Patient-Centered Real-World Evidence:

Methods Recommendations from an Evidence-Based Consensus Process

Acknowledgements

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Patient-Centered Real-World Evidence:
Methods Recommendations from an Evidence-Based Consensus Process

Background

Interest in real-world data (RWD) and real-world evidence (RWE) among health care stakeholders, including patients, regulators, and value assessors has grown over the past two decades. In the United States, initiatives such as the FDA Sentinel Initiative, the National Institute of Health's AllofUs project, and the Patient-Centered Outcomes Research Institute's PCORnet have increased the visibility of RWD and its potential applications.

In parallel, interest in patient engagement and other stakeholder engagement in research has grown substantially. Professional societies such as the International Society for Pharmaceutical Outcomes and Research (ISPOR) and the International Society for Pharmacoepidemiology (ISPE) have formed the Joint ISPOR-ISPE Special Task Force on RWE in Health Care Decision Making to improve the validity and relevance of RWE. The task force included patient and stakeholder engagement as one recommended good-procedural practice when designing, conducting, and disseminating RWE.[4]

Although several examples describing the importance of patient engagement in RWE have been published, there is a paucity of actual examples of patient engagement in study design or implementation.[5–10] A comprehensive understanding of patients' lived experiences can assist researchers in ensuring that studies reflect as closely as possible "real-world" patient experiences and health care as it is delivered.[11] However, there are currently no recommended methods or standards to incorporate patient input that can be applied when designing studies that leverage RWD. Without a set of guiding principles to support and encourage patient engagement in RWE, the status quo is unlikely to change.

Thus, the purpose of this report is to provide RWE stakeholders with consensus on evidence-based recommendations that provide guidance for *how* patient input, gathered through meaningful patient engagement,[12] can be identified and incorporated into the design, conduct, and translation of real-world research that reflects patients' lived experience. Note, the intent here is *not* to replicate the many other existing sources describing how to best capture patient experiences.[13–16] Through extensive in-depth interviews with RWD methodologists, the focus of this report is to build consensus on how data capturing patient experiences can be leveraged within RWD studies to generate patient-centered RWE.

Methods

All phases of this project were guided by a multi-disciplinary stakeholder Advisory Board (AdBoard) (see Acknowledgements). Detailed methods are described in a forthcoming manuscript. The methods are described briefly here.

Definitions

The following definitions were adopted for this project:

- **Patient-Provided Information (PPI):** Broadly encompasses the entirety of information that can be collected from an interaction with a patient(s) or a patient-identified care partner(s).[12]

- **Real-World Data**: Data relating to patient health status and/or the delivery of health care *routinely collected* 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[17]

- **Real-World Evidence:** Evidence regarding the use and potential benefits and/or risks of a medical product 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 and/or pragmatic trials), and observational studies (prospective and/or retrospective).[17]

Interviews

In-depth interviews were conducted with RWD methodologists (n=15) who were provided with two scenarios consisting of background information about the disease, insights from patients about their experiences, a study objective, and a study type (see Figure 1 example). The patient insights stemmed from Voice of the Patient reports published by the Food and Drug Administration (FDA).[18] The hypothetical research questions were drafted by researchers from the NHC and UMB and were finalized by the AdBoard. Interviewees were asked to describe how the insights from patients about their experiences, preferences, and desired outcomes, referred to as PPI would impact their research design, including: 1) developing a refined research question, 2) developing a research protocol, and 3) translating research findings. The interviewees were provided with a visual aid to help guide the discussion (see Appendix 1). The interviews were not intended to capture information to inform a specific study on the scenario, but rather to understand thought processes and mechanisms used to apply as well as integrate the patient experience data when designing a RWD-based study.

Figure 1. Example of One Patient-Provided Information Scenario

Background: Alopecia areata is an autoimmune disease that targets the hair follicles, causing hair loss. The hair loss usually occurs on the scalp, but can also affect the beard, eyebrows, and other areas of the body. In the United States, approximately 500,000 individuals have alopecia areata. Most individuals experience onset of alopecia by the age of 40, with nearly half experiencing onset before the age of 20. For patients with alopecia totalis and universalis, onset is typically before the age of 30. In children, the mean age of onset is between 5 and 10 years of age.

There is no cure and there are no FDA-approved treatments for alopecia areata. However, there are several treatments used off-label to manage it. The most common treatment option is corticosteroid use, which is either administered as an injection intradermally into the skin, or applied topically as a cream, ointment, or gel. Second-line treatment options include calcineurin inhibitors, immunotherapies, and hair-growth-stimulating solutions. In scientific literature, there are reports of other types of treatments that are used to manage alopecia areata, including prostaglandin analog solutions, platelet-rich plasma patches, topical retinoids, cryotherapy, and light-based therapy, such as excimer light. Local treatments are usually used either as a first-line treatment or as a treatment for people who have limited hair loss. Systemic therapies are considered for patients who have more extensive hair loss, or who have a rapid progression of alopecia.

Patient-provided information:
- Alopecia areata patients often report that their illness has led to severe depression. One patient called the mental effects of alopecia "more detrimental than the alopecia itself."
- For some of those participants, their depression led to thoughts of self-harm. One patient stated, "The amount of times I have thought about self-harm and just not existing in general is unexplainable."
- Other patients shared struggles with depression, including some who stated that they had previously attempted suicide.
- Patients emphasize that alopecia is more than a cosmetic disorder, that it is a condition that takes a significant emotional toll on patients.

Study Objectives:
- To study the effectiveness of treatments for depression among patients with alopecia areata.
- To study the effectiveness of treatments for alopecia areata.

