BBCIC
Biologics & Biosimilars
Collective Intelligence Consortium

Expert Panel Final Report

Using Real-World Data/Real-World Evidence to Support Biosimilar and Interchangeable Product Development and Approval: Challenges and Opportunities

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PURPOSE OF THIS REPORT

The Biologics and Biosimilars Collective Intelligence Consortium (BBCIC) engaged IQVIA Government Solutions to assist with an expert panel on July 10th, 2023, and then conducted a follow-up panel meeting on September 8th, 2023, to build on findings from the first panel meeting. The purpose of the expert panel consultation was to develop multi-stakeholder recommendations for the FDA on the use of real-world data (RWD) to meet evidence requirements for biosimilar approvals and determinations of interchangeability.

This report describes the panel proceedings, summarizes the discussions, offers preliminary recommendations based on the proceedings, and proposes the next steps to further develop the recommendations.

BACKGROUND

Biologicdrugs are large, complex molecules made from natural and living sources such as animal cells, plant cells, bacteria or yeast. They have transformed treatment options for patients with complex conditions such as immune-related diseases, cancer, and diabetes. However, they are costly to develop and bring to the market, and therefore costly to patients and the healthcare system more broadly, limiting access to these transformative drugs.[1]

Because biologics are derived from living organisms, they cannot be copied identically to create generic products. However, biosimilar products (biosimilars) can be produced. Biosimilars and interchangeable biosimilars are one way to reign in the cost of biologics, making these important therapies more widely available. Biosimilars are defined by the U.S. Food and Drug Administration (FDA) as a biologic that is highly similar to, and with no clinically meaningful differences from, the reference biologic.[2] Biosimilars undergo a rigorous FDA approval process through an abbreviated regulatory pathway authorized by the Biologics Price Competition and Innovation Act (BPCIA) of 2010, section 351(k) of the Public Health Service Act.[3] Regulatory review of biosimilars emphasizes molecular characterization through analytical assessments and clinical studies (comparative pharmacokinetic (PK) and pharmacodynamic (PD) studies, and clinical immunogenicity assessment); this does not eliminate the need for clinical trials but contributes to the totality of comparative and clinical evidence to support FDA approval. In addition, the FDA has the discretion to require additional clinical trials or post-marketing surveillance.

Like generic drugs, approved biosimilars are equally safe and effective versions of reference products and are usually less expensive.[2] Interchangeable biosimilars are biosimilars that meet an additional statutory standard that can allow a pharmacist to substitute them for a reference product without the prescribing physician's intervention depending on state law. This can make it easier for patients to access more affordable, equally effective treatments.

To obtain an interchangeability designation, the sponsor must demonstrate that the product can be expected to produce the same clinical result as the reference biologic in any given patient, and that the risks or reduced efficacy associated with switching between the product and its reference is not greater than that of using the reference product without a switch.[4]

Section 351(k) of the Public Health Service Act created an abbreviated licensure pathway for biosimilars and interchangeable biosimilars. The use of real-world data (RWD) to generate real-world evidence (RWE) to provide some of the evidence for regulatory approval could further expedite development, review, and approval of biosimilars and interchangeable biosimilars.[5] RWD are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources including data derived from electronic health records, medical claims data, data from product or disease registries, and data gathered from other sources (such as digital health technologies) that can inform on health status.[6] RWE is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.[6] RWD and RWE have been used in a variety of ways, such as external control arms for single-arm trials,[REF] to support and speed up regulatory applications for other kinds of drugs; however, to date, no applications to FDA for biosimilar approvals or determinations of interchangeability have included RWD/RWE.

PANEL PURPOSE AND PROCESS

First Panel Description

On July 10th, 2023, IQVIA facilitated a two-hour online expert panel on behalf of BBCIC to develop recommendations for the use of RWD/RWE to support biosimilar and interchangeable biosimilar approvals.

Nine expert panelists knowledgeable about biosimilars, RWD, and RWE, were convened by BBCIC (see Appendix 1). The goal was to provide specific suggestions to FDA and sponsors on **where** and **how** to integrate RWD into the regulatory process around biosimilars.

To prepare for the panel, IQVIA asked panelists to:

- **Review a report (**Available HERE**)** produced by IQVIA titled "Using Real world Data/Real world Evidence (RWD/RWE) for Biosimilar and Interchangeable Product Development and Approval: Challenges and Opportunities". This report summarizes the regulatory requirements for biosimilar and interchangeable product approvals and highlights where RWD/RWE can be used to improve upon clinical development or meet regulatory requirements, using lessons learned from regulatory applications for other drugs; and

- **Complete an online questionnaire** to inform the expert panel discussion. (See Appendix 2). The questionnaire included:
    - A question asking panelists to share their overall reaction to the report
    - Closed-ended questions, to serve as part of a modified Delphi process, listing several possible uses of RWD/RWE identified in the report, and asking panelists whether they support, support with caveats, or do not support this use in the context of applications for biosimilar approvals or interchangeability determinations
    - A preview of three case studies that would be used as discussion prompts during the panel discussion, with a request for feedback to help to improve case study descriptions and discussion prompts
    - Questions to elicit additional use cases where RWD can be used to support biosimilar and interchangeable products regulatory approval; and to identify barriers to adoption of RWD for regulators and for sponsors

The questionnaire and panel were part of a rapid modified Delphi process.[7] A Delphi process develops expert consensus by first eliciting experts' independent opinion through a survey. Results are then shared and discussed, allowing experts to inform and influence each other's thinking. The survey is then repeated, and criteria can be applied to the results to identify items with sufficient consensus to move forward for a specific purpose. A full Delphi process may require many rounds of surveys and discussions to achieve a sufficient level of consensus. For our purposes, we planned a rapid, modified Delphi process requiring one survey, a panel discussion, and one follow-up survey, with the goals of identifying a few promising areas in which to advance the use of RWD/RWE for biosimilar approvals and gathering specific suggestions on how to advance it.

The panel discussion included the following components:

- **Welcome, framing and presentations:** We summarized the issue on which we were requesting input from the panel, briefly summarized the report shared with panelists, and presented results from the Delphi survey

- **Discussion of Delphi results:** Panelists commented on expected and unexpected results, explained the thinking that led to their survey responses, and offered feedback to improve the Delphi survey questionnaire for the next round.

