



# National Health Council

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**Marc Boutin, JD**

Chief Executive Officer  
National Health Council

February 16, 2018

The Honorable Scott Gottlieb, MD  
Commissioner, Food and Drug Administration  
Dockets Management Staff (HFA-305)  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

Re: Patient-Focused Drug Development: Guidance 1 – Collecting Comprehensive and Representative Input; Public Workshop (Docket No. FDA-2017-N-5896)

Dear Commissioner Gottlieb:

The National Health Council (NHC) appreciates the opportunity to provide comments on the FDA's Patient-Focused Drug Development: Guidance 1 – Collecting Comprehensive and Representative Input. Patients with chronic diseases and disabilities are experts in their disease. As such, there is significant value to incorporating patient-provided information into decision-making across the healthcare continuum, including FDA's regulatory decisions regarding medical products. We applaud the FDA for its continued action to encourage and guide meaningful patient engagement, including developing guidance and tools to assist stakeholders.

The NHC is the only organization that brings together all segments of the health community to provide a united voice for the more than 133 million people with chronic diseases and disabilities and their family caregivers. Made up of more than 100 national health-related organizations and businesses, the NHC's core membership includes the nation's leading patient advocacy organizations, which control its governance and policy-making process. Other members include professional and membership associations, nonprofit organizations with an interest in health, and representatives from the pharmaceutical, generic drug, insurance, medical device, biotechnology, and communications industries.

In support of the public workshop held on December 18, 2017, FDA released a set of draft documents – the Patient Focused Drug Development (PFDD) Public Workshop on Guidance 1 Collecting Comprehensive and Representative Input Discussion Document (Discussion Document); Attachment to Discussion Document Appendices; and Draft Standardized Nomenclature and Terminologies for the Series of FDA PFDD Guidances (Glossary). Our comments below refer to the material contained in these draft documents.

## I. *Overarching Comments*

### 1. *Guidance Development Process*

The NHC appreciates the opportunity to participate in the December 18<sup>th</sup> Public Workshop and provide comments to the FDA in response to the glossary and discussion document via the docket. As the Agency develops future guidances, the NHC recommends it consider avenues to co-develop these materials with patients and

patient organizations from the beginning of the development process in addition to seeking feedback and reaction to the FDA's work.

## *2. The FDA Workforce*

Throughout the PDUFA VI negotiation process, the FDA acknowledged the need to be more flexible in addressing workforce shortages. The NHC appreciates the need to address workforce issues, as the skills and expertise of the staff reviewing patient experience data can differ from the traditional roles of the FDA reviewers. To this end, the NHC stands ready to support the Agency to ensure the skills and expertise of the FDA staff align with the function of their role.

## *II. Draft Standardized Nomenclature and Terminologies for the Series of FDA PFDD Guidances (Draft Glossary)*

The NHC recognizes the importance of a single glossary of terms in ensuring that all stakeholders are using the same standard terms and definitions. Inconsistent use of terms leads to confusion and inaccurate understanding of the concepts that underlie the science of patient engagement and collection of patient-provided information. It is critical that consensus definitions be developed and used consistently. To that end, the NHC and Genetic Alliance hosted three multi-stakeholder events in 2016-2017 to inform the development of a document<sup>1</sup> containing suggested language for the FDA to consider for a guidance on patient engagement (final document attached as Appendix C). This document includes definitions for terms identified by stakeholders as key to patient engagement. We thank the Agency for incorporating some of the definitions developed through this work in the FDA's Draft Glossary.

However, we discuss below a few concerns regarding and suggested changes for a number of the definitions included in the FDA Draft Glossary.

### *1. Patient engagement*

The Draft Glossary defines "patient engagement" as "[a]ctivities that involve patient stakeholders sharing their experiences, perspectives, needs, and priorities that help inform FDA's public health mission." We believe this definition is unnecessarily and inaccurately restrictive. Recognizing that these definitions are intended for use in FDA guidance, we believe that unless re-cast as "patient engagement for FDA's use," the term "patient engagement" should not be so narrowly defined. Given that FDA encourages patient engagement throughout drug development, and not solely to develop data to submit to the Agency and that other organizations (not just the FDA) are and have been involved in patient engagement for a variety of purposes, "patient engagement" should be defined as "activities that involve patients as active participants in any health-care-related process and/or decision making, including but not limited to patients as partners sharing their experiences, perspectives, needs, and priorities to help inform processes and decisions related to drug development and approval."

### *2. Caretaker*

FDA should clarify that the term "caretaker" does not include a paid caretaker (e.g., a paid health care aide) by revising the definition to read "[a] person who helps a patient with daily activities, health care, or any other activities that the patient is unable to perform himself/herself due to illness or disability. This person may or may not have decision-making authority for the patient and is not the patient's health care

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<sup>1</sup> The National Health Council and Genetic Alliance, Patient-Focused Drug Development – Recommended Language for Use in Guidance Document Development, February 2017, available at: <http://www.nationalhealthcouncil.org/sites/default/files/NHC-GA%20Feb2017.pdf> (accessed Jan. 25, 2018).

provider *or paid health care aide.*” (addition in italics). In addition, while we recognize the value of engaging with caretakers, it is important that the FDA acknowledge that a caretaker’s perspectives do not necessarily align with those of the patient but may be needed when a patient is unable to provide information.

### 3. *Patient-centered outcome*

We find the phrasing of the definition, “an outcome that is important to patients’ survival, functioning, or feelings as identified or affirmed by patients themselves, or judged to be in patients’ best interest by providers and/or caregivers when patients cannot report for themselves” to be unclear and suggest revising it to read “[a]n outcome that is important to patients *in terms of* survival, functioning, or feelings...” (addition in italics).

### 4. *Patient experience data; patient input; patient-provided input; patient perspective*

The 21<sup>st</sup> Century Cures Act defines “patient experience data” as those that: “(1) are collected by any persons (including patients, family members and caregivers of patients, patient advocacy organizations, disease research foundations, researchers, and drug manufacturers); and “(2) are intended to provide information about patients’ experiences with a disease or condition, including—“(A) the impact of such disease or condition, or a related therapy, on patients’ lives; and “(B) patient preferences with respect to treatment of such disease or condition.” We believe the additional elements added to this definition to get to the FDA’s proposed definition make the term inaccurately broad. For the term to be clearly understood, it should be limited only to patient *experience*, and not be interpreted to encompass perspectives, needs and priorities, which are not experiences.

With the term “patient experience data” defined properly to solely include patient *experience*, we suggest the FDA add the term “patient-provided information” as the umbrella term to denote the myriad types of patient-provided data. The NHC prefers the multi-stakeholder, consensus-driven definition below:

*Patient-provided information (or patient-provided input): a range of information that comes directly from patients such as, but not limited to: views, experiences, preferences, needs, opinions, and priorities. This can include their overall view of their condition, its natural history, and impact on their life (e.g., patient-reported outcomes such as symptoms, function, and quality of life); experience with available treatments; description/view on which outcomes are important; patient preferences, goals, desires, concerns, perceptions, or opinions; or the relative importance of any issue as defined by patients. Patient-provided information is relayed by the patient regarding their subjective experience and opinions. It does not include all medical information on a patient (e.g., genetic testing information, pathology results) that may be about the patient but comes from other sources.*<sup>2</sup>

The NHC also recommends the FDA produce a visual depiction to help stakeholders understand the differences among these terms. The NHC Venn diagram of patient-provided information may be a useful starting point in that process (see Appendix C).<sup>2</sup>

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<sup>2</sup> *Id.*

To align with the recommendations above, the following corresponding revisions would need to be made to the Glossary (these and all definitional changes would also need to be reflected in the Discussion Document):

- The definition for *patient input* should be removed as no longer needed (as this term is included in the above definition as patient-provided input)
- *Patient perspective*: A type of *patient-provided information* that specifically relates to patients' attitudes or points of view especially regarding their condition or its management. Patient perspectives may include (but are not limited to): perceptions, goals, priorities, concerns, opinions, and preferences. (*italics replace "patient experience data" in the current draft definition*)

We also caution that because "patient experience data" is a term of art in the *health care delivery* context, there is a very real risk for confusion. In health care delivery, patient experience data is referred to in reference to quality-of-care and includes collecting data from patients regarding their views on their experience receiving care from a provider, hospital, or other delivery system. For example, the Agency for Health Research and Quality has supported the development of the Consumer Assessment of Healthcare Providers and Systems (CAHPS®) surveys,<sup>3</sup> which ask consumers and patients to report on and evaluate their experiences with health care. The CAHPS® program defines "*patient experience*" as: "the range of interactions that patients have with the health care system, including their care from health plans, and from doctors, nurses, and staff in hospitals, physician practices, and other health care facilities. The terms patient satisfaction and patient experience are often used interchangeably, but they are not the same thing."<sup>4</sup>

The CAHPS surveys are quality-reporting tools widely used by most hospitals, networks, insurance plans and providers. Those stakeholders familiar with the term from the care delivery context may inaccurately assume it means the same in the FDA regulatory context even though the use is clearly very different with different intended purposes. Because the term is used in context-specific ways, the FDA should be very clear about the use of this term to avoid confusion; we recommend the FDA refine its definition to do so.

