Dear Acting Commissioner Woodcock:

The National Health Council (NHC) applauds the Food and Drug Administration (FDA) for continuing to advance the Agency’s approach to Real-World Data (RWD) and Real-World Evidence (RWE) and encourages the Agency to continue its efforts of clearly detailing their approach in guidance to ensure transparency for all stakeholders. The NHC appreciates the opportunity to provide comments on the FDA draft guidance “Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision Making for Drug and Biological Products” and is looking forward to continued collaboration with the Agency.

Patients must continue to be a primary focus in RWE generation to support the drug development process.

As the FDA, health researchers, policymakers, and patient advocates establish standards and structure for
using RWD as evidence in regulatory and clinical decision making, patients must continue to be the primary focus.

The Agency has made great strides to ensure the patient voice is considered within the framework for RWE and RWD as it is being developed. We appreciate the continued focus to enhance patients’ voices and ensure decisions throughout the product-development and regulatory-approval processes capture and use patient perspectives. Specifically, NHC is pleased to see the FDA incorporating the following items related to RWD and RWE:

- Engagement opportunities throughout the process of developing guidances and processes on appropriate uses for RWE;
- Guidance on specific RWD sources, in this case electronic health records (EHRs) and medical claims data;
- Impact of health disparities on sourcing accurate and representative data from the real world; and
- Identifying the overall limitations and benefits of specific RWD sources.

As the FDA continues to focus on these important pillars and revises existing guidance documents to advance the RWE Program, the NHC urges the Agency to consider the following to help ensure the patient community can contribute to RWE generation and utilization which, ultimately, is used to develop and optimize treatments for the patients.

**Patient experience data and patient engagement must be better integrated in RWD and RWE to address therapeutic needs**

The FDA should strengthen its RWE Program by using patient experience data and patient engagement to support regulatory decisions. This includes, but is not limited to, decisions about product effectiveness, label changes such as a change in dose, dose regimen, route of administration, and post-marketing safety surveillance. In these circumstances, patient experiences outside of health care system interaction (i.e., a claim indicating a visit happened) can help clarify patient adherence and treatment behaviors.

Inclusion of patient experience data will also be critical in the design and success of hybrid trials that include both traditional and pragmatic clinical trial elements. In each of these cases, 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 and that patient needs are given the appropriate level of consideration during the regulatory process. Patient experience data informs how closely real-world data reflects patients’ lived experiences.\(^1\)

**Effective communication and engagement with patients on the RWE Program are essential for the success and development of the program**

We applaud the FDA’s commitment to a wide range of engagement opportunities, such as demonstration projects, workshops, guidance documents, and internal processes, throughout the process of developing guidances on the appropriate use of RWE. Many patients, however,

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have little understanding of RWE and the discussions among the scientific and regulatory communities related to the use of RWD. To ensure the patient perspective is integrated into regulatory decision-making with RWD and RWE and patients trust and understand the decisions made, the NHC recommends the FDA co-create, with the patient community, educational materials on the RWD and RWE, sources and uses of RWE, and key issues they should be aware of regarding RWE.\

More specifically, the patient community requires reliable and effectively communicated resources that facilitate its understanding of the FDA’s potential uses of RWE, the data collection methods and data sources applicable to RWE, the limitations and advantages of different data sources, how RWE is used in regulatory decision-making, the use of RWE for treatment protocols, and how to distinguish between sources of good quality RWE and “junk science” or anecdotes, among other topics.

In this era where mistrust and misinformation about health information and data has flourished, it is imperative the FDA address communication issues on RWE upfront. Patient education on RWE will help establish trust in the use of RWD during the regulatory process. This is necessary so that patients engage with the health care community, understand the value of the information they provide in RWD sources, and can help facilitate the use of RWE as appropriate through technological and therapeutic advancements.