- **Case study discussion**: Three case studies were offered to anchor and test panelists' thinking about acceptable RWD/RWE uses within specific contexts. The purpose of this component of the discussion was to elicit richer, more nuanced discussion and practical insights. Panelists were asked to comment in writing using Mentimeter (a web-based application), then were invited to talk about it. The case studies focused on the following scenarios:

    - ***Case study 1****:* Biosimilar approval for rare cancer. Proposed RWD source: linked EHR-registry. Proposed RWD use: to solve recruitment challenges for clinical studies that will address residual uncertainty about biosimilarity after comparative analytical assessments.
    - ***Case study 2***: Biosimilar approval for a common inflammatory disease. Proposed RWD source: International data from a country with rich EHR clinical data and patient history. Proposed use: in lieu of additional comparative studies.
    - ***Case study 3***: Product under development as an interchangeable biosimilar for a common inflammatory disease. Proposed RWD source: large claims database. Proposed RWD use non-inferiority study in lieu of a traditional switching study.

Because the discussion was very rich, the panel did not have sufficient time to address all three case studies. IQVIA, BBCIC and panelists made a choice together to focus on Case Studies 1 and 3. The topic of international data, from Case Study 2, arose naturally in the open discussion.

In addition to panelists and the IQVIA and BBCIC teams, the panel discussion was attended by observers from the U.S. FDA and other interested parties. Panelists were informed of the observers' presence. Observers were instructed not to comment during the panel.

We initially intended to conduct the second round of Delphi voting during the panel itself, so that panelists could respond while the discussion was still fresh in their minds. However, panelists and the BBCIC and IQVIA teams found the discussion so valuable that they chose to postpone the second round of the Delphi survey until after the panel discussion.

Second Panel Description

After holding the first panel discussion, there were still topics that had not been fully explored so the panelists generously agreed to participate in a second two-hour panel discussion held virtually on September 8th, 2023. This discussion was facilitated by BBCIC staff and designed to delve deeper into the themes that emerged from the first panel. The second panel discussion topics were outlined based on the results of the first panel discussion and included the following components:

- **Welcome and recap of first panel**: We summarized the first panel discussion and highlighted topics that would benefit from a more detailed discussion.

- **Discussion topics**:
    - Data quality and provenance
    - RWD/RWE integration into regulatory decisions
    - Barriers to use and opportunities for advancing RWD

RESULTS

Participation

Seven of nine panelists responded to the online survey prior to the first panel discussion. All nine panelists attended both panel discussions.

General feedback on the pre-panel report

Seven panelists provided general comments on the report as part of the pre-panel survey. Five panelists found the report to be a helpful summary, three felt it was a bit basic or did not include sufficient detail specific to the context of biosimilars, and one found it challenging to assess the impact and use of RWD/RWE from the report. Unedited comments are provided below for reference:

Panelist overall comments on the report
It was a good big-picture view of the ongoing issues, but it does not contain the subtle nuances that makes it challenging to use RWD/RWE for biosimilar regulatory decisions
Summary of RWD/ RWE use in FDA regulatory decisions.
Well done
Helpful to orient readers to process, good ideas for future work, perhaps basic for those who work in the field.
High-level and not specific to RWE in biosimilar development
A good quick summary
I found the report challenging to assess in terms of impact and use of RWD/RWE.

Key take-aways from Delphi survey results (Round 1) and first panel discussion

In the pre-panel survey, panelists identified two main barriers that could inhibit use of RWD for biosimilar approvals.

- Regulatory concerns about RWD quality and its relevance for biosimilar approvals and determinations of interchangeability (6 of 7 pre-panel survey respondents)

- Sponsor concerns about the return-on-investment for RWD development and use, given the costs, uncertainty about regulator acceptance, and potential lost development time compared to competitors if regulators do not accept the proposed RWD use (7 of 7 pre-panel survey respondents)

In the ensuing discussion of Delphi survey results and case studies, respondents (n=7) voted to either “support” or “support with caveats” the following potential applications for RWE with no dissenting votes:

- Generate hypotheses and study endpoints
- Identify biomarkers or other clinical datapoints for use in clinical development
- Target patients for study recruitment
- Assess trial feasibility
- Increase linkage across registries and databases
- Leverage international data on products already approved/marketed outside the U.S.

Notably, there was near unanimous support (n=5 voting “support” and n=2 voting “support with caveats” for two concepts: using RWD to generate hypotheses and study endpoints, and leveraging international data on products approved/marketed outside the US. The latter of these two is particularly striking for biosimilars as European countries have used biosimilars widely in routine clinical care, including switching patients between products, for many years. This may offer opportunities to understand real-world safety and effectiveness before RWD is available or mature in the US where biosimilars may not be as widely used or are too new to generate useable RWD.

Table 1 below provides additional details on panel comments; a description of each proposed use case provided in the pre-panel Delphi survey; a summary of comments provided in the pre-panel questionnaire; and key take-aways from the panel discussion including comments on the first-round Delphi survey results, case study discussion comments posted by panelists in Mentimeter, and open discussion. The table also lists recommended changes to the Round 2 Delphi questionnaire, including changes to the wording of one question, deletion of another, and new questions about additional use cases proposed by panelists. We have made these edits in the Delphi Round 2 survey questionnaire (See Appendix 3).

Summary of Panel Discussions

Overall, panelists had positive views toward the potential of RWD in regulatory approvals, but they did express some concern about RWD quality and its relevance for biosimilar approvals and determinations of interchangeability. During the panel discussions, four themes emerged regarding barriers and opportunities for RWD for regulatory purposes: 1) data sources and availability, 2) data quality and relevance, 3) challenges in integrating RWD in the regulatory process, and 4) potential applications of RWD.

1. Data Sources and Availability

Patient Registries

Panelists discussed sources of RWD, suggesting that most studies use claims data and/or electronic health records (EHR) databases that are readily available, though usually for a fee. They noted that understanding strengths and limitations associated with each and data source selection is essential in designing appropriate RWD studies. One panelist encouraged the use of registries as a rich source of clinical outcomes that may not appear in other data sources. They noted that registries can be challenging and resource-intensive to build and require participation by providers and clinics to routinely submit their data for inclusion, but it introduces an opportunity to create databases with data that will ultimately be needed for disease-related research purposes. While registries are still limited in number and scope (e.g., limited to a specific disease) they suggested that several registries in the U.S. and in Europe may offer opportunities to leverage data that are already available. A few examples of well-established registries were mentioned: the SEER cancer registry in the US, a British dermatology database, a German registry for rheumatoid arthritis, a Ukrainian registry for inflammatory bowel disease, and Sweden has the Artis database for anti-rheumatic therapies. Panelists also mentioned that professional societies, particularly for medical specialties or specific disease states, also often have registries that align with the population they represent. All of these could be leveraged for studies that could be relevant for regulatory decisions.