##### 5. *Patient-focused (also referred to as patient-centered)*

The NHC finds the definition of the terms "patient focused"/ "patient centered" problematic because it omits the act of actively engaging with patients. As currently drafted, the definition reads: "Ensuring that patients' experiences, perspectives, needs, and priorities are meaningfully incorporated into decisions and activities related to their health and well-being." We believe it is critical that any definition of "patient focused" or "patient centered" reflect that patients should be valued as partners in the enterprise. Patient-centered means doing things *with* patients, not *for* or *to* patients. Meaningful patient engagement can only exist as a continuous, bi-directional partnership with patients. This omission renders the current definition fatally flawed.

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<sup>3</sup> Agency for Healthcare Research and Quality website, "About CAHPS," available at: <https://www.ahrq.gov/cahps/about-cahps/index.html> (accessed Jan. 31, 2018).

<sup>4</sup> *Id.*

We recommend the FDA use the following multi-stakeholder, consensus-driven definition:

*Patient centered* – any process, program, or decision focused on patients in which patients play an active role as meaningfully engaged participants and the central focus is on optimizing use of patient-provided information.<sup>5</sup>

In addition, we understand that some stakeholders confuse the terms “patient-centered outcomes” and “patient-reported outcome” (PRO). As such, we ask the FDA to make an effort to explicitly distinguish the two terms from one another in the Glossary (and the Discussion Document, as needed). We believe this is a very important distinction that is widely misunderstood. We acknowledge that the methods used to develop PROs can be useful to collecting and analyzing all kinds of patient-provided information and there is knowledge to be leveraged. However, *not all patient-centered outcomes are PROs and not all PROs are patient-centered outcomes.*<sup>6</sup> It is important to clarify that the addition or development of a PRO does not necessarily mean that patient centeredness has been achieved. The PRO that was developed may be unimportant to patients.

### *III. PFDD Public Workshop on Guidance 1 Collecting Comprehensive and Representative Input Discussion Document (Discussion Document)*

We appreciate the Agency’s consideration of information from external sources in the FDA’s PFDD Public Workshop on Guidance 1 Collecting Comprehensive and Representative Input Discussion Document (Discussion Document). To that end, the NHC formed patient-driven, multi-stakeholder working groups with the purpose of offering key stakeholders, including the Agency, all-inclusive and consensus-based recommendations on this topic (current recommendations attached as Appendices C and D). Below, we outline our comments and suggestions for the FDA to consider when finalizing the Discussion Document.

First, the NHC recommends the FDA include the following in the guidance:

- A statement that the guidance is intended not just for innovators of therapeutic biopharmaceuticals, but also for anyone that engages patients during medical product-development and review. The NHC envisions that this guidance (and all planned PFDD guidances) will be relevant and applicable to all stakeholders.
- A statement that the guidance aims to *encourage* engagement with patients (i.e., not just collecting data from patients, but partnering with them), but does not *require* it.
- A clear articulation that if patient engagement is conducted appropriately (i.e., the way envisioned by the Agency as described in the guidance), that such interaction is not promotional in nature. Such a statement would go a long way in dispelling the perception among some that meaningful engagement with patients during (at least some phases of) drug development and review is too risky to be pursued.

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<sup>5</sup> *Id.*

<sup>6</sup> FDA website, “Roadmap to Patient-Focused Outcome Measurement in Clinical Trials,” available at: <https://www.fda.gov/downloads/drugs/developmentapprovalprocess/drugdevelopmenttoolsqualificationprogram/ucm370174.pdf> (accessed Jan. 31, 2018).

- A statement that the FDA is receptive to innovative and non-traditional methods, and that the Agency recognizes that the science of patient input is an evolving field. This is important to encourage stakeholders to use innovative methods and push the envelope when thinking about meaningful patient engagement.

Second, we agree with the FDA that the issue of representativeness is a key consideration and an important goal in any plan for collecting patient-provided information. The NHC recently released a white paper *Tackling Representativeness: A Roadmap and Rubric*<sup>7</sup>, discussing insights from a multi-stakeholder roundtable on the topic of representativeness (attached as Appendix D). That document provides a set of consensus-based recommendations and key considerations regarding characteristics of “good” patient representativeness, offering a tool for those engaging patients to help them think about how to (as best as possible) achieve representativeness for their research objective.

The six key principles outlined in the document are:

- *Define* – Clearly define the objective(s) for each engagement effort
- *Understand* – Understand as much as possible about the full population and subpopulations and challenges to reaching them
- *Specify* – Develop a description of the minimum target(s) for representativeness for the engagement activity
- *Plan* – Develop a plan to achieve the minimum target(s) defined
- *Evaluate* – Develop an evaluation plan to assess progress on achieving target(s) or if they need to be adjusted based on new information
- *Document* – Record how patient representativeness was defined, targeted, achieved, and assessed<sup>8</sup>

Third, the NHC requests the FDA include discussion in the guidance to clarify the association between this guidance and clinical outcome assessments (COAs) and patient-preference information (PPI). While this guidance does not discuss COAs or PPI, we understand this guidance as relating to the “precursor” work required to develop a COA or collect PPI (e.g., collecting patient-provided information that informs the development of a COA or design of a study to collect PPI). We believe that making this relationship clear will help readers connect the dots between the series of progressive guidances and minimize any perception that the focus of this first guidance is irrelevant to COAs or PPI.

Finally, we understand the FDA plans to develop a repository of patient-experience data submitted to the Agency. We ask the FDA to clarify how this repository relates to the 21<sup>st</sup> Century Cures Act requirement that the Agency publish a brief statement of the patient-experience data submitted and reviewed for a product application. The NHC supports the development of a data repository for patient-provided information as long as posting data in the repository is voluntary and strongly encouraged, but not required of any stakeholder. The NHC also suggests the Agency clarify what does and does not constitute a minimum quality threshold for these data. We appreciate the increased transparency that making this data public brings and believe that this will lessen the “waste” of this data (as data not shared is wasted) and reduce the overall burden to patients (as patients are not providing the same information over and

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<sup>7</sup> The National Health Council, *Tackling Representativeness: A Roadmap and Rubric*, available at: <https://www.nationalhealthcouncil.org/sites/default/files/Representativeness%20in%20Patient%20Engagement.pdf> (accessed Jan. 25, 2018).

<sup>8</sup> *Id.*

over to numerous stakeholders). However, as expressed above (section “5. Patient-focused”), there is no substitute for active engagement with patients as partners in the medical product development lifecycle. The FDA should specify that accessing and using data from the repository is not a substitute for meaningful engagement with patients. In considering the most useful format this information could take, the NHC requests the FDA consider issuing a standardized report template for the data in a readable format, similar to the information provided in the *Voice of the Patient* reports issued after the FDA-hosted PFDD public meetings, but with standardized formatting.

In conclusion, the NHC fully supports the FDA’s public workshops and PFDD guidance documents as important opportunities for stakeholders to work with the Agency to make meaningful patient engagement in drug development and review *the norm*. With this goal in mind, the NHC continues to work with multi-stakeholder groups to develop new insights and materials to move the discussion and patient engagement forward. Our multi-stakeholder working groups recently produced two documents with suggested recommendations on “Foundational definitions in patient engagement” and “Who is involved in engagement” (Appendices A and B, [beginning on page 8](#) of this document) related to comprehensive and representative patient input on burden of disease and current treatments. The Agency may find it useful to review these documents as it develops its guidance. The NHC recommends that in addition to requesting input through public workshops and on draft documents the Agency also consider engaging patients and other stakeholders earlier in an effort for co-development. The NHC stands ready to assist and support the FDA in its work and will continue to convene the NHC’s patient and multi-stakeholder members to provide input, feedback, and assist in other ways deemed necessary to advance PFDD. The NHC will continue to develop materials to assist the FDA and other stakeholders, and we look forward to further stakeholder collaboration on encouraging meaningful patient engagement, developing tools to collect data, and more broadly integrating patient input into drug development and regulatory decision-making.

Please do not hesitate to contact Eric Gascho, our Vice President of Policy and Government Affairs, if you or your staff would like to discuss these issues in greater detail. He is reachable by phone at 202-973-0545 or via e-mail at [egascho@nhcouncil.org](mailto:egascho@nhcouncil.org).

Sincerely,



Marc Boutin, JD  
Chief Executive Officer

Attachments

**Appendix A:** The National Health Council, Approaches to Collecting Comprehensive and Representative Patient Input on Burden of Disease and Current Treatments: Foundational Definitions, December 2017

**Appendix B:** The National Health Council, Approaches to Collecting Comprehensive and Representative Patient Input on Burden of Disease and Current Treatments: Who is Involved in Engagement, December 2017

**Appendix C:** The National Health Council and Genetic Alliance, [Patient-Focused Drug Development – Recommended Language for Use in Guidance Document Development](#), February 2017

**Appendix D:** The National Health Council, [Tackling Representativeness: A Roadmap and Rubric](#), November 2017

# **APPENDIX A**

## **Approaches to Collecting Comprehensive and Representative Patient Input on Burden of Disease and Current Treatments:**

### **[FOUNDATIONAL DEFINITIONS]**

#### **Purpose of this document:**

To offer multi-stakeholder, consensus-based language to key stakeholders, including the Food and Drug Administration (FDA or the agency) to help advance its work in this area. This document reflects National Health Council (NHC) patient driven, multi-stakeholder membership recommendations for consideration in upcoming patient engagement guidance documents.

