearly reported.	Date-stamp the deposited study protocol with attestation regarding the nature of data pre-looking (e.g. feasibility numbers to support power calculation vs outcome rates by exposure) Date-stamp all revisions to the protocol with rationale for changes
2	**Selective reporting of favorable findings** A non-randomly selected denominator of studies makes it difficult to conduct comprehensive evidence reviews	Avoid **selective reporting of studies** so that evidence aggregators and decision-makers can conduct balanced evidence summaries.	Establish a comprehensive repository containing date-stamped protocols and results tables for all studies that are initiated to facilitate evaluation of publication bias Create incentives to register hypothesis-evaluating RWE studies like the requirements that journal editors have placed on RCTs, and EMA for PAS studies.

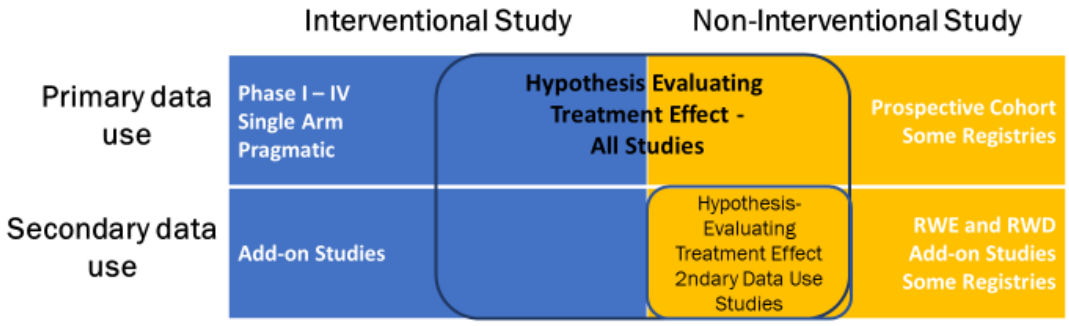
"Trust, but verify"

INTRODUCTION

In the government, consumer markets, and the financial sector, transparency is a critical element and policy tool to engender trust across stakeholders and to enable the judgement of the quality of information being exchanged. It is intended to aid decision makers to set priorities and reach decisions that are legitimate and fair—and perceived as such [1]. In evidence-based medicine, these needs are similar. Regulatory, coverage and reimbursement, and other healthcare decision-makers need to be able to evaluate and make informed decisions based on high-quality, relevant evidence. The growing interest in the use of data from clinical practice, also referred to as 'real-world' data (RWD), and the derivations of these data into real-world evidence (RWE) to help inform these decisions creates urgency to develop processes that promote trust in the evidence generation process and enable decision-makers to evaluate the quality of the methods and resulting evidence from 'real-world' studies [2-6]. The need for increasing credibility in RWE is becoming more important as studies are being performed for purposes of informing healthcare decisions with more acceptance and impact, especially as access to underlying data is increasingly difficult due to distrusted data networks and privacy laws, and as more studies are being performed with multiple underlying databases.

Study registration—particularly for hypothesis evaluating treatment effectiveness (HETE) studies—has been proposed as an important mechanism for improving transparency and trust [7]. However, existing study registries such as ENCePP/EU-PAS and ClinicalTrials.gov are either currently oriented toward studies involving primary data collection such as (randomized) controlled trials or, in preliminary investigation, lack many of the features that should be incorporated in a study registry system designed to improve transparency and trust for studies performed on secondary data. This paper outlines an approach designed to facilitate the registration of HETE studies based upon secondary use of existing data such as insurance claims and electronic health records or patient registry data, particularly those testing hypotheses regarding effectiveness and/or safety of two or more interventions. While other types of patient-contributed data from wearables and apps are also increasingly part of the digital data landscape, it is outside the purview of this paper to discuss the specific use or impact of these data at this time. Figure 1 shows a schematic regarding how interventional and non-interventional studies as well as primary and secondary data relate. This paper refers particularly to research on secondary non-interventional data use studies (performed on data for use that it was not originally intended for, such as electronic medical records or health care claims) for purposes of evaluating hypotheses about treatment effects. Essentially studies using retrospective analysis intended to evaluate causal inference of effectiveness or safety to support decisions between two or more compared treatments. Terminology related to data sources and study types are often dependent on the stakeholder preferences and can be confusing. This paper uses particular terminology in order to distinguish between how data are used rather than how they are collected. Therefore, table 1 clearly defines how terms are used in this paper as well as how they relate to other similar terms.