International Data

European data offers some unique opportunities for biosimilars given the extra decade of experience and broad use in most countries. Furthermore, many non-US countries, especially in Europe, generally have a more integrated network of healthcare data that may facilitate better within-country data uniformity due, in many cases, to regionally or nationally administered healthcare. A common concern among panelists was in potential differences in population clinical and demographic characteristics that may confound the interpretation of any treatment effect; however, it was noted that data from country-level healthcare administration (e.g., national healthcare systems in European contruies) may have less internal confounding as treated patients will likely be more representative of the overall population, compared to the subset of data from patients only covered by commercial insurance or from a single geographically limited health system. This is an important question to investigate. There were lingering questions regarding the appropriateness of European populations to predict treatment effect in a US population, even with matching techniques such as propensity scores as those do not capture some of the less-measurable influences of diet and lifestyle that may be unique. It would also be valuable to understand more clearly whether or not observed treatment effects are different in US versus European patient populations.

Panelists discussed another unique feature of data from non-US countries is related to product switching. Many European countries utilize a tender system that implements non-medical switches between products that panelists felt could be leveraged and applied to a US regulatory, or even clinical decision-making, context. In some countries such as Denmark, the conversion of the Danish population to a product that won the tender is extremely rapid, often within weeks. While there is less of a difference in product launch dates now between countries, and there seem to be more contemporaneous product development programs, panelists noted that there are still instances in which biosimilar products have already been marketed with broad utilization in Europe that have not experienced the same level of utilization in the US, suggesting it could be useful to leverage those data to reduce or eliminate the need for a clinical study.

There are a few potential challenges, however. One challenge discussed in the context of biosimilar or interchangeable biosimilar approvals was the required link in clinical safety and effectiveness to the US reference product. For RWD, this linkage would likely have to be made via other data to bridge between European-marketed biosimilars and US-marketed biosimilars in terms of safety and effectiveness. Panelists felt that was a solvable problem, although it would require additional data to establish that bridge. In considering interchangeable biosimilars which may require an assessment of product switching between biosimilars and reference products, panelists suggested a potential challenge related to hidden sources of bias, such as whether the people who are switching are representative of the population who do not switch. This is remedied in instances where patients are transitioned due to non-medical policies such as a tender contract. As always, the availability of outcome measures is key to know whether relevant data are collected and if there is consistency in treatment and data recording practices.

A very important consideration panelists raised was that the most relevant or predictive measure for regulatory assessment is demonstrating a similar delta in treatment effect in the same populations treated with the same product. This radically simplifies the question of generalizability with the notion that as long as the treated patients are similar to a control cohort from the same population, then it matters less that a treated population in one country is the same as a treated population in another country if the treatment effect can be demonstrated. One panelist described a scenario suggesting that with matched populations in some healthcare setting, in the United Kingdom (UK) for example, then the net effect, or no difference in effect, in that population is sufficiently predictive of what is likely in other populations even if the baseline population characteristics differ from the study population. In this scenario, any difference in confounders or covariates is effectively removed by the matched cohorts. In comparing a biosimilar and reference product in a UK population, it is reasonable

to conclude that there are no clinically meaningful differences, and therefore it shouldn't matter what population is in consideration. Panelists suggested it would require a stretch to scientifically think why a difference would not be detectable. This concept reflects the principle that assessing the most sensitive population to detect a difference or treatment effect is sufficient to extrapolate to other populations (or indications).

2. Data Quality and Relevance

Data quality and relevance for regulatory purposes were prominent concerns among the panelists. One challenge for the group was to understand what “quality” means in the context of RWD fitness for regulatory use, and to understand how the quality of available data influences the types of questions that can be answered. Panelists agreed that missingness is often a concern, as is generalizability of the data beyond the population captured in the database. One of the most significant problems identified with data quality, was consistency of measurement and the availability of endpoints or variables of interest to meet evidentiary standards for regulatory decisions. For example, panelists noted, if a pharmacokinetic (PK) endpoint is chosen for a drug that typically does not have therapeutic drug monitoring, then PK will not be captured in an EHR or the documentation in any secondary data source. Similarly, if the approach to clinical care or method of measurement or reporting is inconsistent or differs between providers, or has changed over time, then the data may be inconsistent or introduce bias that may or may not be identifiable or measurable.

Another challenge raised is that different data are available from different databases. One solution could be through the linkage of disparate data sources such as claims and EHR to provide a more comprehensive picture. There are efforts underway to develop linkages, but it is a difficult and expensive process and requires both an infrastructure to harmonize data, and a willingness to contribute proprietary data to such an effort.

Panelists noted that the nature of the data also may pose challenges in study design as summarized here. EHRs vary individually by site. Further, RWD is often unstructured and is typically collected for documentation or delivery of routine clinical care in the EHR, and billing and reimbursement in administrative claims. There may be overlapping symptoms that without distinct outcomes that are difficult to differentiate in RWD. Panelists noted that some conditions may be better suited to assessment if there are distinct and interpretable characteristics that are observable in RWD. For example, they highlighted that oncology is one disease category that is often well suited for RWD assessment from a data quality and feasibility standpoint as patients are monitored very regularly on a broad set of criteria. There are treatment guidelines to suggest optimal care, although ultimately it is up to the clinician to decide, but standard workflows integrated into medical record systems could improve data collection. The data are frequently discrete and quantifiable (e.g. laboratory results).The challenge, however, is that clinical outcomes may not be collected in claims data and is best suited to assessment using EHRs or registry data. It is noteworthy to add that some clinical outcomes may not be readily available in the HER (e.g., reports on radiology scans or some pathology tests) and would require additional efforts to obtain the data.

The lack of a denominator for the US is such a huge problem as to what is representative of the population. A lot of registries or discrete data sources have denominators, but it is not always available, and it is impossible to know whether the collected data are truly representative of the population of interest. Being able to find a matched group and a relevant set of outcomes or multiple outcomes that are informative for clinical effectiveness and safety is not always straightforward.

3. Challenges in integrating RWD in the regulatory process

While some panelists shared experience in successful implementation of RWD, others noted lingering confusion regarding use of RWD in a regulatory context, including concerns about data quality, standardization, privacy issues, and potential biases and confounding factors that need careful consideration. They expressed concerns on the return-on-investment for RWD development and use, given uncertainty about regulatory acceptance. They agreed it is just as important to understand where RWD may *not* be useful for regulatory decisions. They expressed a desire for innovative ideas to bring biosimilars to market more efficiently, and there may be opportunities to incorporate RWD towards that goal, but there is a need for clarity on how to use RWD for regulatory purposes and seeking out approaches that extend beyond external control arms. Panelists stressed the importance of creating a structured framework for applying RWD with confidence and assessing it for a regulatory decision. While FDA has issued guidance to inform the use of RWD to meet regulatory needs, there is opportunity for more clarity particularly for biosimilars. Furthermore, just because RWD is available, does not mean it is useful. It can be difficult to translate the clinical experience of patients going to see their doctors and reporting normal clinical care into meaningful outcome measures based on those RWD.