#### **Objectives for the recommended language proposed:**

- Provide definitions for terms related to collecting comprehensive and representative patient input on burden of disease and current treatments

#### **Recommended Language**

##### **I. Introduction**

In developing this document for consideration by the U.S. Food and Drug Administration, the National Health Council convened a working group led by patient advocacy organizations and comprised of representatives from different sectors of the health care system to create a united voice on the approaches to collecting comprehensive and representative patient and caregiver input on burden of disease and current therapy. This document also builds on previously submitted work by the National Health Council and Genetic Alliance.<sup>9</sup> This document offers consensus-based thinking on foundational definitions to assist in the agency’s goals related to their commitment to develop guidance on patient engagement in the sixth authorization of the Prescription Drug User Fee Act (PFUDA VI).

##### **II. Proposed Foundational Definitions**

**Comprehensive** – To be thorough and inclusive in the collection of data from patients and caregivers on disease and treatment burden, covering the full gamut of their experiences - e.g., physical, functional, emotional, social, etc. – and includes all domains of the disease that are important to them. An effort to be comprehensive means thoroughly considering the questions needed to explore and how deeply to evaluate each aspect of burden.

**Representative** – Refers to the sufficient number and types of people included in the engagement activity to ensure that those engaged can speak for the target population. It refers to “who” and “how many”

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<sup>9</sup> National Health Council. Patient-Focused Drug Development – Recommended Language for Use in Guidance Document Development, (<http://www.nationalhealthcouncil.org/sites/default/files/NHC-GA%20Feb2017.pdf>)

individuals to include in an interaction to, as closely as possible, engage with individuals that represent the broader, targeted patient population.<sup>10</sup>

**Meaningful Patient Input** – Patient input refers to the contribution of a range of patient-provided information<sup>11</sup> contributed, directly or indirectly, at any point during the product lifecycle. Meaningful input has two attributes: the type of information collected and how it was collected. Meaningful includes patient report of their overall view of their condition and its natural history and impact on their life (e.g., patient reported outcomes such as symptoms, function, and quality of life); experience with available treatments; description/view on which outcomes are important; preferences, goals, desires, concerns, perceptions, or opinions; or the relative importance of any issue as defined by patients.<sup>12</sup> The data are typically collected through engagement activities that bidirectional, reciprocal, and continuous; where communications are open, honest, and clear<sup>7</sup> and where engagement goals, participants, methods, desired impacts, and actual impacts are clearly outlined and transparent.<sup>13</sup>

**Burden of Disease** – Refers to patient (or caregiver) perspectives on the impact of disease (not just in terms of survival, but also in terms of symptoms, function, and well-being). It serves to identify from the patient (or caregiver) the personal load they bear due to illness, their needs due to disease and whether their needs are being met by current care options. Assessment of unmet needs can also serve to identify targets for interventions.<sup>14</sup>

**Burden of Treatment** – Refers to patient (or caregiver) perspectives on the impact of treatment (not just in terms of survival, but also in terms of symptoms, function, and well-being). It serves to identify from the patient (or caregiver) the personal load they bear due to treatment, their needs due to treatment and whether their needs are being met by current care options. This includes medication management, self-monitoring, visits to the doctor, laboratory tests, lifestyle changes, etc. Coping with these health care tasks requires time, action, and cognitive effort from patients and caregivers.<sup>15</sup>

**Unmet Medical Need** – A condition, as defined by the patient, whereby treatment or diagnosis is not addressed adequately by available therapy; this includes immediate need for the defined population (i.e., need to treat a condition with no or limited treatment options), individual needs (i.e., need for additional treatment options due to safety or efficacy deficits of available treatments, individual preference or goals) or a broader need for society (e.g., to address the development of resistance to antibacterial drugs).<sup>16</sup>

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<sup>10</sup> National Health Council. Tackling Representativeness: A Roadmap and Rubric.

(<https://www.nationalhealthcouncil.org/sites/default/files/Representativeness%20in%20Patient%20Engagement.pdf>).

<sup>11</sup> National Health Council. Patient-Focused Drug Development – Recommended Language for Use in Guidance Document Development,

(<http://www.nationalhealthcouncil.org/sites/default/files/NHC-GA%20Feb2017.pdf>)

<sup>12</sup> See footnote 2

<sup>13</sup> See footnote 2

<sup>14</sup> Biotechnology Innovation Organization, Parent Project Muscular Dystrophy. Key Considerations for Developing & Integrating Patient Perspectives in Drug Development: Examination of the Duchenne Case Study,

([https://www.bio.org/sites/default/files/BIO\\_PPMD\\_Paper\\_2016.pdf](https://www.bio.org/sites/default/files/BIO_PPMD_Paper_2016.pdf)).

<sup>15</sup> Tran, V.T., et al., Adaptation and validation of the Treatment Burden Questionnaire (TBQ) in English using an internet platform. BMC Med, 2014. 12: p. 109. [<https://minimallydisruptivemedicine.org/2015/06/29/burden-of-treatment-the-work-of-being-a-patient/>]

<sup>16</sup> U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics, (<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf>).

***Drug Development Process*** – Refers to the activities undertaken to conceptualize, study, register, market and monitor a medicinal product during which patient engagement can take place. Not limited to the lifecycle of one specific drug, but to the overall processes and actions from earliest stages (before candidate molecule consideration to product or therapeutic obsolescence). For example, it may include understanding the natural history of a disease (or group of diseases) from the patient perspective prior to selecting candidate for pre-clinical study.)<sup>17</sup>

***[APPENDIX B - NEXT PAGE]***

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<sup>17</sup> Proposed PFDD Conceptual Framework. Adapted from: Clinical Trials Transformation Initiative’s Patient Groups & Clinical Trials Expert Meeting summary; National Health Council’s Dialogue/Advancing Meaningful Patient Engagement in Drug Research, Development, and Approval; model proposed by Perfetto et al. Med Care. 2015 Jan;53(1):9-17. Accessed at <http://www.pharmacy.umaryland.edu/media/SOP/wwwpharmacyumarylandedu/centers/cersievents/pfdd/mcersi-pfdd-proceedings-rubric.pdf>

## ***APPENDIX B***

# **Approaches to Collecting Comprehensive and Representative Patient Input on Burden of Disease and Current Treatments: *[WHO IS INVOLVED IN ENGAGEMENT]***

### **Purpose of this document:**

To offer multi-stakeholder, consensus-based language to key stakeholders, including the Food and Drug Administration (FDA or the agency) to help advance its work in this area. This document reflects National Health Council (NHC) patient driven, multi-stakeholder membership recommendations for consideration in upcoming patient engagement guidance documents.

### **Objectives for the recommended language proposed:**

- Provide current thinking on who can and should be engaged in collecting comprehensive and representative patient input on burden of disease and current treatments.

### **Recommended Language**

#### **I. Introduction**

In developing this document for consideration by the U.S. Food and Drug Administration, the National Health Council convened a working group led by patient advocacy organizations and comprised of representatives from different sectors of the health care system to create a united voice on the approaches to collecting comprehensive and representative patient and caregiver input on burden of disease and current therapy. This document also builds on previously submitted work by the National Health Council and Genetic Alliance.<sup>18</sup> This document offers consensus-based thinking on foundational definitions to assist in the agency's goals related to their commitment to develop guidance on patient engagement in the sixth authorization of the Prescription Drug User Fee Act (PFUDA VI).

Those involved in engagement for collecting information on comprehensive and representative patient and caregiver input on burden of disease and current treatment typically include the patients<sup>18</sup> providing information and those who are collecting the patient-provided information<sup>18</sup> for drug development purposes.

#### **II. Who is Engaged: Providing Information**

Those providing the patient perspective include: patients, patient advocates, patient advocacy groups/organizations, and patient experts (patients who have taken on an expert or consultant role). The perspectives of people at risk for a disease or condition (e.g., BRCA1 carriers, genetic carriers of disease, people living in regions of infectious disease epidemics) may also be considered in certain drug

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<sup>18</sup> National Health Council. Patient-Focused Drug Development – Recommended Language for Use in Guidance Document Development, (<http://www.nationalhealthcouncil.org/sites/default/files/NHC-GA%20Feb2017.pdf>)

development settings (e.g., gene therapies, vaccine development or other prophylactic treatments). Caregivers (typically unpaid, family caregivers, not paid professional caregivers) are also important sources of information about patients, especially when patients are unable to provide the information themselves or when the information provided by the patient provides an incomplete picture of the burden of disease or burden of treatment.

The context of a particular interaction (e.g., the objectives and format of the interaction; the point in product development in which the interaction occurs) will inform which entities are involved in a particular interaction or series of interactions with patients.<sup>19</sup> For example, an individual patients' input on what is clinically important may be more useful for some circumstances whereas a patient advocacy organization's input is needed to contextualize the patient population at large, including at certain stages of a disease or to provide early guidance on who to engage and on what issues (i.e., to avoid gaps or carryover of incorrect assumptions into future patient engagement).