Study Type:
- Retrospective cohort study

Question:
- How would this patient-provided information impact your decision-making throughout the steps outlined in the research-design framework?
- What are the steps where you don't think patient-provided information would be useful?

Interview transcripts were analyzed and developed into a draft set of recommendations, that were reviewed by the AdBoard and revised for clarity. The draft set of recommendations are presented in Appendix 2.

eDelphi Survey

To gather additional feedback on the draft recommendations, an eDelphi survey was conducted. In brief, the eDephi method uses a structured communication method with a panel of experts on a particular topic to generate a group opinion or decision. Invited participants with expertise in the use of RWD included outcomes researchers, data scientists, epidemiologists, value assessors, and patient representatives identified by the project team and the AdBoard (n=44 participants invited). Out of those that were invited, roughly 60% participated (n=26 participated). Non-participation was due to time constraints or non-responsiveness. Those who did not respond were more likely to be based outside the United States.

Participants were asked to assess their agreement with individual recommendations using a Likert scale, and given an opportunity to provide feedback using a free text box (see Appendix for sample survey). Recommendations were revised based on feedback, and a second eDelphi survey round was completed. All statements achieved consensus with the lowest agreement level at 80%. The revised recommendations were reviewed by the AdBoard for clarity and are presented in this report. During AdBoard review, several recommendations were condensed into an overarching recommendation and rephrased for greater clarity.

Methods Recommendations

High-quality RWD studies and RWE evaluations are not conducted by RWD researchers in silos. Instead, they are a product of meaningful engagement of relevant key stakeholders that contribute various sources of knowledge, insights, and expertise throughout the design, execution, and reporting of studies. While these recommendations are targeted toward RWD researchers striving to generate patient-centered RWE, it is necessary to note that the suggested steps cannot be completed by RWD researchers alone. Enhancing RWD to include PPI is a collaborative effort. RWD researchers must leverage their colleagues' various skillsets and the insights from patients, patient organizations, and caregivers to comprehensively and efficiently elicit and incorporate PPI into RWD studies.

The consensus recommendations are organized into three themes:

- Developing a Patient-Centered Research Question and Study Design

- Disseminating Research Findings

- General Considerations

Developing a Patient-Centered Research Question and Study Design

These recommendations help RWD researchers develop and refine a research question. The starting point is a preliminary research question. A literature review and stakeholder engagement contribute to a refined research question anchored in the PICOTS framework and a corresponding hypothesis.

1   **As part of a literature review, include search terms to support the retrieval of qualitative research that describes patient/caregiver's information needs.**

Patient input may help increase the awareness of important gaps in information needed by patients and/or caregivers for their decision making. Qualitative data describing these information gaps may already exist and can be more efficient than primary data collection. Traditional databases, such as PubMed, are potential sources of qualitative data. The availability of grey literature and white papers, such as FDA-led or externally led Voice of the Patient reports[18] and patient journey maps published by patient organizations should also be considered as potential sources of qualitative data.

2   **Sources of patient-experience data and patient insights often also describe questions patients have about their disease or treatment. Depending on the study objective/audience, these patient-identified questions should be prioritized.**

Questions important to patients and caregivers usually highlight areas of unmet need. These questions can be incorporated into research planning, study outcome selection, or other study design features. This helps ensure that the research conducted is meaningful and relevant.

3   **Understand and document the diversity of patients and patient experiences when designing a study that relies on RWD.**

Qualitative research, collaborations with patient organizations, and published studies representative of diverse patient populations can help characterize experiences from different patient subpopulations. This can help ensure alignment between the preliminary research question and the patient population/subpopulation targeted, as well as data-source selection. Consider how social determinants of health impact patients' interactions with the health care system, including care seeking and insurance coverage.

4   **Before designing the research protocol, consider developing a conceptual framework or patient-journey map in collaboration with patients to help better understand the disease from their perspective.**

A conceptual framework for the condition of interest, study population, or type of research question may already exist in the literature and should be leveraged when available. If a relevant conceptual framework cannot be identified, then RWD researchers should work in collaboration with other stakeholders, such as patient groups, to develop the framework. At a minimum, the framework should include supporting documentation for each of the PICOTS elements (population, intervention, comparator, outcome, timing, and setting). This documentation helps define the rationale and provide supporting documentation for study-design decisions. Collaboration with patients can occur on a large scale (e.g., conduct a

primary patient-experience mapping exercise) or small scale (e.g., rely on existing qualitative studies, discuss and refine with a small group of patients).

5   When identifying a data source to conduct a RWD study, consider the role of patient registries.

Patient registries are curated by many patient organizations and are intended for research purposes. They often include variables specific to the condition of interest and relevant to the study population not captured in traditional RWD datasets. Patient registries may be an appropriate substitute or supplement to traditional RWD sources, especially in areas of high unmet need such as rare diseases. They can be helpful in studying questions prioritized by patients and/or caregivers. Just as one would with any other research, be mindful of and feel comfortable asking questions about any biases and limitations that may be present in registry data sources.

6   Consider how patient input gathered during the literature review and development of the conceptual framework could contribute to study decisions, including how to define and operationalize:
- **Population/subgroups**
- **Inclusion and exclusion criteria**
- **Comparators**
- **Study period**
- **Exposure**
- **Outcome of interest/endpoint**
- **Covariates**
- **Confounding**

Examples of leveraging patient-experience data include:

o   Identifying relevant subpopulations to examine in studies. These include those based on gender, age, socioeconomic factors, co-morbidities, etc.
o   Identifying "real-world" treatment comparators. Patients may not always have access to treatments considered as "comparators" by researchers due to constraints resulting from varying insurance benefit designs. Patients may also describe the role of treatments that may not be promoted by the health system (e.g., homeopathic medicine), but nevertheless are used by patients.
o   Defining the study period to ensure it is sufficiently long enough to capture the full extent and lasting influence of interventions of interest. Patient experiences may also help make study periods more applicable. For example, it may not be necessary to have a one-year washout period, even if it has been used in prior studies in the same population.
o   Identifying possible confounders and/or covariates in an analysis where the outcome is pre-defined.