4. Potential applications of RWD

In the US, RWD has not yet been used for regulatory decision making regarding biosimilars or interchangeable biosimilars, but it has been included in regulatory approvals for other biologic and small molecule products with techniques that may translate to biosimilar reviews.[8-10] Often RWD has been used to create external control arms in single-arm studies for rare diseases.[11] Panelists discussed the need for more specific information on how to use RWD for regulatory purposes and identifying approaches that extend beyond external control arms. They agreed it is just as important to understand where RWD may *not* be useful for regulatory decisions.

The concept of using RWD from patients who have used a reference drug as an external comparator arm in assessments has potential application to the biosimilars. In some scenarios, a panelist suggested, using an external comparator arm with the reference product may be preferred, specifically in oncology as this approach could use existing patients without requiring new exposure to the reference product in a clinical trial setting, but instead would only require new exposure to a biosimilar. This approach may also alleviate some concerns with recruiting enough patients for clinical trials, especially in biosimilar clinical trials where the bulk of drug development is in analytical characterization. The Real-World Evidence Program framework from the FDA states that RWD may be appropriate when a control arm is unethical or not feasible, and when we expect the effect size to be large.[12] In the case of biosimilars, we expect no difference, so panelists suggested clinical trials may not have an adequate sample size to be meaningful to detect a small (or zero) effect, and it may be an opportunity for RWD in a context beyond the current FDA framework. Detecting rare events requires a large sample size that is often available in RWD databases, but it does require confidence in the quality and completeness of data.

Not everyone on the panel was comfortable with the abilities or limits of RWD to suggest a perfect scenario for use, but suggested there may be opportunities in products that are harder to develop where RWD could provide meaningful answers. For example, one panelist observed that for products that are difficult to develop due to limitations in the ability to conduct an equivalence study, there may be a role for RWD to answer questions around this uncertainty. They also suggested that RWD could help drive physician adoption by demonstrating that biosimilars are safe and effective in routine clinical use, without having to rely on resource-intensive clinical trials to build prescriber confidence.
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RWD in Rare Diseases

Panelists briefly discussed rare diseases and orphan products which do not necessarily apply to biosimilars, but they felt it was a viable use for RWD. In the assessment of products to treat rare diseases, which are often catastrophic for patients, panelists noted that available evidence may be less comprehensive than for common diseases with enough patients for a large clinical trial. They were careful not to imply that rare diseases have lower evidence or standards, but it's an area where RWD has been useful through external control arms and patient selection.[9]

RWD for Interchangeable Biosimilars

One promising use of RWD, panelists identified, could be in supporting an interchangeability designation which requires additional evidence demonstrating that switching between reference products and biosimilars does not result in worse safety outcomes or a change in clinical effect than if a patient remained on the reference product. This is a unique concept in the U.S. as it is a designation that allows a pharmacist to automatically substitute an interchangeable biosimilar for the reference product without first consulting with the prescriber, subject to state laws.[2] Panelists agreed that real world clinical experience, people moving from the reference product to biosimilars or vice versa, may inform conclusions that align with the statutory criteria to demonstrate safety and effectiveness. For example, panelists suggested data from Europe, where there is a longer history of biosimilar use including non-medical switching due to national or regional policy changes or product purchase agreements, could readily generate evidence on outcomes relating to product switching in routine clinical care.

They provided a further example in the sequential approval scenario in which a manufacturer seeks biosimilarity first, followed by interchangeability, if the biosimilar has been approved in Europe and there are data showing no difference in PKs or effectiveness associated with switching, and there are RWD to show the similarity in the population in the U.S., it seems this could support a regulatory decision of interchangeability instead of requiring a clinical study.

RWD for Clinical Trial Optimization and Other Study Designs

Panelists discussed using RWD to optimize cohort size or patient characteristics for trial selection. While they agreed this is less likely to be useful for biosimilars, it may be useful for novel product development to select a safety signal from other products with a similar mechanism, or reducing the number of study arms if there is enough RWD available. Several clinical trials, not for biosimilars but for other products, have been embedded within a patient registry that leverage RWD, and pragmatic or point-of-care trials that may be useful assuming data quality and fitness are appropriate for the research question.[10]

Another source of RWD that panelists felt could be useful is those generated from mobile health technologies or wearable devices that could be leveraged for clinical trials. They noted this may be one solution for proactively collecting RWD to measure an endpoint important for assessment of safety and effectiveness. For example, they noted that insulin or glucose monitoring devices record data, and CPAP devices collect real-time data, automatically report it, and it is incorporated into patient EHRs. It is a passive process for the patient, but a potentially rich source of data. It requires care in study design to ensure the patient is using the device properly, or using it at all. Panelists agreed that patient reported outcome data is somewhat subjective and noisy so it may be hard to interpret, and by definition it is not quantitative, but that doesn't diminish its usefulness.

Final Comments from Attendees

To close out the panel session, we asked all attendees to offer one item that they learned or that emerged from the discussion that they felt was particularly relevant. Here is a summary of responses:

- There are potential data sources not commonly used in the US, such as patient-reported outcomes and patient-authorized linkage of specific data, and for biosimilars, broader and longer clinical experience that may offer opportunities to advance RWD through international collaboration.
- RWD may be useful for assessing treatment adherence and patient-reported outcomes.
- It is important to understand data fitness for use to guide selection of appropriate data sources based on the research question of interest.
- Suggest leveraging existing data sources while prioritizing continued enrichment and improvement to broaden RWD fitness for use.
- It is worth exploring opportunities on consistent data collection, including creative approaches to gathering different data (e.g., biometrics)
- The research community still hasn't agreed on how to use RWD, so this work will be instrumental in advancing application of RWD by better defining how to apply RWD in this context.
- If the desired data don't already exist, then panelists expressed enthusiasm for figuring out new approaches to get the data that may encourage decisions for how (and when) to devote time and resources to new data collection or curation.
- The FDA is interested in how and under what circumstances RWD could inform regulatory decisions, so pharmaceutical companies should be empowered to approach FDA to help define the precedence.
- Continuing to improve transparency with regulatory decisions would be very informative and support pharmaceutical companies in proposing more RWD studies.