The provider of patient-provided information will vary depending on the context and circumstance. For example, family caregivers may provide information on behalf of children or patients who may not have the capacity to engage.<sup>2</sup> Family caregivers may also engage in lieu of individual patients to provide the specific perspective of the caregiver. Similarly, patient advocacy organizations can provide a perspective that uniquely captures the heterogeneity of a patient population. They also may act as a key conduit for sponsors or researchers seeking to engage with a particular patient population.<sup>20</sup>

FDA recognizes that patients can assume different roles in these engagements. Patients can serve as advisors or consultants to provide input on research questions, study designs, or patient engagement plans. In addition, patient interactions can be formal or informal. Formal interactions may include arrangements that stipulate roles, responsibilities, any contractual obligations of the parties, as well as compensation. Informal interactions may consist of brief or temporary engagements (e.g., social media interactions).<sup>20</sup>

### **III. Who is Engaged: Collecting Information**

Those collecting the data generally are sponsors, academic researchers, patient advocacy organizations, health care providers, professional societies, FDA, and those contracted to collect information or act as an intermediary between these entities and patients. For example, in the context of designing clinical trials for a particular drug, the sponsor of drug development program will generally be the primary entity collecting the data, or they may have a contract research organization working on their behalf. FDA may also collect patient provided-information at many points before and during drug development. Academicians conducting research, such as developing patient-reported outcome measures may also have a role.

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<sup>19</sup> National Health Council. Tackling Representativeness: A Roadmap and Rubric. (<https://www.nationalhealthcouncil.org/sites/default/files/Representativeness%20in%20Patient%20Engagement.pdf>).

<sup>20</sup> National Health Council. Sponsor-Patient Interactions During Drug Development: Good Practice Insights on Patient Engagement. Retrieved from <http://www.nationalhealthcouncil.org/sites/default/files/Sponsor-Patient%20Interactions%20during%20Drug%20Development.pdf> (Accessed November 9, 2017).

***APPENDIX C (NEXT PAGE)***



# **Patient-Focused Drug Development – Recommended Language for Use in Guidance Document Development**

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**This document was prepared by the National Health Council and Genetic Alliance with the intent of submission to the Food and Drug Administration to encourage adoption, wholly or in part, by the Agency.**

**February 2017**

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# Patient-Focused Drug Development – Recommended Language for Use in Guidance Document Development

## First in a Series of Recommended Guidance Documents for Food and Drug Administration Consideration

### Purpose of this document:

1. The National Health Council (NHC) and Genetic Alliance (GA) have been dedicated to furthering patient engagement in drug development and hosted three multi-stakeholder events to inform the development of draft guidance document language, language that could be offered to the Food and Drug Administration (FDA or the Agency) to help advance its work in this area. This document reflects the NHC and GA language recommendations for FDA consideration in future patient engagement guidance documents.

### Objectives for the recommended language offered in this document:

1. Convey to the public that the Food and Drug Administration supports and encourages, but does not require, patient-focused drug development activities.
2. Provide definitions for the various terms used related to patient-focused drug development to encourage standardization.

### Recommended Language

#### I. Introduction

Patient input during drug<sup>1</sup> product research, development, review, and post-marketing evaluation is critical to the development and life-cycle management of treatments that meet patient needs, enhance the research and approval processes, and improve patient outcomes. Historically, FDA has sought input from patients who serve as members on FDA Advisory Committees<sup>2</sup> and during sponsor meetings discussing specific products. This document supports the Agency's focus on

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<sup>1</sup> The term drug as used in this guidance refers to both human drugs and biological products unless otherwise specified.

<sup>2</sup> See FDA website, About the Patient Representative Program, (<http://www.fda.gov/ForPatients/About/ucm412709.htm>) (last visited February 16, 2016).

expanding and formalizing the collection and use of patient input through the Patient-Focused Drug Development (PFDD) initiative<sup>3</sup> and providing a more structured benefit-risk framework.<sup>4</sup>

FDA values the perspectives of patients and is committed to encouraging patient input throughout drug development and product reviews.<sup>5</sup> The Agency recognizes patients as experts and believes patients can bring their experiences to bear to enhance regulatory decision-making.

FDA's guidance documents, including draft guidance that might include this language, do not establish legally enforceable responsibilities. Instead, they describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in Agency guidance means that something is suggested or recommended, but not required.

## II. Background

Patient-provided information (PPI) is an important, and necessary, component in drug development and product review. For example, the insights that patients provide on a range of topics, from their experience living with their disease to their priorities for treatment outcomes, helps sponsors ensure that their products meet the needs of patients and helps FDA assess a product's benefits and risks. For sponsors to obtain this insight, they need to engage in non-promotional interactions with patients for research purposes. These interactions are appropriate, though they are set by different guidelines and intended to provide sponsors with patient insights that are integral to successful drug development and product review.

In 2012, Congress passed the Food and Drug Administration Safety and Innovation Act (FDASIA), which included provisions to enhance patient engagement in drug development and product reviews,<sup>6</sup> such as section 1137, which required FDA "to develop and implement strategies to solicit the views of patients during the medical product development process and consider the perspectives of patients during regulatory discussions."<sup>7</sup> Since that time, patients have had a growing number of opportunities to become involved in drug development and product review, including serving on FDA Advisory Committees, providing input during specific product meetings with sponsors, and participating in FDA's PFDD meetings.

### A. What is "patient-provided information"?

For the purposes of this guidance, "patient-provided information" describes information a patient contributes directly at any point during the product lifecycle. As defined in Section III, the term broadly encompasses the entirety of information that can be collected from an interaction with a patient. Section IV also provides definitions for other similar terms and describes their

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<sup>3</sup> See Prescription Drug User Fee Act V Patient-Focused Drug Development; Consultation Meetings; Request for Notification of Patient Stakeholder Intention To Participate, 77 Fed. Reg. 58848 (Sept. 24, 2012).

<sup>4</sup> See FDA website, Enhancing Benefit-Risk Assessment in Regulatory Decision-Making, (<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>) (last visited February 11, 2016).

<sup>5</sup> See also for CDRH, FDA's *Guidance for Industry and Food and Drug Administration Staff; Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications* issued on March 28, 2012 (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM296379.pdf>); see also FDA's *Draft Guidance for Industry, Food and Drug Administration Staff; and Other Stakeholders; Patient Preference Information – Submission, Review in PMAs, HDE Applications, and De Novo Requests, and Inclusion in Device Labeling* issued on May 18, 2015 (<http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm446680.pdf>).

<sup>6</sup> See Food and Drug Administration Safety and Innovation Act (FDASIA), Pub. L. 112-144, 126 Stat. 993 (2012).

<sup>7</sup> See FDASIA § 1137.

relationship relative to one another. The focus should be the patients view on their disease(s)/condition(s), desired attributes for treatments, experiences with treatments, benefit-risk preferences, and desired goals and outcomes. It should not be primarily focused on any one product.

PPIIn includes, but is not limited to, information from patients about:

- the natural history of the disease
- the impact of the disease or condition on patients and their family caregivers, and how it affects their daily activities, physical functions, and quality of life
- outcomes that are most important to the patient, both clinical and non-clinical (e.g., goals for daily activities, symptom reduction, or a standard of quality of life)
- patients' preferences for treatment delivery methods and opinions about side effects
- experience on treatment(s) including symptoms and side effects and how the treatment impacts their daily activities, physical functions, and quality of life

As illustrated by this list, PPIIn covers a wide variety of input from the patient regarding the patient's experience, preferences, and needs. However, PPIIn does not include all information obtainable about a patient. For example, pathology results are "patient information" and distinct from PPIIn because they are not conveyed directly by the patient.

## **B. What are FDA's PFDD initiative and patient-focused drug development?**

FDA's PFDD initiative, a commitment under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V), has allowed the Agency to more systematically gather patients' and family caregivers' perspectives on living with a disease, the symptoms that matter most to them, and their experiences with available therapies.<sup>8</sup> As part of this initiative, FDA has committed to holding public meetings, each focusing on a specific disease area.<sup>9</sup> FDA summarizes the input it receives during these meetings in a publicly reported series entitled, "Voice of the Patient."<sup>10</sup> The information provided by patients at these meetings is critical to the Agency's understanding of the needs and preferences of patients diagnosed with these diseases. FDA can use this patient input to inform the Agency's regulatory decision-making, especially when assessing a product's benefit-risk profile. For diseases for which a formal FDA PFDD meeting is not planned, FDA recommends patient groups consider holding their own, external PFDD meetings and has provided insights on how to do so.<sup>11</sup>

FDA's PFDD initiative represents just one way in which PPIIn can be integrated into the product lifecycle. The broader term "patient-focused drug development" refers to meaningful engagement of patients throughout the product lifecycle, from the early stages of discovery to post-market studies, and extends beyond the Agency's recent activities.

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<sup>8</sup>See Footnote 12 *Patient-Focused Drug Development: Disease Area Meetings Planned for Fiscal Years 2013-2017*, <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm347317.htm> (last visited February 16, 2016).

<sup>9</sup>See Footnote 12 *Patient-Focused Drug Development: Disease Area Meetings Planned for Fiscal Years 2013-2017*, <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm347317.htm> (last visited February 16, 2016).

<sup>10</sup> See *The Voice of the Patient: A Series of Reports from FDA's Patient-Focused Drug Development Initiative*, <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm368342.htm> (last visited February 16, 2016).

<sup>11</sup> See *Externally-led Patient-Focused Drug Development Meetings*, <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm453856.htm> (last visited February 16, 2016).

### **C. Who is involved in patient-focused drug development?**

In general, the exchange that takes place during patient interactions to collect patient-provided information involves:

Those *gathering patient-provided information*, which can include, but is not limited to, sponsors, academic researchers, health care providers, professional societies, special interest groups, patient groups, FDA, and those contracted to collect information or act as an intermediary between another entity and patients.