7 Consider how patient experiences clarify utilization patterns or missing data in a RWD dataset.

Understanding patient experiences outside of health care can help clarify patient adherence and treatment behaviors. Understanding barriers to insurance coverage can assist in creating more representative cohorts when using traditional RWD sources.

Disseminating Research Findings

Traditional dissemination approaches such as research-conference presentations or publication in peer-reviewed journals are typically insufficient for reaching patient audiences. Patient groups or community-based organizations can be effective partners in translating research findings to make them accessible to patient audiences. They can assist in tailoring the language, and suggest methods and conduits (e.g., clinical vs. community settings).

8 Leverage patient groups and existing qualitative research, when available, to identify how patients access information and develop a dissemination strategy that includes those communication vehicles.

Common sources of information for patients include online forums, patient conferences, and/or patient advocacy or professional society websites. Researchers can outreach to patient- or community-based organizations involved in the study to identify the best way to reach the target audience. Many of these organizations have newsletters and other media vehicles that can be useful for the dissemination of study findings. In addition, there may be existing qualitative research describing how patients access information. This should be further employed as a resource.

Research findings should always be shared back with patients involved in a study as partners or as subjects.

9 Patient-provided information can illuminate specific study confounders.

Patient insights can often be used to identify variables not captured by traditional datasets as potential confounders. These variables influence both the treatment and outcome of interest and may introduce bias when not accounted for. RWD researchers should ensure that all patient-identified confounders, when available, are accounted for in statistical analyses. However, if a patient-identified variable(s) is missing from the dataset, not being able to account for that variable should be described as a study limitation. Instead of relying on a blanket statement describing limitations of administrative claims, specific missing variables should be described to aid readers in interpreting findings.

10 Translation efforts should seek to set a research agenda to enhance future work.

Study communications should clearly articulate new research questions emerging as a result of the 1) study findings; 2) data gaps identified when attempting to account for and incorporate PPI while conducting the study; and 3) methodological limitations encountered, including innovative approaches piloted as part of the study and unmeasured confounders identified by PPI.

A clear feedback loop is important for any patient-centered research.

General Recommendations

This theme includes recommendations that are general in nature and important to consider when conducting research with RWD.

11 More frequent and impactful opportunities are needed for various health care stakeholders to provide input on the RWD collected and RWE evidence needs.

To promote alignment between data availability and data needed to develop patient-centered RWE, data stewards (vendors, health care systems, governments) should offer stakeholders, including patient representatives, researchers, and decision-makers, opportunities to highlight missing variables and potential confounders that frequently result in study limitations. Similarly, RWD researchers should engage relevant stakeholders, including patient representatives and clinicians who rely on RWE, to provide input on evidence needed and identified gaps. Together, these opportunities can lead to more relevant, meaningful, and reliable RWE for all stakeholders.

12 Multistakeholder collaboration is essential to ensure RWE is relevant and reliable. All relevant health care stakeholders should be engaged to refine research questions and ensure research protocols are designed to help inform decision-making.

Physicians, nurses, physical therapists, pharmacists, and other providers have frequent, direct contact with patients. While these providers can help provide additional insights into the patient's experience, it is important to note that they cannot serve as a proxy or a substitute for patients. Additional stakeholders such as medical coders can help researchers navigate data anomalies in diagnoses codes and/or other codes.

13 The health care stakeholder community should test the application of these recommendations through pilot studies, refine them, and define best-practice methodologies to ensure (over time) patient-centered RWE research becomes mainstream.

Conclusion

The 13 consensus recommendations emerging from this study can be used by researchers as a framework to conduct more patient-centered RWD studies. Applying these recommendations can help improve the relevance of RWE to patient communities

of interest; foster greater multi-disciplinary participation and transparency in RWD research; and aid researchers in documenting study-design decision rationale, study findings, and study limitations. These recommendations are broadly applicable to different types of RWD-based research, including RWE for regulatory decision-making, health technology/value assessment, and clinical practice guideline development.

Patient engagement needs to occur in all three phases in RWD study design; planning, execution, and RWE evaluation (figure 1).This project is a first step to enhancing RWE through the engagement of patient communities and incorporation of PPI. These recommendations provide a starting point for further pilot testing by researchers as part of specific research projects. As researchers gather additional experience through applying the methods recommendations, further refinement of these consensus recommendations may lead to "best practices."

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Draft Recommendations Developed Following Methodologist Interviews

I. *Draft - Developing a Refined Research Question*

- Include search terms to retrieve qualitative research as part of a literature review. PPI may help increase awareness of important gaps in information needed by patients and/or caregivers. Qualitative data describing these information gaps may already exist and provide efficiency over primary data collection.
- Understand and document the diversity of patient experiences when designing a study that relies on RWD. Qualitative research, collaborations with patient organizations, and published studies that rely on patient registries may help characterize populations without the selection bias that can be present in insurance-based databases. This can help ensure alignment between the preliminary research question and the patient population/subpopulation targeted, as well as data source selection.
- Before designing your research protocol, consider developing a conceptual framework or patient-journey map depicting patient experiences. This can be helpful documentation of the rationale behind study-design decisions and data-source selection.
- When identifying a data source, consider the role of patient registries. Patient registries are intended for research purposes and often include variables not captured in traditional RWD datasets. They may be helpful in studying questions prioritized by patients and/or caregivers.