Recommendations

Key recommendations offered by the panel and by the project team, based on the discussion, are listed below:

- **Continue working to overcome barriers to RWD adoption for biosimilar approvals and determinations of interchangeability.** Barriers to RWD use include regulators' concerns about RWD validity, compounded by industry concerns about the cost of RWD/RWE and risk of rejection by regulators. Nonetheless, several panelists advocated for continued efforts to identify appropriate uses of RWD to accelerate approvals without compromising safety and efficacy. Some of the solutions proposed by panelists include:
    - More education about RWD;
    - Publication of relevant, citable research to demonstrate its value for accelerating the approval process while providing robust results for regulators;
    - More consensus-building efforts both in the U.S. and internationally on the uses of RWD.
- **Talk to FDA early about proposed RWD uses.** Panelists agreed "the devil is in the details" when it comes to RWD use for regulatory approvals. Thus, they concluded that there needs to be a dialog between FDA and sponsors beginning as early as possible during the application process to discuss specific proposed uses of RWD so that FDA can determine appropriateness on a case-by-case basis. Indeed, RWD use should be planned from the beginning as it can help to inform the study protocols.
- **Enrich RWD with lab, registry, primary data collection, and international data.** Panelists noted that claims and EHR data alone may not be sufficiently rich for most regulatory purposes. They recommend continued investments in RWD to enrich it with lab data, patient registry data, and primary data collection. Panelists also encouraged further exploration of the

use of international data. However, panelists also noted that patients in the U.S. differ from non-U.S. patients and may need to be matched on health status. Furthermore, it would be valuable to understand whether or not data from national-level healthcare delivery are more representative, with less internal confounding, than data from subsets such as only including commercially insured patients. It would also be valuable to determine whether treatment effects differ in European patient populations compared to US patient populations, the extent of any differences, and the potential impact any differences could have on generalizability across countries.

- **Focus on the most promising uses of RWD.** Panelists identified several promising uses for RWD to support regulatory approvals for biosimilars and determinations of interchangeability. This includes the use of RWD to:
    - Hone novel, sensitive study endpoints as alternatives to PK studies (using international, EHR, or patient-generated data to validate novel endpoints);
    - Target participants for clinical trials;
    - Support interchangeability determinations using RWD to demonstrate safety and to replace switching studies.
- **Avoid less promising use cases.** Panelists identified several potential uses for RWD that they determined were less promising in the context of biosimilars and interchangeability determinations:
    - RWD for clinical studies, except to optimize recruitment;
    - Natural history studies and hypothesis generation, which would have been done in the development of the reference biologic and do not need to be repeated.
- **Assess data quality and fitness for use.** Panelists emphasized the importance of data quality, particularly related to availability of measurements that are useful in answering the research question. Considerations and solutions include:
    - Leverage data from registries, including the European experience;
    - Promote and develop linkages between disparate data sources to enrich outcome measures and increase the field of questions appropriately answered;
    - Explore innovative ways to collect data such as medical devices that automatically track behavior and clinical endpoints;
    - Incentivize consistency and reliability of data capture among clinicians
- **Be innovative in applying RWD**. Panelists identified challenges with using RWD for regulatory decisions, but stressed that there are creative opportunities that should be pursued:
    - Leverage European experience particularly for products that were available sooner than in the US;
    - Studies can be conducted in non-US populations as long as the cohorts in the study are well-matched and the change or no-difference in treatment effect (delta) is

measurable as this is predictive of the delta in other populations even if they differ from the test population;

- Be proactive in using RWD and consider practical areas to advance science and methodology to meet evidentiary needs.

Conclusion

We thank all participants in these two, informative expert panels where we had the opportunity to dig into detail on the challenges and opportunities of using RWD/RWE for FDA regulatory decisions. This summary will be publicly available on the BBCIC website (www.bbcic.org).

Table 1. Proposed RWD uses and panelist responses

RWD proposed use	Delphi voting result	Panelist comments pre-panel online survey	Key take-aways from Panel discussion
1. RWD to generate hypotheses and study endpoints *Description:* RWD is often used to inform study questions, hypotheses, and endpoints associated with traditional randomized controlled trials (RCTs). By leveraging RWD, a sponsor can adjust prespecified hypotheses and endpoints to better align with regulatory requirements	• Support: 5 • Support with caveats: 2 • Do not support: 0	• RWD is a necessity because there are not enough incentives for other pathways since they are long and costly • We don't really need RWD to refine comparative clinical efficacy studies--we need them to replace them. So, we don't need to generate hypotheses and study endpoints. • Save costs and time • [There are] Methodological considerations when endpoints are not consistently measured [in RWD]	• Hypothesis generation would have occurred with the originator biologic, so it is not needed for biosimilar approvals/ interchangeability determinations • Remove "to generate hypotheses" for Round 2 of the Delphi questionnaire • For biosimilars, RWD may be useful to identify alternative endpoints (different from the ones used to support approvals of the reference product) that could be attributed to changes in exposure to the reference product vs. the biosimilar during switching studies. To identify these sensitive endpoints, it could be useful to mine data beyond the traditional meta-analyses that have been conducted.
2. RWD to Identify biomarkers or other clinical datapoints for use in clinical development *Description:* RWD can help facilitate improved identification of potential biomarkers or other important clinical data points for use in clinical development. These data may come from labs, available genomic analyses, or even the free text from provider medical records	• Support: 2 • Support with caveats: 5 • Do not support: 0	• Often, the biomarkers or endpoints that the FDA requires are not routinely utilized in clinical practice. This is especially true for PK/PD studies • Combining all types of biomarker data sources will be difficult at best • Some RWD is of poor quality. Need to be sure that the data are high quality and account for risk of bias • Same as in 4. Comparative efficacy studies in biosimilar development programs are not intended to re-establish efficacy for a biosimilar. We need to focus more on "no clinically meaningful differences" and how to get that from RWD	• One panelist noted that endpoints specified by FDA have focused on PK-type endpoints, which would not be present in RWD. • Panelists explored whether RWD could be used to identify alternative endpoints that would accomplish the same goals. • The main concern with the use of novel endpoints is that if a biosimilar is approved based on an alternate endpoint that is not a good proxy, safety could be compromised. The FDA would need to see the details of a proposed alternative endpoint to determine its suitability to remove doubt about safety and efficacy. • One panelist re-iterated the pre-panel comment that RWD plays a very different role in demonstrating substantial evidence of effectiveness, vs supportive information for "no clinically meaningful differences".
3. RWD for reviewing clinical pathway analyses to inform the design of pragmatic clinical trials *Description:* These types of analyses involve the systematic and comprehensive review of real-world treatment modalities, including the steps involved in diagnosis, treatment selection, and follow-up care. By analyzing clinical pathways sponsors can better design clinical studies (e.g., pragmatic trials and switching studies) by better understanding clinical practice.	• Support: 2 • Support with caveats: 4 • Do not support: 1	• Unlike an innovator medicine, we're not looking for an unmet need to address clinical development. The goal is to demonstrate similarity, not for safety/efficacy • Good idea so long as account for heterogeneity, bias, etc. that exists in RWD • I don't think this is particularly relevant for biosimilar development programs	Not discussed