Those *providing patient-provided information*, which can include, but is not limited to, individual patients, family caregivers, individual patient advocates, or patient advocacy organizations (defined as “patients”, see Section IV).

The context of a particular patient interaction (e.g., the objectives and format of the interaction; the point in product development in which the interaction occurs) informs which entities are involved in a particular interaction or series of interactions with patients. For example, in the context of designing clinical trials for a particular drug, the sponsor of that drug will generally be the primary entity collecting PPI. FDA may also collect PPI at many points before and during drug development. Patient interaction during drug development is not limited to sponsors and FDA; academic researchers, professional societies, or patient advocacy organizations may also gather PPI to inform their own and others research efforts. Guidance may encourage the use of PPI in PFDD by all stakeholders.

The provider of PPI also will vary depending on the circumstance. For example, family caregivers may provide information on behalf of children or patients who may not have the capacity to engage. Family caregivers may also engage in lieu of individual patients to provide the specific perspective of the caregiver. Similarly, patient advocacy organizations can provide a perspective that uniquely captures the heterogeneity of a patient population. They also may act as a key conduit for sponsors or researchers seeking to engage with a particular patient population.

FDA recognizes that patients can assume different roles in these engagements. Patients can serve as advisors or consultants to provide input on research questions, study designs, or patient engagement plans. In addition, patient interactions can be formal or informal. Formal interactions may include arrangements that stipulate roles, responsibilities, any contractual obligations of the parties, as well as compensation. Informal interactions may consist of brief or temporary engagements (e.g., patients responding to a survey).

### **D. Why include patient-provided information in disease research and drug development?**

Draft guidance may include language recognizing the value of PPI to those who are conducting disease research and drug development. Understanding from patients their experience of living with a disease over time is critical to, for example, understanding the natural history of a disease and identifying unmet medical needs. In addition, PPI can identify the symptoms of a disease that are most bothersome to patients, the clinical outcomes patients care most about, ways to make a clinical trial less burdensome to patients, and treatment characteristics patients prefer. If integrated into decision-making and product planning, this

information can help product sponsors develop drugs that align with patient preferences and needs, and gather outcome data patients care about.

Patients can advise on any number of drug-development challenges to help ensure new drugs better meet patient needs and goals and enhance patient outcomes. Guidance may include language to encourage sponsors and other involved stakeholders to engage patients early and continuously in the drug development process to prevent avoidable misalignment between patient needs and preferences and development decisions and processes. This will help ensure study protocols reflect patient input, and the data captured are important to patients. In addition, early engagement can help produce product labeling that includes information important and understandable to patients.<sup>12</sup>

Sponsors and other stakeholders can better understand the heterogeneity of patient perspectives by engaging patients. Knowledge about how a disease impacts patients across age, disease severity, and disease progression (e.g., newly diagnosed or having lived with the disease for decades), as well as the heterogeneity of treatment effects across patients, can also inform drug development.

Many of the approaches and considerations for engaging patients can also be more broadly applied to research and development processes for all medical products, as well as basic disease-specific research (e.g., natural history studies). PPI can provide value to all clinical research, and researchers should consider meaningfully engaging patients to support their studies in general.

### III. Overview and Scope

This document provides FDA with recommended language of current perspectives on PPI. This language applies in general, unless otherwise stated, to engagement with patients with regard to a disease, condition, or therapeutic area. In many instances, patient engagement happens unrelated to any specific product or products. When it does relate to a product or products, it can include research prior to discovery or development and the complete lifecycle of a drug (the “product lifecycle”). Research prior to discovery or development includes studies on the natural history of disease and identifying unmet medical need, and is typically disease- or therapeutic-area focused. It may not include any reference to any treatments as it may be too early in the development process for such discussion. The product lifecycle includes the discovery, research, and development tied to a specific product (e.g., clinical trials to demonstrate safety and efficacy of the product); regulatory review of that product for market approval or licensure; and post-approval study and development of that product (e.g., post-marketing commitments, surveillance that continues for as long as a product is available, or submission for new indications). There are nuances that differentiate the types of engagement needed throughout the product lifecycle. In this document, the term “product lifecycle” encompasses this full timeline, pre-product and post-approval. In this document, the word “research” refers to all phases of research from pre-product to post-approval, and therefore, includes research about the disease or therapeutic area alone, with or without reference to treatment.

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<sup>12</sup> See Footnote 5 *Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders; Patient Preference Information – Submission, Review in PMAs, HDE Applications, and De Novo Requests, and Inclusion in Device Labeling.*

This document recommends definitions of the principal concepts and key terms related to engaging patients outside of and during the product lifecycle. Information provided by patients during these interactions may inform FDA's thinking on a disease, condition, or therapeutic area, such as understanding the impact a disease has on patients' lives and the outcomes that are important to patients with that disease. It may also inform FDA premarket review of Investigational New Drug Applications (INDs), New Drug Applications (NDAs), Supplemental New Drug Applications (sNDAs), Biologics License Applications (BLAs), Supplemental Biologics License Applications (sBLAs), Investigational Device Exemption (IDEs), Premarket Approval (PMAs), (sPMAs) and ongoing safety surveillance.

Submission of PPI to FDA is voluntary. The information submitted should inform decision making. PPI can be useful to, among other things:

- Identify unmet medical need;
- Understand the natural history of a disease;
- Identify outcomes that patients care about;
- Develop clinical trial protocols that minimize burden to patients;
- Understand patient experiences with current treatments and daily living with their disease;
- Identify patient preferences, goals, and opinions, including those of a diverse patient population (and the heterogeneity within);
- Identify with which benefits and risks outcomes matters most to patients and the tradeoffs patients are willing to make between benefits and risks; and
- Refinement of materials such as informed consent, clinical trial recruitment materials, patient information leaflets, package inserts, PLS, etc.

This document recommends that FDA encourage product sponsors and other stakeholders to meaningfully engage patients throughout the product lifecycle. This document recommends the Agency welcomes submission of PPI from sponsors and other stakeholders, and engage in a dialogue with the relevant review division on PPI. This document, including the defined terminology, may be informative to other stakeholders, including patient groups and academic researchers, who collect and submit PPI to the FDA. This document recommends the Agency encourages sponsors and other stakeholders that are considering PPI for submission to FDA to communicate with the relevant FDA review division to discuss their plans for patient engagement as early in the process as possible. The next section consists of NHC recommendations to define key terms related to patient-focused drug development.

#### IV. Defining Key Terms for Patient Engagement

**Patient engagement**, in drug development and product review, means involving patients as active participants in these processes. Simply enrolling and following patients as passive research subjects in a clinical trial does not rise to the level of patient engagement. Instead, patients should be treated “as valued and valuable partners whose input, advice, and guidance is sought and implemented” throughout these processes.<sup>13</sup> FDA recognizes that patient engagement extends well beyond drug development and approval. However, for the purposes of this document, the focus is on patient engagement prior to and throughout a product's lifecycle.

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<sup>13</sup> A. Hoos A, *et.al.*, “Partnering with Patients in the Development and Lifecycle of Medicines: A Call for Action,” *Therapeutic Innovation & Regulatory Science*, (2015).

FDA recognizes the need for standard terminology regarding patient engagement in drug development and approval. Key terms are defined or described for the purposes of this guidance as follows:

**Patient** – “those (people) having or at risk of having the medical condition(s) whether or not they currently receive medicines or vaccines to prevent or treat a disease” as well as “the family and those caring for those with the medical condition(s),” patient advocates, and patient groups.<sup>14</sup>

The definition of “patient” is intentionally broad in an effort to capture the myriad of valuable input to be gained from each of the listed individuals and organizations (i.e., individuals suffering from a condition, family caregivers, patient advocates, and patient advocacy organizations) without excluding a valuable perspective. However, we recognize that each type of individual or organization may not always be appropriate to speak for the person with the condition in all contexts and situations. When this guidance refers to the single person with the illness, the phrase, “individual patient,” is used.

**Sponsor** – an entity that takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, a government agency, academic institution, private organization, or other organization.<sup>15</sup> The sponsor may also be the entity responsible for submitting a new product application for FDA review.<sup>16</sup>

There are many terms to describe different types of patient information. For the purposes of this document, it is recommended FDA focuses on **patient-provided information (PPI)**, defined below. To distinguish patient-provided information for the purposes of this guidance, other types of **patient information** are defined as follows (see also Figure 1 on page 11):

**Patient information** – broadly means all information regarding a patient from any source, such as patient-provided information as well as other medical information about a patient, including but not limited to: test results (e.g., genetic, pathology, imaging), identifying information, family history, provider opinion, and any other information in a patient’s medical records.<sup>17</sup>

**Patient-provided information (or patient-provided input)** – broadly means a range of information that comes directly from patients such as, but not limited to: views, experiences, preferences, needs, opinions, and priorities. This can include their overall view of their condition and its natural history and impact on their life (e.g., patient-reported outcomes such as symptoms, function, and quality of life); experience with available treatments; description/view on which outcomes are important; patient preferences, goals, desires, concerns, perceptions, or opinions; or the relative importance of any issue as defined by patients.<sup>18</sup> *Patient-provided is information relayed by the patient regarding their subjective experience and opinions.* It does not include all

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<sup>14</sup> See Footnote 6.