II. *Draft - Developing a Research Protocol*

- Consider how PPI may be useful in informing and/or refining all phases of research-protocol development. The clinical context, complexity, type of research, and intended audience may impact assessment of feasibility and clarify to which phases PPI is applicable. For example, in a safety analysis where the outcome is pre-defined, PPI can be useful in identifying possible confounders or covariates.
- Consider PPI when defining the study period to ensure that it is sufficiently long to capture the full extent and the lasting influence of study events. Considering PPI may also help make study periods more precise. For example, it may not be necessary to have a one-year washout period, even if it has been used in prior studies in the same population.
- Leverage PPI to identify "real-world" treatment comparators. Patients may not always have access to treatments considered as "comparators" by researchers due to constraints resulting from health benefit designs. Patients may also

describe the role of treatments that may not be promoted by the health system (e.g., homeopathic medicine), but nevertheless are used by patients.

- PPI often describes questions that patients have about their disease or treatment. Depending on the study objective/audience, these patient-identified questions should be prioritized and incorporated into study outcome selection.
- Recognize and consider how PPI can explain missing data or utilization patterns in an RWD dataset. For example, PPI may identify factors that influence patient adherence to treatments or follow-up instructions.
- Researchers can use PPI to identify relevant subpopulations to examine in studies. These include subpopulations based on gender, age, socioeconomic factors, clinical co-morbidities, etc.

III. *Draft - Translation Phase*

Traditional dissemination approaches such as research-conference presentations or publication in a peer-reviewed journal are typically insufficient for reaching patient audiences. Patient groups or community-based organizations can be effective partners in translating research findings to be accessible to patient audiences. They can assist in language translation and suggest methods and conduits (e.g., clinical vs. community settings).

- Researchers can outreach to relevant patient- or community-based organizations to identify the best way to reach the constituency of interest in a way that is representative of both the disease experience and local contexts.
- Identify if existing qualitative research describes how patients access information. This may include online forums, patient conferences, and/or professional society websites.

PPI often identifies variables not captured by traditional datasets as potential confounders, influences on treatment, outcomes, etc.

- If the patient-identified variable(s) is missing from the dataset, then not being able to account for it should be described as a study limitation. For example, instead of relying on a blanket statement describing limitations of administrative claims, specific variables should be described to aid readers in interpreting findings.
- Translation efforts should seek to set an agenda to identify possible questions or research approaches that could improve future work.

IV. *Draft - Other Recommendations*

- Other stakeholders, such as health care providers, payers, etc. should be engaged to refine research questions and to ensure that research protocols are acceptable to inform decision-making.
- To promote alignment between data availability and RWD-needs to develop patient-centered RWE, data stewards (vendors, health care systems,

governments) and or RWE researchers should offer relevant stakeholders, including patient representatives, researchers, and decision-makers who rely on RWE, with opportunities to provide input on the disease and treatment experience, which can lead to more relevant/reliable research and findings. Efforts should be made to leverage stakeholder input to identify and overcome possible data and methods deficiencies.

- The health care stakeholder community should test application of these recommendations, refine them, and define standard or best-practice methodologies in PPI to ensure (over time) incorporating PPI in RWE research becomes mainstream.

Notes
- Researchers that work with RWD do not have to be the ones collecting the PPI. PPI collected by others can and should be leveraged.
- PPI is important, but does not preclude the importance of the other sources of information (e.g., peer-reviewed literature, engagement of other stakeholders) – it is complementary and can enhance it.
- Consider how rigorous the collection methods/how representative the PPI you identify is of the target population.
- In some cases, PPI may be transformational; in others, it may result in fine-tuning.

**Leveraging Patient-Provided Information to
Develop Patient-Centered Real-World Evidence:**

Draft Recommendations Revised (Post eDelphi)

Background

There is growing interest in using "real-world" data (RWD) and resulting real-world evidence (RWE) to support regulatory decision-making and value assessments of medical products. To improve the validity and relevance of real-world evidence (RWE), the Joint International Society for Pharmacoeconomics and Outcomes Research (ISPOR)-International Society for Pharmacoepidemiology (ISPE) Special Task Force on RWE in Health Care Decision Making included stakeholder engagement as one recommended good-procedural practice when designing, conducting, and disseminating RWE.

However, there are currently no studies or relevant publications describing how patient-provided information (PPI) - gathered through meaningful patient engagement - can be translated by researchers into more patient-centered RWD research designs that reflect patients' lived experiences. Without a set of guiding principles for how translation of PPI can be transparently accomplished and, in a way, acceptable to decision-makers and researchers alike, this recommendation is likely to be ignored.

Founded in 1920, the National Health Council (NHC) brings diverse organizations together to forge consensus and drive patient-centered health policy. We are interested in understanding how the ISPOR-ISPE task force recommendation to engage stakeholders when conducting RWD-based studied can be operationalized to achieve patient engagement. While RWE has not traditionally been developed with patient partners, patient engagement and patient-provided information can be leveraged to ensure RWE study designs reflect patient experiences to the greatest extent possible. Indeed, patient engagement can help RWD-researchers to better understand the lived experiences of the "subjects" whose experiences makes up "real-world data."

Purpose of Study

The purpose of the study is to derive a set of recommendations that can be provided to RWE stakeholders describing *how* patient-provided information (PPI) - gathered through meaningful patient engagement - can be translated by researchers into more patient-centered RWD research designs that reflect patients' lived experiences.