RWD proposed use	Delphi voting result	Panelist comments pre-panel online survey	Key take-aways from Panel discussion

4. RWD to target patients for study recruitment
 	
Description: Registries or health system EHRs can be used to target potential patients for clinical trials to enhance trial generalizability, identify desired patient sub-groups or prognostic indicators for enriched patient pools, and create efficiencies for stratified studies and/or in evaluating endpoints of interest.12
	• Support: 4
	• Support with caveats: 3
	• Do not support: 0
		• I think this is one of the biggest areas where RWD will be useful, especially when considering switching studies
		• Easiest way to assess an available population. Concerned that given structural racism and limitations of our health system we will not be reaching underserved pops. May need to carve out pops, additional data sources for that
		• Again, the goal is to obviate the need for a comparative efficacy study. I'm not sure the use described in this case is particularly relevant for biosimilars.
			• One panelist expressed doubt about the feasibility of this use case, especially for rare conditions
			• Another panelist described where their organization has implemented this use case outside the biosimilars context.
			• Commenting on Case Study 1 (RWD use to remedy challenges with patient recruitment), panelists commented:
			  • RWD can be used for site selection and/or patient enrollment.
			  • RWD can be used to develop diversity plans for trials
			  • Rare disease registries are a kind of RWD that would be useful for recruitment for rare diseases

5. RWD to assess trial feasibility *Description:* RWD is critical for understanding how various inclusion/exclusion criteria will impact the available patient pools within a given geographical region or site. To maximize enrollment in studies with strict inclusion/exclusion criteria, RWD can help investigators build distributed research cohorts when finding patients is challenging.	• Support: 3 • Support with caveats: 4 • Do not support: 0	• Re: trial feasibility, would support whether a trial can be done or not. Would be more hesitant in using RWD to impute endpoints on a trial to account for poor accrual or high drop out. • Not sure if this is useful for biosimilar development programs. In any case, it is not the optimal use of RWD in biosimilar development.	• One panelist indicated feasibility assessments for trials seem more appropriate for new drugs. Thus, this use case would be more relevant outside the biosimilars context. This panelist indicated this would be a secondary priority for biosimilar approvals. • In response to Case Study 1, a panelist indicated if a clinical trial is needed, RWD should be used to explore how different inclusion and exclusion criteria would impact the feasibility of a protocol, to avoid problems with recruitment. Other panelists concurred. • Other panelists indicated a clinical trial might not be needed for biosimilar if molecules are analytically similar
6. RWD to inform statistical model development *Description:* RWD can help to provide the empirical basis for prior probability distributions in Bayesian statistical models	• Support: 4 • Support with caveats: 2 • Do not support: 1	No comments	• Commenting on Case Study 1, one panelist posted this comment on Mentimeter: "Given methodologies change over time, comparing current data for the biosimilar to historical data for the ref prod is quite risky for the developer and creates interpretation issues for regulators". • Commenting on Case Study 1, one panelist posted in Mentimeter: "Hypothetically, RWD can be used to create hybrid control arms so that they contain both prospectively enrolled and RW patients. However, the outcomes of interest need to be routinely measured.
7. RWD to leverage disease natural history studies *Description:* Contextual information about disease progression generated from RWD underlies RWE on the benefits and risks of treatment options. Disease natural history studies can be used to inform clinical development, and supplement approval applications.	• Support: 4 • Support with caveats: 2 • Do not support: 1	• In certain situations, this might be used to support interchangeability • Need to acknowledge the missingness of certain pops/representation needed; additional studies may be needed to specifically recruit/obtain data from underrepresented pops. • Natural history might be useful if disease manifestations are consistent enough to use as expected rates	• Panelists agreed that this RWD use does not apply to biosimilars because natural history studies would have already been done in the development of the biologic. • Panelists recommended this item be removed from Round 2 of the Delphi survey.

RWD proposed use	Delphi voting result	Panelist comments pre-panel online survey	Key take-aways from Panel discussion
8. RWD to expand pragmatic trial adoption *Description:* These types of clinical trials can be integrated into the health care system and facilitate data collection at the point of care. Pragmatic RCTs can be open label and can use usual care or alternative therapies as controls.	• Support: 3 • Support with caveats: 3 • Do not support: 1	• We have to be cautious that the pragmatic trial may not result in an adequately sensitive endpoint to detect a difference (if there is one) • RWD can be used in pragmatic trials (PT). The success of PT using RWD can demonstrate the usefulness but I'm less certain RWD can expand adoption • Devil is in the details of what data can be collected	• One panelist expressed surprise at the "50-50" level of support for using RWD to inform pragmatic clinical trials. • No further discussion took place on this topic as panelists prioritized other topics for discussion.
9. RWD to expand single-arm trials with external comparators *Description:* When randomization is not feasible or ethical, single-arm studies are crucial. RWD can be used as the basis for external controls (historical or contemporaneous).	• Support: 4 • Support with caveats: 2 • Do not support: 1	No comments	• Commenting in Mentimeter about Case Study 2, a panelist wrote: "A single arm study for a biosimilar is challenging to consider when the intent [of] the study is to evaluate similarity between the reference product and the biosimilar".
10. RWD to increase linkage across registries and databases *Description:* RWE will benefit from better linkage between clinically rich registry data, often used in oncology or rare disease settings, and expansive electronic healthcare data like administrative claims or EHRs. Combining registry data with data collected from pragmatic or other clinical trials can also substantially reduce study-related burdens (e.g., data collection) on both patients and investigators.	• Support: 4 • Support with caveats: 3 • Do not support: 0	• Linkages can be quite costly--need to be very careful to assess linkage feasibility and appropriateness with smaller scale proof of concepts • Definitely think the utility of RWD will lie in the ability to get interpretable data • Seems promising	• In response to Case Study 1 (biosimilar approval for a rare cancer, use of linked EHR-patient registry database to understand utilization of the reference product and overcome difficulty recruiting patients for a clinical study) – several panelists commented that for rare diseases, patient registries can be useful to evaluate clinical similarity (safety and efficacy). • Another panelist questioned whether there is sufficient EHR-registry linked data to consider this use-case.