**The RWE Program can only flourish if patients are better educated about the use of data and privacy rights are protected**

Patients often lack clarity about who owns data about their health and often struggle to access their own medical records. While HIPAA may allow for data sharing, privacy issues remain a concern for patients and standards of protection to ensure anonymity must be clarified.

Patients are concerned about efforts that seek to commoditize data about them, without a clear focus on improving their care or their ability to engage in collaborative decision-making about treatment options. If the importance and mechanisms for protection of patient privacy rights are not conveyed to the patient community, it can result in distrust between patients and the health care community. Without trust, the RWE Program cannot flourish – after all, RWE generation relies on the data collected from patients with their consent.

In addition, the NHC has learned through its own qualitative work on patients’ understanding of and views on RWE that patients can become fearful and concerned when they learn their health data, though de-identified, are being used for RWE research without their knowledge. They do not understand that at some point in the past, they likely provided consent for the data use.\(^2\)\(^3\)\(^4\)

We encourage the FDA to continue to focus on establishing appropriate methods and procedures to protect patient information as well as ensure communication of these protective

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methods is reaching the patient community in a manner that is digestible and accessible. Too often, informed consent processes are not codeveloped with patients; thus, these communications are not fully understood by the patients who are impacted. Additionally, patients need the tools to better understand how to access, edit, and add to their own data. Websites such as OpenNotes.org and HealthIT.gov are two examples of efforts to increase patient access to their medical information. However, most of the public does not know they exist or the advantages they might offer. Strengthening co-creation with the patient community for better dissemination, understanding, and use, will enhance these and efforts, which will in turn enrich the generation and use of RWD and RWE.

**The health care community needs clarity around the limitations as well as advantages of different types of RWD sources, such as EHRs and patient registries**

The NHC appreciates the FDA’s focus on traditional data sources such as medical claims data and EHRs as specific repositories of RWD that can be used to generate RWE. However, it is important to continually clarify that patient experience information has been mostly non-existent within these sources. Unless a patient’s experience is recorded as a clinical event by a health care provider, data such as patient-reported information about the impacts a disease and/or treatment have on their and their families’ lives, specific changes in a patient’s response to medication, or non-serious adverse events will not be captured. The isolated recording of a health care use event (e.g., doctor visit, prescription dispensed, or hospitalization) in RWD generation is necessary, but not fully sufficient, in providing a comprehensive depiction of the safety and effectiveness of therapies in the real-world. RWE will not adequately describe the impact or safety concerns associated with a product through the simple capture of utilization.

For example, EHRs and medical claims data are not able to consistently demonstrate the validation of patient exposure to drugs or therapies (i.e., whether patients are adhering to their prescriptions, thus, exposed to the drugs as intended). Patient registries and other RWD sources, as well as patient input, can help validate whether the operational definition of exposure adequately mirrors the conceptual definition in certain circumstances. In other words, where EHRs and medical claims data sources may fall short, other RWD sources can provide the additional context needed to help ensure the evidence generated around a product accurately represents what occurs in the real-world.

The NHC looks forward to guidance the FDA plans to publish on the potential gaps, or shortcomings, in information in specific RWD sources and how best to address these issues, including through utilization of other RWD sources such as patient registries that can provide distinct advantages, and urges timely publication. We encourage the Agency to continue to include information on these gaps throughout related guidance.

The NHC also encourages the FDA to support the creation of patient-centered core impact sets (PC-CIS), disease- and/or population-specific, patient-prioritized lists of the impacts a disease and/or its treatments have on patients, caregivers, and families’ lives. A PC-CIS helps researchers, regulators, policymakers, and others to align around the impacts most important to patients and families. For RWE, a PC-CIS can guide the FDA, companies, and researchers to ensure they are capturing the study and regulatory endpoints important to patients, identify gaps in data that need to be filled, and interpretation of RWD. The NHC would welcome the FDA’s support on the socialization of PC-CIS across government with industry, guidance on PC-CIS development and use, and methods development and infrastructure for PC-CIS development by
In-depth guidance that considers the use of RWD to inform the treatment of co-morbid conditions is necessary

Randomized clinical trials (RCTs) often exclude patients who have multiple comorbidities to ensure internal validity of findings. RWD presents a critical opportunity to supplement RCTs by identifying subpopulations with comorbidities to further understand the effectiveness and safety of therapies as applied to these patients based on the availability of relevant data from the RWD sources used.