Draft Recommendations Revised (Post eDelphi Survey 1)

I. *Developing a Refined Research Question*

- Include search terms to retrieve qualitative research as part of a literature review. PPI may help increase awareness of important gaps in information needed by patients and/or caregivers. Qualitative data describing these information gaps may already exist and provide efficiency over primary data collection.
- Understand and document the diversity of patient experiences when designing a study that relies on RWD. Qualitative research, collaborations with patient organizations, and published studies that rely on patient registries may help characterize populations. This can help ensure alignment between the preliminary research question and the patient population/subpopulation targeted, as well as data source selection. Just as you would with any other research, be mindful of and feel comfortable asking questions about selection bias that may be present in patient registries.
- Before designing your research protocol, consider developing a conceptual framework or patient-experience map in collaboration with patients. This can be helpful documentation of the rationale behind study-design decisions and data-source selection.
- When identifying a data source, consider the role of patient registries. Patient registries are intended for research purposes and often include variables not captured in traditional RWD datasets. They may be helpful in studying questions prioritized by patients and/or caregivers.

II. *Developing a Research Protocol*

- Consider how PPI will inform research-protocol development. The clinical context, complexity, type of research, and intended audience may impact assessment of feasibility and clarify to which phases PPI is applicable. For example, in a safety analysis where the outcome is pre-defined, PPI can be useful in identifying possible confounders or covariates.
- Consider PPI when defining the study period to ensure that it is of sufficient duration for capturing important and relevant outcomes related to the study events. Considering PPI may also help make study periods more precise. For example, it may not be necessary to have a one-year washout period, even if it has been used in prior studies in the same population.
- Leverage PPI to identify "real-world" treatment comparators utilized by and accessible to patients. Patients may not always have access to treatments considered as "comparators" by researchers due to constraints resulting from health benefit designs. Patients may also describe the role of treatments that

may not be promoted by the health system (e.g., homeopathic medicine), but nevertheless are used by patients.
- Depending on the study objective/audience, these patient-identified questions should be prioritized and incorporated into study outcome selection.
- Recognize and consider how PPI can explain or reduce missing data or utilization patterns in an RWD dataset. For example, PPI may identify factors that influence patient adherence to treatments or follow-up instructions.
- Researchers can use PPI to identify relevant subpopulations to examine in studies. These include subpopulations based on gender, age, socioeconomic factors, clinical co-morbidities, etc.

III.   *Translation Phase*

Traditional dissemination approaches such as research-conference presentations or publication in a peer-reviewed journal are typically insufficient for reaching patient audiences. Patient groups or community-based organizations can be effective partners in translating research findings to be accessible to patient audiences. They can assist in language translation and suggest methods and conduits (e.g., clinical vs. community settings).
- Researchers can outreach to patient- or community-based organizations involved in the study to identify the best way to reach the constituency of interest in a way that is representative of both the disease experience and local contexts.
- Identify if existing qualitative research describes how patients access information. This may include online forums, patient conferences and/or professional society websites.

PPI often identifies variables not captured by traditional datasets as potential confounders, influences on treatment, outcomes, etc.
- If the patient-identified variable(s) is missing from the dataset, then not being able to account for it should be described as a study limitation. For example, instead of relying on a blanket statement describing limitations of administrative claims, specific variables should be described to aid readers in interpreting findings.
- Translation efforts should seek to set an agenda to identify possible questions or research approaches that could improve future work.

IV.   *Other Recommendations*
- Other stakeholders, such as health care providers, payers, etc. should be engaged to refine research questions and to ensure that research protocols are acceptable to inform decision-making.
- To promote alignment between data availability and RWD-needs to develop patient-centered RWE, data stewards (vendors, health care systems, governments) and or RWE researchers should offer relevant stakeholders,

including patient representatives, researchers, and decision-makers who rely on RWE, with opportunities to provide input on the disease and treatment experience, which can lead to more relevant/reliable research and findings.

- The health care stakeholder community should test application of these recommendations through pilot studies, refine them, and define standard or best-practice methodologies in PPI to ensure (over time) incorporating PPI in RWE research becomes mainstream.

Notes
- Researchers that work with RWD do not have to be the ones collecting the PPI. PPI collected by others can and should be leveraged.
- PPI is important, but does not preclude the importance of the other sources of information (e.g., peer-reviewed literature, engagement of other stakeholders) – it is complementary and can enhance it.
- Consider how rigorous the collection methods/how representative the PPI you identify is of the target population.
- In some cases, PPI may be transformational; in others, it may result in fine-tuning.

Appendix: Delphi Round 1

Background

There is growing interest in using "real-world" data (RWD) and resulting real-world evidence (RWE) to support regulatory decision-making and value assessments of medical products. To improve the validity and relevance of real-world evidence (RWE), the Joint International Society for Pharmacoeconomics and Outcomes Research (ISPOR)-International Society for Pharmacoepidemiology (ISPE) Special Task Force on RWE in Health Care Decision Making included stakeholder engagement as one recommended good-procedural practice when designing, conducting, and disseminating RWE.

However, there are currently no studies or relevant publications describing how patient-provided information (PPI) - gathered through meaningful patient engagement - can be translated by researchers into more patient-centered RWD research designs that reflect patients' lived experiences. Without a set of guiding principles for how translation of PPI can be transparently accomplished and in a way acceptable to decision-makers and researchers alike, this recommendation is likely to be ignored.

Founded in 1920, the National Health Council (NHC) brings diverse organizations together to forge consensus and drive patient-centered health policy. We are interested in understanding how the ISPOR-ISPE task force recommendation to engage stakeholders when conducting RWD-based studied can be operationalized to achieve patient engagement. While RWE has not traditionally been developed with patient partners, patient engagement and patient-provided information can be leveraged to ensure RWE study designs reflect patient experiences to the greatest extent possible. Indeed, patient engagement can help RWD-researchers to better understand the lived experiences of the "subjects" whose experiences make up "real-world data."