Figure 1. Data Use and Study Type Relationship Schematic



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67 Table 1. Terms and Definitions

Term	Definition
Real-World Data (RWD)	Data relating to patient health status and/or the delivery of routine health care from a variety of sources. RWD can come from a number of sources, for example: Electronic health records (EHRs), Claims and billing activities, product and disease registries, patient-generated data including in home-use settings, data gathered from other sources that can inform on health status, such as mobile devices
Real-World Evidence (RWE)	Clinical evidence regarding the usage and potential benefits or risks of an intervention derived from analysis of RWD. RWE can be generated by different study designs or analyses, including but not limited to, randomized trials, including large simple trials, pragmatic trials, and observational studies (prospective and/or retrospective).
Primary Data Use	Utilizing data gathered by the researcher for a specific purpose and analysis. Example – phase III clinical trials
Secondary Data Use	Utilizing data in an analysis that has been collected for another purpose besides that required by the study at hand. Examples include healthcare claims or electronic medical records. But also includes secondary analysis of clinical trial data. This term is used *in place of* Observational Data which may not cover all types of secondary data use.
Interventional Study	Study in which participants are assigned a particular treatment or specifically no treatment in order to measure the impact of receiving the treatment.

Non-Interventional Study	Study participants do not receive any specific treatment, they are treated according to standard of care. Data are often evaluated using epidemiological methods.
Hypothesis Evaluation Treatment Effect (HETE) Study	Study that evaluates the presence or absence of a prespecified effect and/or its magnitude. The purpose of a HETE study is to test a specific hypothesis in a specific population. When evaluated in conjunction with other evidence, the results may lead to treatment recommendations by providing insights into, for example, whether a treatment effect observed in RCTs gives the same result in the real world where low adherence and other factors alter treatment effectiveness.

While the 'highest bar' for methods and transparency may be for regulatory use and health technology assessment (HTA), payers and others who use data to make evidence-based healthcare decisions for populations, rather than for an individual patient, are increasingly looking to RWE studies to augment the data pool. Numerous regulatory agencies, health technology assessment agencies, and professional societies have published guidelines for the design, conduct, and analytic methods to be used in RWE studies [8-19]. These guidelines have addressed issues such as quality of underlying real-world data collection and curation, appropriate methods for causal inference when these studies evaluate hypotheses of treatment effectiveness, adequate reporting of the study results, and the ability to reproduce study results. As high-quality RWE is actively being generated and is having a positive impact on decision making [20-24], the need for continued generation of such high-quality evidence will further heighten the standards that investigators and consumers of such evidence apply to such studies.

RWE studies based upon the secondary analysis of data are unique in several ways. First, in the past, secondary RWE has predominantly been used to generate hypotheses rather than test hypotheses. However, there is increasing usage of existing secondary data for hypothesis evaluation, most successfully in the area of pharmacovigilance - post approval safety studies such as the distributed networks SENTINEL in the United States and the Canadian Network of Observational Drug Effect Studies (CNODES) in Canada. There are also several ongoing efforts to replicate clinical trial results with RWD to show the capabilities of high-quality studies conducted in non-interventional data sources [add references to OPERAND and others if possible]. Second, RWE studies often make use of non-interventional secondary data that can be obtained and analyzed relatively quickly, once the researcher has access to the dataset and a set analysis goal. While exploratory analyses in the specified data source(s) are often necessary to understand the relevancy and quality of the dataset for the proposed analysis, due to this easy access to the full complement of data, including outcomes, there are concerns that the analyst may make decisions regarding the analysis of the data to drive the results in certain directions. This may lead to cherry-picking selected findings which could include post-hoc changes in imposing inclusion/exclusion criteria, selecting patient sub-groups, defined study outcomes/endpoints, or exploring alternative analytic approaches. Without a transparent pre-specification of hypotheses, data sources, protocols and analysis plans, concern about these issues can undermine confidence in results reported in HETE studies. The third issue, which is not unique