Patients see this opportunity for the use of RWE to inform the treatment of comorbid conditions. While we are pleased with the FDA’s inclusion and need for examination of study-population characteristics, including comorbidities, as effect modifiers on a drug’s effectiveness or safety, more specific guidance, and methods development on the use of RWD in identifying and treating co-morbid conditions is necessary.

Health disparities can have tremendous impact on the availability and/or comprehensiveness of RWD

The NHC believes that maintaining a focus on the impact of health disparities within RWE can help promote regulatory decision-making that is inclusive and patient centric.

We appreciate the FDA’s mention of “continuity of coverage” and how it may affect RWD, as outlined in the guidance document on EHRs and medical claims data. Continuity of care, or lack thereof, is one of many reasons why RWD from claims data and EHRs may contain equity-related gaps that must be addressed. We encourage the FDA to further discuss the disproportionate effect of continuity of coverage issues, on underserved and underrepresented populations. More specifically, we encourage the FDA to provide clarity on how sponsors can promote research that is inclusive to ensure appropriate representativeness in patient-focused drug development. Without such representativeness in the RWD sources, analyses will be biased and could possibly result in discrimination. Therapies will continue to benefit some populations more than others and safety and effectiveness concerns for specific subpopulations may go unnoticed.

The FDA should provide clarity around the type and level of detail necessary in demographic data to ensure all relevant subpopulations are represented in the RWD or that – at the very least – it is clear who is and who is not represented. This is particularly important for EHR and claims data, as they may not accurately reflect real patient diversity, disease experience, preferences, or outcomes due to missing subpopulation representation, and the clinical and payment emphasis of such sources.

Guidance needs to clarify the definition of patient-generated data and differentiate between patient-reported outcomes and patient-centered data

We recommend that the FDA clarify the definition of patient-generated data when used in guidance. There is confusion in the field about this term. **The NHC defines patient-generated health data as health-related data created, recorded, or gathered by or from patients (or family members or other caregivers) to help address a health concern.**
A definition would not only provide clarity, but it would also help to confirm to stakeholders that not all patient-reported outcome (PRO) measures are patient centered and not all patient-centered outcomes are necessarily patient reported, as confusion continues to be highly prevalent. For an outcome measure to be patient centered, it must capture a concept of interest patients identify as being highly important to them – these measures for the concept can be PROs, another type of clinical outcome assessment (COA), or even a clinical measure. It is patient centered because patients identified it as important, not because it can only be reported by patients.

When it comes to RWE, we are fearful that RWD database sources, in an effort to become or appear more patient centered, will collect off-the-shelf PRO measures for inclusion in RWD without consideration of whether or not the measure captures concepts of interest to the patient population and/or if the measure is truly fit for purpose. Ad hoc additions of questionnaires can add undue burden for patients and the health care system. We highly encourage the collection of PRO data that is patient centered and fit for purpose, that takes into consideration the appropriate relevance of the data, level of burden, intended use, and appropriate interpretation. FDA clarity can help with these issues.

**Conclusion**

The NHC thanks the FDA for its commitment to the RWE program and the integration of the patient perspective in its guidance, as well as for the opportunity to comment on the guidance “Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision Making for Drug and Biological Products”. We hope that the comments provided by the NHC can help the FDA and health care industry provide effective and safe therapies to all patients in need.

Please do not hesitate to contact Eric Gascho, Vice President of Policy and Government Affairs, if you or your staff would like to discuss these issues in greater detail. He is reachable via e-mail at egascho@nhcouncil.org.

Sincerely,

Randall L. Rutta  
Chief Executive Officer