Purpose of Study

The purpose of the study is derive a set of recommendations that can be provided to RWE stakeholders describing *how* patient-provided information (PPI) - gathered through meaningful patient engagement - can be translated by researchers into more patient-centered RWD research designs that reflect patients' lived experiences.

What you are asked to do:
You have been invited to serve on a multi-stakeholder eDelphi Expert Panel. You are being invited for your expertise in epidemiology, economics/econometrics, medical product regulatory decision-making, value assessment, patient engagement, or other related field. You will be asked to respond to several electronic surveys. In the first survey, you will be asked for feedback on a set of definitions and recommendations for applying PPI to RWE development. The recommendations were drafted based on in-depth interviews with 15 RWD methodologists. They were asked to describe how PPI stemming from actual patients could be applied to hypothetical study designs. In subsequent surveys, you will be asked to rank items in terms of "Most important" to "Least Important" for each category. We will conduct up to three surveys. We expect the first survey to take you the most time (approximately 30 minutes). The second and third surveys should take no more than 20 minutes to complete.

Potential Risks:
Breach of confidentiality or privacy are potential risks in this study. We will minimize this risk by providing all surveys directly to you and any identifying information will only be available to the research team.

Potential Benefits:
You will not benefit directly from participating. However, you are contributing your insights on a topic that can benefit the patient and research community in the future.

Alternatives to Participation and Right to Withdraw:
Your participation indicates your consent to participate. Your alternative is to not take part in the Expert Panel, and you may withdraw your consent at any time.

Contact
If you have general questions, please contact NHCPrograms@nhcouncil.org. If you have concerns or complaints, please contact the study PI, Dr. Elisabeth Oehrlein at eoehrlein@nhcouncil.org or 202-973-0540.

Thank you for your time and please go to the next page to begin!

1 What is your email? (*This is to help us track submissions in each round.*)

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2 Do we have permission to acknowledge your participation in this work in future publications? (*This will not be associated with your individual responses. After the study is complete, the research team will receive a list of those who agreed to be acknowledged.*)

○ Yes (1)

○ No (2)

3 How would you describe your recent experience with real-world data (RWD)/real-world evidence (RWE)?

☐   Primarily designing/contributing to studies that rely on RWD (4)

☐   Primarily interpreting/evaluating/applying RWE findings (5)

☐   Patient engagement with/without focus on RWE (6)

☐   Primarily RWE-related policy (e.g., how is RWE used) (7)

☐   Other (8) _____

4 What stakeholder group do you represent? (*Select the one that applies to your day-to-day job.*)

☐ Patient or patient-group staff member (including research staff) (1)

☐ Academic research (2)

☐ Health care provider (3)

☐ Regulatory body (4)

☐ Payer, managed care, employer (5)

☐ Health technology assessment / value assessment (6)

☐ Biopharmaceutical, medical device industry, or technology company (7)

☐ Other (8)

5 How would you rate your agreement with these recommendations regarding **developing a refined research statement**?

 *Definitions: **Patient-Provided Information** (PPI): broadly encompasses the entirety of information that can be collected from an interaction with a patient(s) or a patient-identified care partner. The focus should be the patient's views on their disease(s)/condition(s), desired attributes for treatments, experiences with treatments, benefit- risk preferences, and desired goals and outcomes. **Real-world data** (RWD) and **real-world evidence** (RWE): Data and data-derived interpretation that is based on sources other than conventional, randomized, controlled studies and offers insight to clinical, health-related quality of life, coverage, payment, and other patient outcomes.

	Agreement Level				Comments
	Strongly Disagree (1)	Disagree (2)	Agree (3)	Strongly Agree (4)	Please provide any feedback specific to each statement (1)

Include search terms to retrieve qualitative research as part of a literature review. Patient-Provided Information (PPI) may help increase awareness of important gaps in information needed by patients and/or caregivers. Qualitative data describing these information gaps may already exist and provide efficiency over primary data collection. (1)	○	○	○	○	
Understand and document the diversity of patient experiences when designing a study that relies on RWD. Qualitative research, collaborations with patient organizations, and published studies that rely on patient registries may help characterize populations without the selection bias that can be present in insurance-based databases. This can help ensure alignment between the preliminary research question and the patient population/subpopulation targeted, as well as data source selection. (2)	○	○	○	○	

Before designing your research protocol, consider developing a conceptual framework or patient-experience map depicting patient experiences. This can be helpful documentation of the rationale behind study-design decisions and data-source selection. (3)	○	○	○	○
When identifying a data source, consider the role of patient registries. Patient registries are intended for research purposes and often include variables not captured in traditional RWD datasets. They may be helpful in studying questions prioritized by patients and/or caregivers. (4)	○	○	○	○

6 Do you have any comments or suggested additions related to **developing a refined research statement** that have not been captured above?

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7 How would you rate your agreement with these recommendations regarding **developing a research protocol**?

*Definitions: **Patient-Provided Information** (PPI): broadly encompasses the entirety of information that can be collected from an interaction with a patient(s) or a patient-identified care partner. The focus should be the patient's views on their disease(s)/condition(s), desired attributes for treatments, experiences with treatments, benefit- risk preferences, and desired goals and outcomes. **Real-world data** (RWD) and **real-world evidence** (RWE): Data and data-derived interpretation that is based on sources other than conventional, randomized, controlled studies and offers insight to clinical, health-related quality of life, coverage, payment, and other patient outcomes.