only to RWE studies, is concern about publication bias. Only publishing favorable results or journals' tepid interest in publishing negative confirmatory results dilutes access to the total evidence base. Totality of evidence requires information about, and results from, most studies on the topic, including ones with negative results. If there is adequate transparency about how the individual studies were conducted, greater access to a fuller universe of studies will also allow better comparison of study results and methods across studies for a given hypothesis. This issue is even more dire for RWE studies compared to RCT's due to fewer journals prioritizing publication of such studies combined with their lack of publication in study registries.

In 2017, ISPOR, the Professional Society for Health Economics and Outcomes Research, and ISPE, the International Society for Pharmacoepidemiology, created a joint task force regarding good procedural practices to address these concerns and enhance confidence in the evidence derived from hypothesis testing RWE studies. In one of the ISPOR-ISPE Special Taskforce Report papers, the first three recommendations focused on improving the transparency of HETE RWE studies [7]. These included the need for researchers to declare at the outset whether the study is a HETE study — requiring specific 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 on a publicly available registration site prior to the conduct of the study analysis. The third recommendation addressed publishing the study results with an attestation to conformance and/or deviation from the initial study protocol and the original analysis plan.

The ISPOR-ISPE Taskforce recommendations to improve the transparency of research methods are not unique. Previous proposals called for registration of non-interventional studies [25-27], but pre-registration remains uncommon. Recognizing that published recommendations alone are insufficient without action, a gathering of experts occurred February 25-26, 2019 at the National Harbor, MD, USA, to explore the structural and practical challenges to the successful implementation of the recommendations made in the joint ISPOR/ISPE task force publication. The meeting was hosted by ISPOR and included 30 invited experts representing regulatory agencies, pharmaceutical companies, contract research organizations, academia, HTA bodies, study registry holders, patient organizations, journal editors, and others.

The meeting and the continued discussions of the steering committee formed the basis of the RWE Transparency Initiative, encompassing a partnership (initially) among ISPOR, ISPE, the National Pharmaceutical Council (NPC) and the Duke-Margolis Center for Health Policy. The participants defined the overarching objectives and discussed recommendations for top priority next steps to encourage registration of hypothesis evaluating RWE. The goal was to come to consensus on considerations and recommendations that will help establish a culture of transparency for study analysis and reporting of hypothesis evaluating RWE studies on treatment effects. This White Paper outlines the recommended next steps the initiative hopes to implement towards making registration a common practice, which include specifying the rationale for registration of RWE studies, defining which studies should be registered and in what timeframe, describing the details for how and when analytic deviations should be considered, posting results, and discussing incentives to encourage registration.

RECOMMENDATIONS FOR TRANSPARENCY INITIATIVE NEXT STEPS

A culture of transparency for non-interventional RWE studies used for evaluating treatment effects will take time to build and requires commitment at the stakeholder, organizational, and individual research team levels. Transparency should encompass all aspects of research, from initial RWD sourcing and curation, through study protocol development and analysis, to reporting of results. The recommendations outlined below specifically focus on the role of registration of the study protocol and analysis plan prior to study execution to improve replicability of the study and limit the concern for data dredging and 'cherry-picking' positive results. The recommendations also include version control of protocols and analysis plans and posting of results to limit (peer review) publication bias. These recommendations are summarized and presented in Table 2. Discussions of data sourcing and curation are beyond the scope of this paper but are being addressed by others, such as the ongoing collaborative work by The Duke Margolis Center for Health Policy [ref]. While the intention is to start 'small' – encouraging researchers to register in currently available sites such as EU-PAS – the goal is to evaluate such sites in parallel and work with the registry holder(s) to optimize for registering HETE RWE studies.