RWD proposed use	Delphi voting result	Panelist comments pre-panel online survey	Key take-aways from Panel discussion
11. RWD to leverage international data on products already approved/marketed outside the U.S. *Description:* Biosimilar designations are sometimes made by other international regulatory bodies like the European Medicines Agency before FDA approval. Although sometimes limited by differences in healthcare systems and medical practice, using patient-level data from other countries on already marketed products can create natural experiments on the safety and effectiveness of products marketed outside the U.S.	• Support: 5 • Support with caveats: 2 • Do not support: 0	• Comparing International RWD must be in comparable subgroups, cultures, and behaviors • Absolutely support. There's no justification for American exceptionalism here. Some people may be sicker in American due to obesity and poorer access to health care. But with proper matching (e.g., an obese 50 yr. old in US may be more similar to a 75 yr. old in Spain than a 50 yr. old) I see no reason why to not do that. • This would be great if the data available were detailed enough to answer questions of clinical meaningfulness. Pre-panel comments on what would help to overcome barriers to adoption of RWD for biosimilar applications and determinations of interchangeability: • - Re: targeting populations, leveraging the existing interest in reducing health disparities. In international data, a good analysis with matching/PS to demonstrate that there are similar pops in other countries, and we should leverage their extensive data. • International agreement of useful RWD for specific scenarios	• There was considerable interest in and discussion around the use of international data. • Panelists felt that international data, EHR data, and patient generated data could be used to validate endpoints but note that international patients differ from U.S. patients in health status (panelists disagreed on whether this matters, and whether patients should be matched on health status). • Biologic/biosimilar switching might happen more commonly in other countries, making switching studies easier
12. RWD: Build on innovative free text data mining *Description:* Natural language processing (NLP) of free text or unstructured data in EHRs to better capture biomarkers, social determinants, or other granular clinical information can expand the available RWD for regulatory use. Implementation of NLP coupled with other advanced analytics like machine learning algorithms can help untap important insights which can inform the development of a clinical study program.	• Support: 2 • Support with caveats: 3 • Do not support: 2	• Text is individualistic. comparing across providers may be impossible. • Support with better text data mining methods. Quite frankly, existing methods produce a lot of poor-quality work with irrelevant or spurious text findings. • I don't rule out anything, but I'm not clear on how this is going to be useful.	Not discussed

RWD proposed use	Delphi voting result	Panelist comments pre-panel online survey	Key take-aways from Panel discussion
13. RWD: integration of mobile health technologies *Description:* The expanded use of mobile health technologies can help decrease the burden associated with primary data collection and can expand the available biometric RWD; these data could be combined with patient reported outcomes to allow for a more comprehensive assessment of all relevant patient information.	• Support: 3 • Support with caveats: 2 • Do not support: 2	• If absolute linkage is possible. • Everyone lives on their phones, and patients love telehealth. The data available there are very informative and can lead to insights not captured in a single health care visit • Again, this seems like it presumes a comparative clinical efficacy study is needed.	Not discussed
14. RWD: Use of common data models for network studies *Description:* Standing up large, federated data networks that rely on a common data model (CDM) can further facilitate rapid, reactive, and reproducible studies across many data partners simultaneously. Particularly useful in the context of rare exposures/outcomes where an extensive network data could be leveraged, CDMs allow for efficient querying of multiple data partners EHRs or claims data to support large-scale RWE generation.	• Support: 4 • Support with caveats: 2 • Do not support:1	• Support so long as elements of data models are relevant to study question and data missingness is minimized • I think something like this could yield much more interpretable RWD.	Not discussed

RWD proposed use	Delphi voting result	Panelist comments pre-panel online survey	Key take-aways from Panel discussion
15. Other uses of RWD not mentioned in the pre-panel report	N/A	• In situations where there is a rare but serious adverse effect that the FDA is very concerned about but cannot be assessed in clinical trials, a post market commitment using RWD may be necessary. • Report is very inclusive, however, coordination and alignment of international data would be helpful • Recommend focus on getting RWD to the point where it can replace the randomized comparative clinical efficacy study. • Reduce residual uncertainty regarding impacts from switching to support interchangeability	• "Golden opportunity" for RWD to abbreviate comparative clinical studies • Use cases to add to the next Delphi survey: ○ RWD to address residual uncertainty about impacts from switching, to remove concerns about immunogenic response, and address residual uncertainty on safety. • "It's easy" to detect red flags in RWD (e.g., Pure Red Cell Aplasia), but harder to demonstrate safety • "Expanded label use" is a promising RWD use • Use of RWD to secure biosimilar approval is hard b/c product has not been marketed (so no RWD available on its use). The low-hanging fruit is switching studies for determinations of interchangeability. <u>Responses to Case Study 1 stated:</u> • Residual uncertainty could result from analytical differences [differences in molecule structure] • If RWD contains data about immunogenicity post-switch, it could be used to show that switching isn't a concern/ no switching study is needed • Immunogenicity data is not routinely collected [only done in case of suspected safety issue] • One panelist questioned whether switching back and forth occurs with the needed frequency for switching studies (3 switches); others noted it often does in practice • Utility of RWD [for] switching depends on how often patients are switched; tender/formulary turnover is not the same timing as Rx fills <u>Responses to Case Study 3 stated:</u> • If the reference product has clinically significant immunogenicity, what outcomes are we focused on for the biosimilar? • If other biosimilars are marketed, you must account for switching to them as well as the reference product • RWD usability can be impacted depending on reason for switching (clinical or non-clinical).

APPENDIX 1 – PANELISTS CONSULTED

1. Leah Christl, Amgen, Head of Global Biosimilars Regulatory Affairs and Regulatory and R&D Policy
2. Dottie McCabe, Boehringer Ingelheim, Executive Director, Specialty Pharmaceuticals, Clinical Development & Medical Affairs, Immunology and Biosimilars
3. You-Li Ling, Pfizer, Director – Global Access & Value
4. Ed Li, Sandoz, Head, HEOR & Oncology
5. Cheryl Walraven, CVS Clinical Trial Services, Executive Director-Safety Surveillance & Collaboration
6. Jaclyn Bosco, IQVIA, Vice President and Global Head of Epidemiology
7. Cara McDermott, Duke University School of Medicine, Assistant Professor in Medicine
8. Gillian Woollett, Samsung Bioepis, VP, Head Regulatory Strategy and Policy
9. Sarah Yim, FDA, Director, Office of Therapeutic Biologics and Biosimilars/OND/CDER

APPENDIX 2 – DELPHI QUESTIONNAIRE (ROUND 1)

BBCIC Expert Panel Preliminary Questionnaire

Thank you for your willingness to participate in the BBCIC online expert panel discussion on July 10, 2023, from noon to 2pm ET. The purpose of the expert panel is to develop recommendations for the FDA on the use of real-world data (RWD) to meet evidence requirements for biosimilar approvals and determinations of interchangeability.