<sup>15</sup> See 21 CFR 312.3(b).

<sup>16</sup> See 21 CFR 314.3(b).

<sup>17</sup> National Health Council, Genetic Alliance. Integrating the Patient into the Drug Development Process: Developing FDA Guidance, (<http://www.nationalhealthcouncil.org/sites/default/files/NHC-GA-Patient-Engagement.pdf>).

<sup>18</sup> See Footnote 10 National Health Council, Genetic Alliance. Integrating the Patient into the Drug Development Process: Developing FDA Guidance, (<http://www.nationalhealthcouncil.org/sites/default/files/NHC-GA-Patient-Engagement.pdf>)

medical information on a patient (e.g., genetic testing information, pathology results) that may be about the patient but comes from other sources.

**Patient-generated health data** – health-related data created, recorded, or gathered by or from patients (or family members or other caregivers) to help address a health concern.<sup>19</sup>

**Patient perspective information** – a subset of PPI; information regarding the attitude or the point of view of the patient, including anecdotal comments in correspondence to FDA or testimony at Advisory Committee Panel meetings<sup>20</sup> or Patient-Focused Drug Development meetings,<sup>21</sup> patient opinions expressed publicly including through social media, patient responses to qualitative, *ad hoc* surveys, quantitative measurements of patient-reported outcomes, and more.<sup>22,23</sup>

**Patient preference information** – a subset of PPI; qualitative or quantitative assessments of the relative desirability, or acceptability of, attributes that differ among alternatives (e.g., alternative therapeutic strategies).<sup>24</sup> Attributes of a drug or biologic include characteristics such as effectiveness, safety, route of administration, dosing regimens, duration of effect, duration of use, and other product features about which patients express preferences.

**Patient-reported information** – a subset of PPI; information that is reported directly by a patient without amendment or interpretation by a clinician, researcher, or any other entity.<sup>25</sup>

**Patient-reported outcome (PRO)** – a subset of PPI; an outcome measure based on a report that comes directly from the patient (e.g., study subject) about the status of the patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else. A PRO can be measured by self-report or by interview provided that the interviewer records only the patient's responses.<sup>26</sup>

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<sup>19</sup>See patient-generated health data, *HealthIT.gov website, Consumer eHealth*, <https://www.healthit.gov/policy-researchers-implementers/patient-generated-health-data> (last visited April 8, 2016).

<sup>20</sup> See Footnote 2 See FDA website, *About the Patient Representative Program*, (<http://www.fda.gov/ForPatients/About/ucm412709.htm>) (last visited February 16, 2016).

<sup>21</sup> See Patient-Focused Drug Development: Disease Area Meetings Planned for Fiscal Years 2013-2017, <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm347317.htm> (last visited February 16, 2016).

<sup>22</sup> See Footnote 5 *Draft Guidance for Industry, Food and Drug Administration Staff; and Other Stakeholders; Patient Preference Information – Submission, Review in PMAs, HDE Applications, and De Novo Requests, and Inclusion in Device Labeling*.

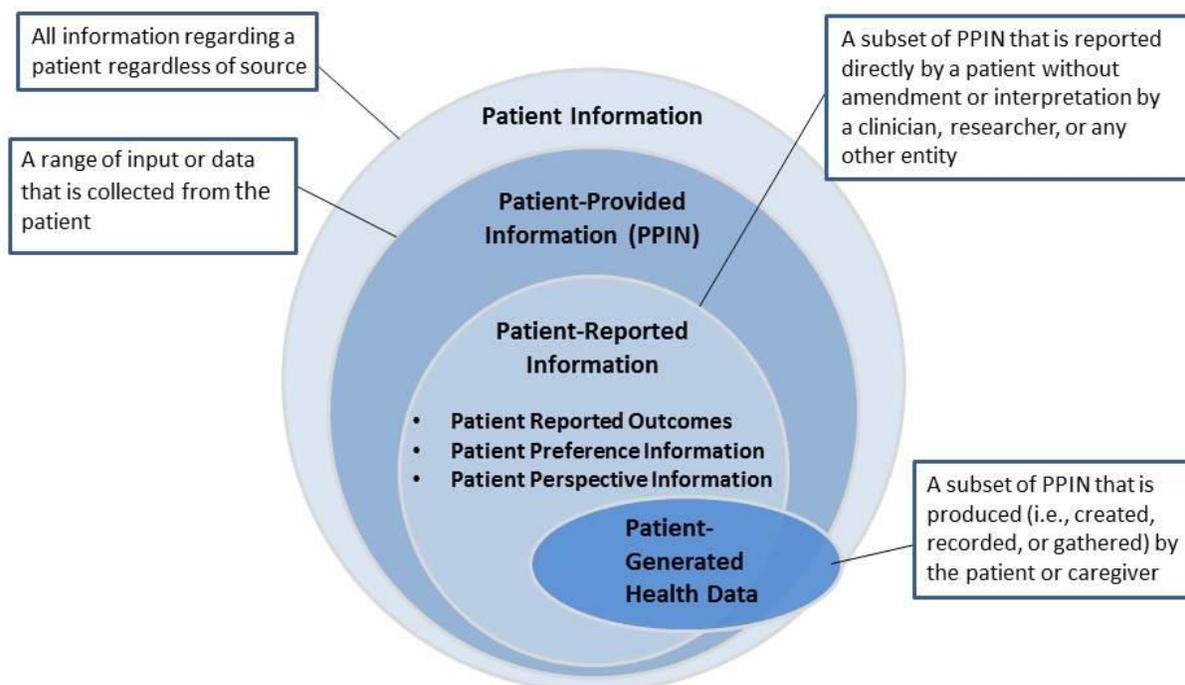
<sup>23</sup> See FasterCures, *Enhancing Integration of Patient Perspective Data in the Drug Development Process, Proposal for PDUFA VI*, (<http://www.nationalhealthcouncil.org/sites/default/files/FasterCures-PDUFA-Comment-Letter-FDA.pdf>).

<sup>24</sup> See Footnote 5 *Draft Guidance for Industry, Food and Drug Administration Staff; and Other Stakeholders; Patient Preference Information – Submission, Review in PMAs, HDE Applications, and De Novo Requests, and Inclusion in Device Labeling*.

<sup>25</sup> See Footnote 10.

<sup>26</sup> See the guidance for industry, *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm193282.pdf>). For the most recent version of a guidance, check the FDA Drug guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> (last visited February 16, 2016).

**Figure 1: Relationship Among Types of Patient Information**



Key terms are defined or described for the purposes of inclusion in a draft guidance document as follows:

**Patient voice** – broadly refers to capturing and utilizing PPI.<sup>27</sup>

**Patient involvement** – broadly refers to patient participation or contribution in a process.<sup>28</sup>

**Patient engagement/interaction** – a specific reciprocal action between a patient or patients and another individual or group for the purposes of collecting PPI from the patient and/or communicating with the patient. Can be formal or informal; direct or indirect (i.e., through a third party such as a patient group).<sup>23</sup> Meaningful patient engagement requires other attributes such as continuous patient interactions on a sustained basis. (See meaningful patient engagement.)

<sup>27</sup>See NHC comments on FDA's Draft Guidance on Patient Preference Information, (<http://www.nationalhealthcouncil.org/sites/default/files/Patient-Preference-FDA-Guidance-Comments.pdf>).

<sup>28</sup>See also: *Patient involvement in the European Union*, [http://ec.europa.eu/dgs/health\\_consumer/dyna/enews/enews.cfm?al\\_id=1259](http://ec.europa.eu/dgs/health_consumer/dyna/enews/enews.cfm?al_id=1259).

**Patient risk tolerance** – A qualitative term reflecting the extent to which a patient will accept the risk(s) of an adverse effect from a treatment for a probable benefit; risk tolerance will vary among patients, which affects individual patient decisions as to whether risks are acceptable.<sup>29</sup>

**Meaningful patient engagement** – Interactions intended to inform decision making that include direct relationships and partnerships with patients that are bidirectional, reciprocal, and continuous; where communications are open, honest, and clear; and where engagement goals, participants, methods, desired impacts, and actual impacts are clearly outlined and transparent.<sup>30</sup>

**Patient need** – a desire or requirement expressed by a patient related to their health.<sup>23</sup>

**Patient-centered** – broadly meaning any process, program or decision focused on patients in which patients play an active role as meaningfully engaged participants, and the central focus is on optimizing use of PPI.<sup>31</sup>

**Patient-informed drug development** – generally refers to drug development that uses PPI to guide or inform decisions but may or may not include patient involvement.<sup>32</sup>

**Patient-focused drug development (or patient-directed drug development or patient-focused medicines development)** – is the meaningful engagement of patients in the research and development of therapeutic products and the various important roles patients can play in improving the processes, from study endpoint selection that reflects outcomes meaningful to patients, recruitment and retention in clinical trials, and more effective post-marketing safety surveillance.<sup>33</sup>

**Patient-Focused Drug Development (PFDD) initiative** – refers specifically to FDA’s patient-focused drug development initiative as part of FDA commitments under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V), which aims to more systematically obtain the patient perspective on specific diseases and their treatments.<sup>34</sup>

**Product Lifecycle** – the entire product development process; research prior to discovery, development, or preference, pre-product research, and throughout the complete to post approval.<sup>35</sup>

The terminology and concepts described here also may be useful in other contexts. Additionally, this document may be informative to other stakeholders who may wish to consider engagement with patients to inform any type of medical product development.