Table 2. Recommendations and Considerations for RWE Transparency Initiative[1]

	Recommendation	Timeframe	Action	Considerations
1	Identify location for registration of Hypothesis Evaluating Treatment Effect using secondary data research studies	Near Term	1. Actively encourage registration on current sites now 2. Initiate discussion with leaders of current registries, NLM/NIH and ENCePP/EMA[1] (already in progress) 3. Look at the Center for Open Science format as a possible new site, if needed, however recognizing that adding another registration site to those already required is not optimal.	1. With a view to modify or enhance existing registration sites 2. Clearly define the study type – HETE RWE studies for decision making (regulatory, coverage, etc) 3. Clearly define, by source and purpose, which HETE studies are within scope
2	Determine what a "good" registration process entails to fit the purpose (to be started and carried out as researchers are encouraged to use registry sites already in existence)	Medium Term	Create multi-jurisdictional 'task forces' to: 1. Survey potential users (submitters of research and users of research) about needs and considerations regarding feasibility, transparency, and confidentiality 2. Design core elements of registration and study protocol 3. Design timing of release of information 4. Pilot test registration site updates and update partner site or new site if required	1. Don't let perfect be the enemy of good - this should be a progressive effort 2. Feasibility - research and reviewer workload 3. Core elements of study registration including website fields and associated documents (e.g. protocol content, statistical methods, results tables) 4. Transparency vs confidentiality ("lock box" with different access levels) 5. Time-stamped registration including data looks and audit trail of changes 6. Starts in parallel with recommendation 1
3	Incentives for routine pre-registration for HETE studies	Long Term	1. Build off collaboration with key stakeholders from task force activities to encourage adoption of pre-registration requirements. 2. Involve key stakeholders from survey of potential users over time. 3. Foster publication of registry findings, similarly to research on registers for clinical trials	1. End users encourage registration of HETE RWE studies: funding bodies, journals, regulators, payers/health technology assessors 2. Provide registry 'use reports' (e.g. quarterly report of registered studies, with key information): e.g. on the website; from time to time published

[1] NLM = National Libraries of Medicine; NIH = National Institutes of Health; EMA = European Medicines Agency; ENCePP = European Network of Centers for Pharmacoepidemiology and Pharmacovigilence

Near Term

Identify location for registration of HETE RWE studies

In the near term, identifying the most suitable location/repository option(s) for pre-registration of HETE RWE studies, with special considerations for non-interventional research, is paramount. Encouraging the behavior of pre-registration of appropriate studies should take place as soon as possible. Several platforms currently exist, and in preparation for the February 2019 meeting, these registration sites were reviewed. (Table 2 - appendix) These registries vary widely in the ease with which RWE studies can be pre-registered, the utility for reporting and tracking details about - study design, results, tracking changes, and awareness with external audiences, and the cost. Using one of the existing platforms specifically, leveraging the experience, expertise, and resources already allocated to these programs is the most expeditious path forward. However, all options should be evaluated including the opportunity to build a new registry under the auspices of a group like the Center for Open Sciences.

Medium Term

Don't let perfect be the enemy of the good - this should be a progressive effort

It will be necessary to evaluate, test, and potentially modify current registration procedures so researchers are encouraged to register their HETE studies. Evaluation criteria will include: the level of interest and feasibility of registry modification; current and future registry criteria; budget requirements to implement changes from both the study registry portal and from the research team perspectives; and ability to gain endorsement as the central registration location. This will require support from leadership from these programs. Discussions with these key stakeholders are underway (e.g., ENCEPP for EU-PAS and National Libraries of Medicine – NIH for ClincialTrials.gov).