	Agreement Level				Comments
	Strongly Disagree (1)	Disagree (2)	Agree (3)	Strongly Agree (4)	Please provide any comments specific to the statement (1)

| Consider how PPI may be useful in informing and/or refining all phases of research-protocol development. The clinical context, complexity, type of research, and intended audience may impact assessment of feasibility and clarify to which phases PPI is applicable. For example, in a safety analysis where the outcome is pre-defined, PPI can be useful in identifying possible confounders or covariates.   (1) | ○ | ○ | ○ | ○ |

Consider PPI when defining the study period to ensure that it is sufficiently long to capture the full extent and the lasting influence of study events. Considering PPI may also help make study periods more precise. For example, it may not be necessary to have a one-year washout period, even if it has been used in prior studies in the same population. (2)	○	○	○	○

| Leverage PPI to identify "real-world" treatment comparators. Patients may not always have access to treatments considered as "comparators" by researchers due to constraints resulting from health benefit designs. Patients may also describe the role of treatments that may not be promoted by the health system (e.g., homeopathic medicine), but nevertheless are used by patients.   (3) | ○ | ○ | ○ | ○ |

PPI often describes questions that patients have about their disease or treatment. Depending on the study objective/audience, these patient-identified questions should be prioritized and incorporated into study outcome selection. (4)	○	○	○	○
Recognize and consider how PPI can explain missing data or utilization patterns in an RWD dataset. For example, PPI may identify factors that influence patient adherence to treatments or follow-up instructions. (5)	○	○	○	○

| Researchers can use PPI to identify relevant subpopulations to examine in studies. These include subpopulations based on gender, age, socioeconomic factors, clinical co-morbidities, etc.   (6) | ○ | ○ | ○ | ○ |

8 Do you have any comments or suggested additions related to **developing a research protocol** that have not been captured above?

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9 How would you rate your agreement with these recommendations regarding the **Translation Phase**?

Traditional dissemination approaches such as research-conference presentations or publication in a peer-reviewed journal are typically insufficient for reaching patient audiences. Patient groups or community-based organizations can be effective partners in translating research findings to be accessible to patient audiences. They can assist in language translation, suggest methods and conduits (e.g., clinical vs. community settings).

	Agreement Level				Comments
	Strongly Disagree (1)	Disagree (2)	Agree (3)	Strongly Agree (4)	Please provide any comments specific to the statement (1)

Researchers can outreach to relevant patient- or community-based organizations to identify the best way to reach the constituency of interest in a way that is representative of both the disease experience and local contexts. (1)	○	○	○	○
Identify if existing qualitative research describes how patients access information. This may include online forums, patient conferences, and/or professional society websites. (2)	○	○	○	○

10 Do you have any comments or suggested additions related to the **<u>Translation Phase</u>** that have not been captured above?

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11 How would you rate your agreement with these **<u>Other Recommendations</u>** not elsewhere categorized?

*Definitions: **Patient-Provided Information** (PPI): broadly encompasses the entirety of information that can be collected from an interaction with a patient(s) or a patient-identified care partner. The focus should be the patient's views on their disease(s)/condition(s), desired attributes for treatments, experiences with treatments, benefit- risk preferences, and desired goals and outcomes. **Real-world data** (RWD) and **real-world evidence** (RWE): Data and data-derived interpretation that is based on sources other than conventional, randomized, controlled studies and offers insight to clinical, health-related quality of life, coverage, payment, and other patient outcomes.

	Agreement Level				Comments
	Strongly Disagree (1)	Disagree (2)	Agree (3)	Strongly Agree (4)	Please provide any comments specific to each statement (1)

Other stakeholders, such as health care providers, payers, etc., should be engaged to refine research questions and to ensure that research protocols are acceptable to inform decision-making. (1)	○	○	○	○
To promote alignment between data availability and RWD-needs to develop patient-centered RWE, data stewards (vendors, health care systems, governments) and or RWE researchers should offer relevant stakeholders, including patient representatives, researchers, and decision-makers who rely on RWE, with opportunities to provide input on the disease and treatment experience, which can lead to more relevant/reliable research and findings. Efforts should be made to leverage stakeholder input to identify and overcome possible data and methods deficiencies. (2)	○	○	○	○

The health care stakeholder community should test application of these recommendations, refine them, and define standard or best-practice methodologies in PPI to ensure (over time) incorporating PPI in RWE research becomes mainstream. (3)	○	○	○	○

12 Do you have any comments or suggested additions related to the **Other Recommendations** that have not been captured above?

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Appendix: Delphi Round 2

Thank you for participating in the first round of our expert panel. As you may recall, the purpose of the study is derive a set of recommendations that can be provided to Real Wolrd Evidence (RWE) stakeholders describing how patient-provided information (PPI) - gathered through meaningful patient engagement - can be translated by researchers into more patient-centered Real World Data (RWD) research designs that reflect patients' lived experiences. The final round prioritizes the drafted statements that reached agreement in the previous round. In this round, you will be asked to rank each statement in order of importance and to provide any final comments or feedback for our research team and advisory board to consider.

 Contact:
If you have general questions, please contact NHCPrograms@nhcouncil.org. If you have concerns or complaints, please contact the study PI, Dr. Elisabeth Oehrlein at eoehrlein@nhcouncil.org or 202-973-0540.

Thank you for your time and please go to the next page to begin!

 Please enter your email (*This is just for tracking purposes.*)

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Below are the revised "Recommendations" related to **Developing a Refined Research Question**. Please rank in order of importance (1 - Most Important, 4 - Least Important).