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<sup>29</sup> See CDRH guidance for industry, *Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions*,

<http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm506679.pdf> (last visited November 7, 2016).

<sup>30</sup> See National Health Council. The Patient Voice in Value: The National Health Council Patient-Centered Value Model Rubric, <http://www.nationalhealthcouncil.org/sites/default/files/Value-Rubric.pdf>.

<sup>31</sup> Epstein RM, Street RL. The Values and Value of Patient-Centered Care. *Annals of Family Medicine*. 2011;9(2):100- 103. doi:10.1370/afm.1239.

<sup>32</sup> See Footnote 10 National Health Council and Genetic Alliance. Integrating the Patient into the Drug Development Process: Developing FDA Guidance. (<http://www.nationalhealthcouncil.org/sites/default/files/NHC-GA-Patient-Engagement.pdf>).

<sup>33</sup> See Clinical Trials Transformation Initiative, CTTI Recommendations: Effective Engagement with Patient Groups Around Clinical Trials, <http://www.ctti-clinicaltrials.org/files/PatientGroups/PGCTrecs.pdf> (last visited February 16, 2016).

<sup>34</sup> See Footnote 3.

<sup>35</sup> See Footnote 20 NHC comments on FDA’s Draft Guidance on Patient Preference Information, (<http://www.nationalhealthcouncil.org/sites/default/files/Patient-Preference-FDA-Guidance-Comments.pdf>).

***APPENDIX D (NEXT PAGE)***



## Tackling Representativeness: A Roadmap and Rubric



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## Introduction

As stakeholders across the health care ecosystem embrace patient centeredness and integrate the patient voice into their processes, decisions, and organizations, meaningful patient engagement has become increasingly important during drug development, regulatory product review, and value assessment. In practical terms, this means that patients, including caregivers, advocates, and advocacy organizations, are active, respected, and full partners in the endeavor, and their views are incorporated into all processes.

To achieve this full engagement, partnering with patients who are *representative*<sup>1</sup> of the target patient community is important. However, the questions of how to define patient “representativeness” and what constitutes a representative sample are integral to successfully achieving the goals of patient engagement. This can often be neglected by those engaging patients, as a standard definition of “patient representativeness” in patient engagement remains elusive.

Aiming to address this issue and assist stakeholders in achieving patient representativeness in their engagements, the National Health Council (NHC) convened a half-day Roundtable on May 8, 2017, with key stakeholders, including representatives from patient groups, life science companies, value-assessment framework developers, payers, research organizations, and the Food and Drug Administration (FDA). The Roundtable focused on the following goals:

- Build consensus around a common understanding of “representativeness” and how it can be applied to patient engagement in: (1) drug development, (2) regulatory decision-making, and (3) value assessment.
- Develop a set of recommendations on good practices to address the challenges of ensuring patient representativeness in patient engagement.

The Roundtable began with a diverse, multi-stakeholder panel discussing how their organizations define patient representativeness and why it is important to them, followed by a series of two breakout sessions in which small groups discussed a specific topic, and came back together as a full group to discuss their thoughts and recommendations. The two breakout sessions focused on: (1) key concepts and characteristics of representativeness and (2) defining what “good” representativeness looks like.

This white paper captures insights from the Roundtable discussion, providing stakeholders with a set of consensus-based recommendations and considerations on characteristics of “good” patient representativeness and identifies gaps and barriers to be addressed in the future. This white paper is not a technical or methodological guidance on patient representativeness in study sampling, nor is it a checklist for organizations looking to say they achieved good representativeness. Instead, it describes key principles with guiding recommendations.

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<sup>1</sup> Importantly, this white paper focuses exclusively on addressing questions of patient representativeness and purposefully excludes the numerous (very important, but distinct from representativeness) considerations relevant to ensuring the broader goal of meaningful patient engagement. Patient representativeness clearly falls within the considerations for ensuring meaningful patient engagement, but it is only one of many factors that contribute to creating a meaningful engagement effort (and developing a patient-centered approach). For example, the NHC’s 2016 Patient-Centered Value Model Rubric identifies best practices associated with six domains of patient engagement in value assessment, including: (1) the importance of patient partnership, (2) transparency to patients, (3) inclusiveness of patients, (4) diversity of patients/populations, (5) the use of outcomes that patients care about, and (6) the use of patient-centered data sources. Patient representativeness is primarily linked to one of these value domains, diversity of patient/populations, but contributes to all domains in the overall goal of meaningful patient engagement in value assessment.

In addition, the Appendix of this white paper includes a roadmap and rubric to help guide stakeholders to plan for and assess achievement of representativeness for their patient-engagement efforts. The roadmap and rubric are meant to serve as a barometer by which stakeholders, including those engaging patients and the patient communities themselves, can evaluate the representativeness of a given patient engagement activity in order to improve current and future activities. The Appendix also includes a hypothetical case study of a patient engagement activity that would follow the roadmap in order to strive for good representativeness.

## Defining Representativeness in Patient Engagement

The following consensus definition of representativeness in patient engagement emerged from the Roundtable discussion:

**“Representativeness” means a sufficient number of and types of people are included in the engagement activity to ensure that those engaged can speak on behalf of the target population. It refers to “who” and “how many” individuals to include in an interaction in order to, as closely as possible, engage with individuals that represent the broader, target patient population.**

Representativeness in patient engagement exemplifies, in desired characteristics and proportion, who and how many individuals from the patient community are needed to take part in one or more engagement activities with the goal of capturing patient-provided information as part of a specific patient-centered effort. It articulates the benchmark characteristics desired to engage the right individuals to capture the range of input needed.

Engaging the right individuals also requires acknowledging that diversity exists not only among patients, but also among different patient groups representing the same condition. These patient groups may offer varying perspectives based on the make of their individual members. It should be the goal of efforts to achieve patient representativeness to acknowledge and balance perspectives.

Importantly, an effort to meet “representativeness” targets for an engagement is distinct from statistical sampling in that it focuses more on identifying individuals with the desired characteristics (and considering any limitations to doing that), rather than meeting a known statistical threshold for the number of patient participants. For example, in sampling, a researcher might identify the need to have a 50 percent female sample to exactly mirror the percentage of women in the broader patient community. In contrast, trying to meet a target for representativeness might require that instead of representing the whole patient community, the engagement needs 50 percent of an advisory committee to be patient community representatives that includes people with early disease, late-stage disease, and their caregivers.

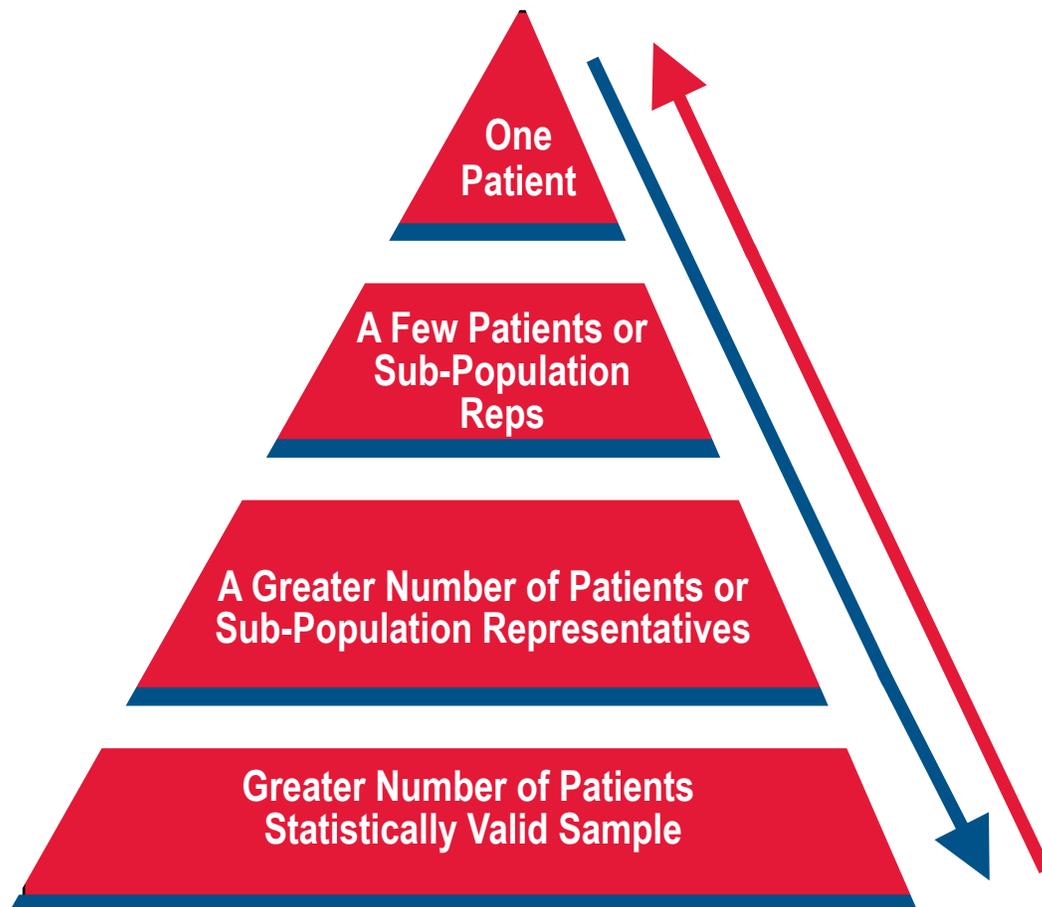
## Context Matters in Achieving Representativeness

One of the main reasons a standard definition of patient representativeness, applicable across all patient-engagement efforts, does not (yet) exist is that context matters. In other words, what a group initiating the interaction (the “sponsor”) is trying to accomplish affects the definition of patient representativeness for that effort.<sup>2</sup>

For example, what “good” patient representativeness looks like when the desired objective is to learn the patient perspective on how easy or difficult it is to follow a care regimen may vary greatly from what “good” patient representativeness looks like when the goal is to determine how patients with cancer define the value of a therapy. As illustrated by Figure 1 below, for some cases, engagement with only one individual patient may be sufficient to achieve representativeness (top of the pyramid), while other engagements may call for individuals from or representing a specific sub-population or numerous sub-populations, and still others (e.g., population-based questions) can require greater numbers of individual patients to represent an entire community or may require a statistically valid sample (bottom of the pyramid).