Determine what registration should entail and when registration should occur

Determinations on additional modifications needed and how workload is affected are paramount to ensuring long-term success. Using the existing platforms as a basis to assess core elements of study registration and associated documents (e.g., protocol content and capability to post results) have been identified, including evaluating the research and reviewer workload. Determining the appropriate balance between the required detail, level of transparency, and confidentiality is critical to ensuring appropriate usage. This requires understanding not just what information will be captured in the registry, but also how to capture it and when. Initially, a minimum set of study characteristics will be needed to begin the registration process with the potential to evolve as the technology and support build. Further consideration will be given to whether a registration template would include a description of exploratory analyses conducted prior to developing the study protocol and/or some type of attestation that the research team has not tested the proposed study hypothesis in the planned study data prior to registering the

study. Definitions of various levels of pre-looking will need to be determined and described such that the attestation process does not become a 'self-policing' exercise.

Further, any solution should address concerns with intellectual property and/or business and competitive considerations, for example, sponsors seeking additional regulatory review of their drug products may have business and competitive reasons for not disclosing proprietary information included in study hypothesis and analytic plans too early in a public venue. Therefore, mechanisms for supporting non-public pre-registration (such as with a time-limited 'lock-box' approach) in which certain users, such as regulatory authorities, would have access by invitation must be investigated.

Before rolling out the full system, study registration requires pilot testing which should include real examples that will be identified as the registration site is created and should include measures to evaluate the impact of registering the studies to demonstrate its value. For example, providing registry 'use reports' (e.g., quarterly report of registered studies, with key information) from time to time outlining registration elements that are incomplete, not reliable, or lack utility will be needed. In addition, user interface survey and information should be sought to improve the usability of the entry fields. This process will be iterative, purposeful, and flexible after implementation to align with advances in science which 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 intention is to make registration of certain HETE RWE studies routine in the same way that clinical trials are now registered. Specifically, this is seen to involve studies intended for regulatory, payer, or other healthcare decision making, including peer-reviewed publication. The benefit of routine registration is to get closer to a full understanding of the totality of planned and completed HETE RWE research. Publication bias makes it more likely to see effects reported in the literature that are tenuous or artifactual as opposed to negative results. The ability to register HETE RWE studies, track their conduct and results all in one searchable location would be a powerful tool to not only provide transparent research but would have the added benefit of increasing the credibility of such research over time. The power of moving closer to the 'totality of evidence' must be considered in context. Ideally this vision would produce a coherent data picture for regulatory or other health care decision-making. However, it must be acknowledged that the aspirational goal of a complete study denominator is likely not achievable. A cultural shift toward increasing the pre-registration of studies — even if not perfect — moves the research field closer to understanding how many attempts were made to make a comparison and decide at the study level if any given study result appears either aberrant or representative.

CONSIDERATIONS

Transparency Does Not Equate to Study Quality

While transparency in reporting study process would clarify the methods, transparency by itself does not equate to study quality [28]. Poorly conducted non-interventional studies may be fully transparent. However, transparency better enables decision-makers to effectively assess the quality and validity of the study presented to them by providing a deeper understanding of why and how the research was conducted, and whether the results reflect pre-planned questions and methods. It also better facilitates replication of results and/or understanding of reasons where findings diverge for apparently similar studies. Conversely, low study transparency makes it difficult for decision-makers to differentiate high quality versus flawed studies, the latter of which has contributed to low confidence in secondary data research using RWD.

Over time, greater transparency of individual studies via registration of HETE RWE studies could lead to higher quality evidence being developed and used to inform decision-making. Registration prior to study start requires researchers to think critically and specify *a priori* all details found in a technical or statistical analysis plan – how they will evaluate the hypothesis being tested; specifying objectives and rationale; how to define and measure exposure, outcomes, inclusion/exclusion criteria, and confounders; and how the data will be analyzed –. There are good practice documents for reviewers that outline elements to consider when evaluating study quality [29-30]. However, an essential condition for that evaluation is access to the original research questions, methods, and analysis plans.

The initiative also recognizes that the publication of all study results, whether in peer review or in searchable format on a study registry site, is a powerful tool for end users of such research, which is often subject to publication bias in similar ways to the evidence from clinical trials. Encouraging the posting of results, particularly for studies that are not published in peer-reviewed journals, in a useful format has great power to improve understanding of the totality of the evidence in the space. Its importance should not be underplayed and certainly is as high a priority for this project as the registration aspect.