To help us prepare for the expert panel meeting, we are asking you to:

- **Review a report (attached to the email you received)** titled "Using Real world Data/Real world Evidence (RWD/RWE) for Biosimilar and Interchangeable Product Development and Approval: Challenges and Opportunities."
- **Complete the online questionnaire below**
  The questionnaire includes both open and closed-ended questions that will feed into a Delphi process to develop consensus. To answer some of the questions, you will need to review RWD use cases attached to the email you received. We anticipate this questionnaire will take you approximately 30 minutes to one hour to complete. Thank you for your participation.

Section 1

Introduction

1.Your full name

2.Your title and affiliation.

3.Along with this questionnaire, you were provided a draft report. What was your overall impression/reaction on the report?

Section 2

Several general proposed uses of RWD are listed in the report (see pages 9-10 of the report for detailed descriptions). Please indicate below which of these proposed uses of RWD you would support in the context of applications for biosimilar approvals or interchangeability determinations. Please just share your first reaction. You will have a chance to answer these questions again after the panel discussion on July 10th so that we can see how panelists' thinking evolves as a result of the discussion.

4. RWD to generate hypotheses and study endpoints.

- ○ Support
- ○ Support with caveats
- ○ Do Not Support

5.Please share any comments, explanations, or ideas below

6.RWD to Identify biomarkers or other clinical datapoints for use in clinical development.

- ○ Support
- ○ Support with caveats
- ○ Do Not Support

7.Please share any comments, explanations, or ideas below

8.RWD for reviewing clinical pathway analyses to inform the design of pragmatic clinical trials.

- Support
- Support with caveats
- Do Not Support

9.Please share any comments, explanations, or ideas below

10.RWD to target patients for study recruitment.

- Support
- Support with caveats
- Do Not Support

11.Please share any comments, explanations, or ideas below

12.RWD to assess trial feasibility.

- Support
- Support with caveats
- Do Not Support

13.Please share any comments, explanations, or ideas below

14.RWD to inform statistical model development.

- Support
- Support with caveats
- Do Not Support

15.Please share any comments, explanations, or ideas below

16.RWD to leverage disease natural history studies.

- Support
- Support with caveats
- Do Not Support

17.Please share any comments, explanations, or ideas below

18.RWD to expand pragmatic trial adoption.

- Support
- Support with caveats
- Do Not Support

19.Please share any comments, explanations, or ideas below

20.RWD to expand single-arm trials with external comparators.

Support

- Support with caveats
- Do Not Support

21.Please share any comments, explanations, or ideas below

22.RWD to increase linkage across registries and databases.

Support

- Support with caveats
- Do Not Support

23.Please share any comments, explanations, or ideas below

24.RWD to leverage international data on products already approved/marketed outside the U.S.

Support

- Support with caveats
- Do Not Support

25.Please share any comments, explanations, or ideas below

26.RWD: Build on innovative free text data mining.

Support

- Support with caveats
- Do Not Support

27.Please share any comments, explanations, or ideas below

28.RWD: integration of mobile health technologies.

Support

- Support with caveats
- Do Not Support

29.Please share any comments, explanations, or ideas below

30.RWD: Use of common data models for network studies.

Support

- Support with caveats
- Do Not Support

31.Please share any comments, explanations, or ideas below

32.Are there other areas not mentioned in the report, where RWD can be used to support biosimilar and interchangeable products regulatory approval?

33.What do you think are the biggest barriers to overcome before **regulators** will accept RWD as evidence to support biosimilar/interchangeability applications?

34.What do you think are the biggest barriers to overcome before **sponsors** will include RWD as evidence in applications for biosimilars/ interchangeability applications?

35.What do you see as "low-hanging fruit" – areas where use of RWD can be beneficial and would be most acceptable to regulators and sponsors?

36.What could help to overcome the barriers?

Section 3

During the panel discussion on July 10th, we will discuss three use cases to elicit rich dialog, elicit specific suggestions and spark creative ideas for the inclusion of RWD in biosimilar and interchangeability applications. The case studies were attached to the email sent to you with survey. Your brief comments today will help us to have a more productive discussion when we meet.

37.On case study 1. Biosimilar approval for a rare cancer type, how would you change or improve on this strategy using RWD?

38.On case study 2. Biosimilar approval for a common inflammatory condition, how would you change or improve on this strategy using RWD?

39.On case study 3. Biosimilar interchangeability determination for a common inflammatory condition, how would you change or improve on this strategy using RWD?

40.What else would you like to share with us in advance of the panel discussion?

Section 4

Thank you for your time and we look forward to seeing you on July 10th

APPENDIX 3 – REVISED DELPHI QUESTIONNAIRE (ROUND 2)

BBCIC Expert Panel: Delphi Round 2

Thank you for your willingness to participate in the BBCIC online expert panel discussion on July 10, 2023, from noon to 2pm ET. As a follow-up, we're asking panel members to take 5-10 minutes to respond to the following questions on the use of real-world data (RWD) to meet evidence requirements for biosimilar approvals and determinations of interchangeability.

Several general proposed uses of RWD are listed in the report (see pages 9-10 of the report for detailed descriptions). The questions below have been modified based on panel feedback. Please indicate below which of these proposed uses of RWD you would support in the context of applications for biosimilar approvals or interchangeability determinations.

1.Your full name

2. RWD to generate study endpoints.

- Support
- Support with caveats
- Do Not Support

3.RWD to Identify biomarkers or other clinical datapoints for use in clinical development.

- Support
- Support with caveats
- Do Not support

4.RWD for reviewing clinical pathway analyses to inform the design of pragmatic clinical trials.

- Support
- Support with Caveats
- Do Not support

5.RWD to target patients for study recruitment.

- Support
- Support with caveats
- Do Not support

6.RWD to assess trial feasibility.

- Support
- Support with caveats
- Do Not support

7.RWD to inform statistical model development.

- Support
- Support with caveats
- Do Not support

8.RWD to expand pragmatic trial adoption.

- Support

- Support with caveats
- Do Not support

9.RWD to expand single-arm trials with external comparators.

- Support
- Support with caveats
- Do Not support

10.RWD to increase linkage across registries and databases.

- Support
- Support with caveats
- Do Not support

11.RWD to leverage international data on products already approved/marketed outside the U.S.

- Support
- Support with caveats
- Do Not support

12.RWD to build on innovative free text data mining.

- Support
- Support with caveats
- Do Not support

13.RWD to integration of mobile health technologies.

- Support
- Support with caveats
- Do Not support

14.RWD: Use of common data models for network studies.

- Support
- Support with caveats
- Do Not support

15.RWD to address residual uncertainty about impacts of switching.

- Support
- Support with caveats
- Do Not support

16.RWD to address residual uncertainty about safety.

- Support
- Support with caveats
- Do Not support

17.Are there other areas not discussed during the panel where you think RWD can be used to support biosimilar and interchangeable products regulatory approval?

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