To put the statements in order, simply "Drag and Drop" each statement.
Acronyms: Real World Data (RWD); Real World Evidence (RWE); Patient-Provided Information (PPI)

_____ Include search terms to retrieve qualitative research as part of a literature review. PPI may help increase awareness of important gaps in information needed by patients and/or caregivers. Qualitative data describing these information gaps may already exist and provide efficiency over primary data collection. (1)

_____ Understand and document the diversity of patient experiences when designing a study that relies on RWD. Qualitative research, collaborations with patient organizations, and published studies that rely on patient registries may help characterize populations. This can help ensure alignment between the preliminary research question and the patient population/subpopulation targeted, as well as data source selection. Just as you would with any

other research, be mindful of and feel comfortable asking questions about selection bias that may be present in patient registries. (2)

_____ Before designing your research protocol, consider developing a conceptual framework or patient-experience map in collaboration with patients. This can be helpful documentation of the rationale behind study-design decisions and data-source selection. (3)

_____ When identifying a data source, consider the role of patient registries. Patient registries are intended for research purposes and often include variables not captured in traditional RWD datasets. They may be helpful in studying questions prioritized by patients and/or caregivers. (4)

Please provide any final comments or feedback related to the recommendations for **developing a refined research question**.

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Below are the revised "Recommendations" related to **Developing a Research Protocol**. Please rank in order of importance (1 - Most Important, 6 - Least Important).

To put the statements in order, simply "Drag and Drop" each statement.
Acronyms: Real World Data (RWD); Real World Evidence (RWE); Patient-Provided Information (PPI)

_____ Consider how PPI will inform research-protocol development. The clinical context, complexity, type of research, and intended audience may impact assessment of feasibility and clarify to which phases PPI is applicable. For example, in a safety analysis where the outcome is pre-defined, PPI can be useful in identifying possible confounders or covariates. (1)

_____ Consider PPI when defining the study period to ensure that it is of sufficient duration for capturing important and relevant outcomes related to the study events. Considering PPI may

also help make study periods more precise. For example, it may not be necessary to have a one-year washout period, even if it has been used in prior studies in the same population. (2)

_____ Leverage PPI to identify "real-world" treatment comparators utilized by and accessible to patients. Patients may not always have access to treatments considered as "comparators" by researchers due to constraints resulting from health benefit designs. Patients may also describe the role of treatments that may not be promoted by the health system (e.g., homeopathic medicine), but nevertheless are used by patients. (3)

_____ Depending on the study objective/audience, these patient-identified questions should be prioritized and incorporated into study outcome selection. (4)

_____ Recognize and consider how PPI can explain or reduce missing data or clarify utilization patterns in an RWD dataset. For example, PPI may identify factors that influence patient adherence to treatments or follow-up instructions. (5)

_____ Researchers can use PPI to identify relevant subpopulations to examine in studies. These include subpopulations based on gender, age, socioeconomic factors, clinical co-morbidities, etc. (6)

Please provide any final comments or feedback related to the recommendations for **developing a research protocol**.

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Below are the revised "Recommendations" related to the **Translation Phase** of research. Please rank in order of importance (1 - Most Important, 4 - Least Important).

To put the statements in order, simply "Drag and Drop" each statement.

Acronyms: Real World Data (RWD); Real World Evidence (RWE); Patient-Provided Information (PPI)

_____ Researchers can outreach to patient- or community-based organizations involved in the study to identify the best way to reach the constituency of interest in a way that is representative of both the disease experience and local contexts. (1)

_____ Identify if existing qualitative research describes how patients access information. This may include online forums, patient conferences, and/or professional society websites. (2)

_____ If the patient-identified variable(s) is missing from the dataset, then not being able to account for it should be described as a study limitation. For example, instead of relying on a blanket statement describing limitations of administrative claims, specific variables should be described to aid readers in interpreting findings. (3)

_____ Translation efforts should seek to set an agenda to identify possible questions or research approaches that could improve future work. (4)

Please provide any final comments or feedback related to the **translation phase of research**.

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Below are the revised "Recommendations" not currently categorize but listed as **Other Recommendations** for PPI in RWE. Please rank in order of importance (1 - Most Important, 3 - Least Important).

To put the statements in order, simply "Drag and Drop" each statement.

_____ Other stakeholders, such as health care providers, payers, etc., should be engaged to refine research questions and to ensure that research protocols are acceptable to inform decision-making. (1)

_____ To promote alignment between data availability and data needed to develop patient-centered RWE, data stewards (vendors, health care systems, governments) and/or RWE researchers should offer relevant stakeholders, including patient representatives, researchers,

and decision-makers who rely on RWE, opportunities to provide input on the disease and treatment experience, which can lead to more relevant/reliable research and findings. (2)

_____ The health care stakeholder community should test application of these recommendations through pilot studies, refine them, and define standard or best-practice methodologies in PPI to ensure (over time) incorporating PPI in RWE research becomes mainstream. (3)

Please provide any final comments or feedback related to **other recommendations**.

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Thank you for your participation in this expert panel! If you have any general comments or feedback not otherwise captured in our survey process, please feel free to share those in the following comment box:

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Figure 1.

RWE Research Design Framework

NATIONAL HEALTH COUNCIL

Refined Research Question:
- Literature Review
- Data Availability
- Preliminary Research Question
- Target Patient Population
- Gaps in Knowledge/ Rationale
- Hypothesis

→ Synthesize Information/ Plan Study →

Research Protocol:
- Data source/ collection
- Subgroups
- Inclusion and Exclusion
- Confounding
- Study Period
- Study Design
- Exposure
- Covariates
- Outcome of Interest / Endpoint

→ Conduct/ Execute study →

Translation:
- Hypothesis Generation
- Implementation
- Impact/ Implications Assessment
- Interpretation
- Limitations
- Dissemination

← Stakeholder Engagement →