The convened initiative group recognized that transparency is a necessary but not sufficient condition of acceptance of RWE. First, information on how the RWD were curated, transformed, and linked with other data sources to make them 'research-ready' is an important step, but one not outlined in this report. Second, RWE study registration itself may not have the same degree of impact as with clinical trials. Study registry sites have been an important tool for randomized clinical trial research in part because of the natural boundaries (time and money) that limit the ability of another party to quickly conduct an alternative trial to answer the same study question. With RWE, data are often already collected so it may be much easier for another party to quickly conduct an alternative study on the same study question. Moreover, the potential exists to analyze the data in many ways until the right variable combination or methods are found to

reveal results supporting the hypothesis. However, transparency, when complemented by strong methods and deterrents to data dredging as discussed below, will help move the research field in the right direction by providing a richer opportunity to contextualize any individual findings or studies.

Defining the Spectrum of Studies, Definition of "Pre-Looks," and Protocol Revisions

The convened initiative group debated the spectrum of RWE study types in which transparency is critical. For example, RWE studies can range from hypothesis generating studies to HETE studies depending on the study aims. To be clear, the recommendations in this report refer only to HETE RWE studies and particularly to those using existing, non-interventional data (Figure 1). Exploratory hypothesis generation studies serve a critical role in understanding of treatment use and safety. However, these studies are by nature exploratory and specifying preplanned analyses for treatment effect evaluation is usually not feasible; although naturally we encourage transparency to the extent possible with such work.

The convened initiative group recognized the potential unintended consequences associated with reduced conduct of exploratory analyses if additional requirements for transparency were not clearly defined. To clarify this, the convened initiative reiterated the distinction between exploratory hypothesis generation studies and HETE studies based on *a priori* hypotheses and analysis planning that was described in the ISPOR/ISPE Special Task Force report [7]. In the transition from using RWD for hypothesis generation to hypothesis evaluation, there will often be a need to refine and/or replicate the results using different methods, evaluation of orthogonal hypotheses, or use of independent data [31]. Earlier exploratory studies may be used to inform analysis planning for independent HETE studies and are not the subject of these recommendations. However, those exploratory studies should not be constructed in such a way as to serve as the pre-look for the HETE which we discourage (see next paragraph).

In addition to the distinction between exploratory and HETE studies, the convened group discussed issues regarding data "pre-looks" or "pre-tests." While some data pre-looking is a prerequisite for understanding the dataset appropriateness and informing research design (feasibility counts, patterns of care, switching patterns, size of patient populations), it runs the risk of informing study hypotheses or study protocol in a way that may bias the creation of the final analysis plan. Pre-looks or pre-testing are hard to control or audit, but some data source owners actively monitor the amount of data looks and analysis researchers can do prior to 'study start.' Another option is to ask the study team, as part of study registration, to describe and attest to the nature of any pre-looks conducted prior to study registration. While an imperfect solution, if definitions of pre-looking are clear and study teams must attest, then there are grounds to hold teams accountable in the 'court of public opinion' at the very least if something untoward is uncovered. In cases where data access is controlled by a third party (e.g. by governmental agencies for population registries in the Nordic European countries), it adds to

transparency to document the data access date vs. the registration date of the study protocol and analysis plan.

Finally, when conducting a study with RWD not originally collected for research purposes, there are often good reasons to make changes to the initial registered analysis plan; for example, the discovery of a data quality or measurement issue. Remediation may include data processing (return to source file or underlying data), analytic methods, or finding supplemental data. Therefore, some deviation from the initially planned analyses of RWD is expected. However, as part of a transparent research process, deviations and the rationale and timing for making a change should be documented. Unambiguous description of the planned study population (and how that population will be defined) at the time of study registration, with documentation of reasons for deviation from the initial plan over the study lifespan, would address concerns about "data dredging" while acknowledging the need for flexibility in the research process. Providing clarity on the actual 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 study design, implementation, and analysis decisions.

Encouragement vs. Enforcement of Study Registration

Clearly defining which studies *require* registration and for which studies registration is *encouraged* will be key to avoiding confusion. The momentum gained through the mid-term survey and collaboration with stakeholders through the assessment and piloting processes could motivate study registration adoption. However, greater uptake will likely require some incentives for researcher to register studies and to register these centrally. Part of that incentive could come from data source owners as part of the data use agreements. Alternatively, journal editors could require registration as a pre-requisite for publication like ClinicalTrial.gov or IRB certification. Funding bodies such as NIH may also consider requiring registration for certain studies. Finally, payer and regulatory end-users could require registration prior to considering that evidence for market authorization or reimbursement. Regardless, the goals of the Transparency Initiative are to promote the notion that appropriate transparency of data, methods, analyses, and posting of results will increase confidence on assessing the credibility of the HETE RWE studies. Together, this culture and training on good practices may be best encouraged rather than required. Long term, sustainability of the data registration information will be critical for credibility not just of the studies registered but the registration site itself. Sustained access to studies over time is still an underappreciated problem [32].

CONCLUSION

The ISPOR-led RWE Transparency Initiative sought to identify practical implementation steps to build on the foundation of existing study registration sites, identify feasible and practical elements associated with what the registration process will entail, and consider how to facilitate routine registration for HETE RWE studies. The recommendations for next steps and

considerations outlined in this white paper are meant to address the unique characteristics of studies that make secondary use of RWD to generate hypothesis evaluating treatment effect RWE. Other sectors have used transparency as a critical policy tool to engender trust across stakeholders and to enable judgement of the quality of information being exchanged. 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 shine light on study practices so that these end-users of the results are able to make a better determination about study quality for themselves.

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Appendix

Table 3: Overview of Study Registries Currently Available for Observational Non-Interventional Study Registration

Registry Site	ClinicalTrials.gov	EU-PAS	Health Services Research Projects (HSRProj)	Research Registry	Open Science Framework
Funding Source		coordinated by the European Medicines Agency (EMA) and developed in line with the guidelines and principles of the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP)	US National Library of Medicine and maintained by the National Information Center on Health Services Research and Health Care Technology.	International Journal of Surgery Publishing Group	Center for Open Science
Location	https://clinicaltrials.gov	(http://www.encepp.eu	https://hsrproject.nlm.nih.gov/		
Goal		Developed for non-interventional post-authorization studies as mandated by the EU legislation for authorized products	Health services research projects funded by various organizations	Encourage registration of all studies involving human participants, emphasizing the need for observational studies to be registered	Offers a platform to register all types of research
Total number of studies	308,115 studies	1527 studies	35,000 projects	4,282 studies	
# of visitors	116,000 unique visitors daily				
% of observational studies	One-fifth of the registered studies are observational	83.9% observational studies; 3.3% active surveillance; 1.5% clinical trials and 11.3% of studies listed as other	1,026		
Applicability to observational studies	Some fields have been modified for observational studies.			Designed for observational studies, most studies involve surgical procedures	Allows users to create their own branded registry for others to use
Limitations	Not well tailored for observational studies. For example, study	Originally designed as a registry of regulatory studies and thus concerns	Fields most limited to administrative information. The abstract field only allows		

	start is defined as the date the first participant was enrolled, which is not applicable to many observational studies	regarding use for non-regulatory based studies. Regarding use for non-regulatory based studies. Many or most focus only pharmacovigilance and not on the effectiveness assessments	the display of scientific information of the study. No option to upload files such as a protocol or statistical analysis plan		

All figures were taken as of June 10, 2019

Table 4: RWE Transparency Steering Committee

While the Steering Committee took the lead in drafting the whitepaper, it should be acknowledged that the content of this paper summarizes the discussions and suggestions from the full transparency meeting in February 2019. Without all the participants valuable input, this initiative or the paper would not have come to fruition.

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