<sup>2</sup> Tobias Hainz & Daniel Strech (2014) “Which Public to Involve? More Reflection on Collective Agency and Sufficient Representativeness is Needed,” *The American Journal of Bioethics* 14:6, 31–33.

**Figure 1. Representativeness Pyramid**



## Achieving Patient Representativeness through a Process with Minimum Targets

Given the complexity of defining patient representativeness, using numerical measures (e.g., engaging 10 percent of the target population) alone to assess representativeness is typically not enough. Similarly, addressing patient representativeness is met via a checklist of specific requirements or a list of “dos” and “don’ts” is problematic because of the variability across types of interactions. There is simply no “one-size-fits-all” test for whether one has achieved “patient representativeness.”

Instead, addressing representativeness as a process involving a minimum target (or targets) emerged from the Roundtable discussion as the most viable solution. In this model, establishing “good” patient representativeness requires approaching it as an iterative process, using process measurements to assess how close one has gotten to the target measures.

### Patient Representativeness Roadmap and Rubric



The Patient Representativeness Roadmap and Rubric is intended to guide decision-making on representativeness for a given patient engagement activity. The Roadmap and Rubric consist of six guiding principles with examples of what “good” and “poor” processes look like. The six key principles are:

1. *Define* – Clearly define the objective(s) for each engagement effort.
2. *Understand* – Understand as much as possible about the full population and subpopulations and the challenges to reaching them.
3. *Specify* – Develop a description of the minimum target(s) for representativeness for the engagement activity.
4. *Plan* – Develop a plan to achieve the minimum target(s) defined.
5. *Evaluate* – Develop an evaluation plan to assess progress on achieving target(s) or make adjustments if they need to be adjusted based on new information.
6. *Document* – Record how patient representativeness was defined, targeted, achieved, and assessed.

#### **1. Define – Clearly define the objective(s) for each engagement effort.**

The objective, goal, or research question is critical to defining what “good” patient representativeness means for that engagement. Stakeholders should first clearly define their objective(s) for the engagement. The objective guides the entire endeavor from defining the most appropriate engagement method(s) and target patient population(s), as well as informing how to achieve (and how to measure up to) good patient representativeness. Poorly defined objectives can lead to wasted resources when work must be re-done due to use of the wrong method or target patient population (e.g., chosen too few patients with the wrong characteristics to achieve the objective).

The method(s) used to engage patients (e.g., focus groups, surveys, individual discussions, or patient preference studies) should also be considered when defining patient representativeness and a “representative sample” for that engagement activity. For example, conducting patient preference studies may require a greater number of patients to obtain a statistically valid, representative sample than a focus group can accommodate or requires.

## **2. Understand – Understand as much as possible about the full population and subpopulations and the challenges to reaching them.**

Importantly, prior to the engagement, it is important to understand as much about the total patient population of interest to avoid missing critical details (including inadvertently ignoring relevant smaller subpopulations) that can impact how to define a target population. Stakeholders should educate themselves as much as possible, from a variety of sources, about a patient population of interest and avoid assumptions.

Often, researchers and others refer to the case of “hard to reach” populations when they discuss engaging or recruiting subpopulations based on race, ethnicity, income, or geographic location. Often the challenge is not that these individuals are “hard to reach,” (noting that patients resent being referred to in this way), but that ineffective or inappropriate mechanisms for outreach have been employed, or there were no efforts at all. Still, identifying and reaching diverse and underserved populations are key concerns given that not being able to engage them limits representativeness, particularly when the objective is focused on issues specifically relevant to those populations. In some cases, those seeking to engage patients may not know that certain subpopulations exist. As mentioned above, while it may not be possible to identify and contact some patient populations in a specific effort, acknowledging the limitation and the need to address this gap in the future, is important. Ultimately, new ways to identify and reach more diverse and targeted patients are needed.

## **3. Specify – Develop a description of the minimum target(s) for representativeness for the engagement activity.**

Defining the optimal target population – or the patient population that the desired “representative sample” should represent – is key to achieving patient representativeness. Factors influencing the choice of a target population include:

- The total size of the patient population of interest, and the size of the (sub)population that would be impacted by a decision, involved in a topic, or otherwise be relevant.
- The goals and aspirations of the individuals comprising the patient population of interest.
- Characteristics of the individuals comprising the patient population of interest (e.g., age, gender, socioeconomic status, race, patient or caregiver, health literacy, disease state, genetic marker status, preferences, and goals).
- The degree of heterogeneity across the patient population of interest with regard to characteristic(s) of interest.
- Whether caregivers, parents, or other advocates for patients are included in the patient population of interest.

Those engaging with patients should consider all of the factors above to determine the appropriate target population(s) and define (along with engagement objectives) how many and which (i.e., with what combination of characteristics) patients to engage to achieve patient representativeness. In addition, setting the target population will also serve as a baseline to define “good” patient representativeness and to measure performance. For example, a patient population with a low degree of heterogeneity (i.e., variation in characteristic(s) of interest) may require fewer patient representatives to encompass, understand, and reflect the views and priorities of – and thereby achieve representativeness of – the entire patient population.

An important consideration in determining the target is distinguishing between what an individual patient provides (e.g., their personal experiences with disease and treatment) versus what a patient representative might provide (e.g., a patient advocate with who provides their experience, but also data on a range of patient views), both of which have high value. Again this is related to context and objective. If the engagement activity is early data gathering, individual patient experiences are a vital starting point. As data gathering continues, it will include a growing body of evidence from larger numbers of representative patients that will support and expand the information individuals have provided. (See Figure 1.)

#### **4. Plan – Develop a plan to achieve the minimum target(s) defined.**

For each patient engagement effort, clearly defining and developing a plan for achieving the minimum target(s) should be outlined prior to the engagement and with patient input. Stakeholders need to also consider the following engagement factors when developing a plan for achieving patient representativeness:

- Burden on patients (and ways to minimize that burden);
- How ready patients are to contribute in a meaningful way (i.e., “patient readiness”);
- Whether a single patient can be identified to represent a community;
- Power imbalances that might occur during the engagement (e.g., a committee of 20 physician specialists with one patient member) and ways to mitigate imbalances; and
- Responsibilities of the patient representative(s) as well as the patient’s perception of their responsibilities.<sup>3</sup>

Achieving patient representativeness can often prove difficult given practical limits on time, funds, and other resources, including public information. For example, in situations where little information (or only outdated information) about a patient population is available, including more patient perspectives becomes even more important, though they may be difficult to gather. Furthermore, the feasibility of reaching members of a patient population, and the willingness (or lack thereof) of those patients to engage, impact the ability to access and engage members of the target population, thus effecting the ability to achieve representativeness.

Given this reality, it is important that limits on feasibility and resources do not cause stakeholders to avoid trying to achieve patient representativeness altogether. Stakeholders should not “let the perfect be the enemy of the good,” but make every reasonable effort to accurately define patient representativeness for their engagement and to come as close as possible to achieving it.

#### **5. Evaluate – Develop an evaluation plan to assess progress on achieving target(s) or make adjustments based on new information.**

Any plan for achieving patient representativeness should include continual assessment and refinement. Such an iterative and evolving process allows for flexibility and integration of new information and learnings. As in the beginning, patients should be involved in the refining of any plans, definitions, or minimum targets throughout the entire engagement, and their input should be integrated into decision-making. Stakeholders should continue to ask questions, listen and learn, and refine plans to get as close to “optimal” patient representativeness as possible for that engagement (i.e., follow where patient input is leading). This is also represented in Figure 1. The arrows beside the pyramid depict bidirectional feedback to refine processes for patient representativeness (e.g., the blue arrow denotes a process begun by talking with one patient to build awareness of a broader patient community that leads to wider engagement).

<sup>3</sup> Kath Maguire & Nicky Britten (2017) “How can anybody be representative for those kind of people?” Forms of patient representation in health research, and why it is always contestable, *Social Science & Medicine* 183: 62-69.

## **6. Document – Record how patient representativeness was defined, targeted, achieved, and assessed.**

It is important that stakeholders document the processes and outcomes of defining a target(s) and creating achievement and assessment plans, recording their processes of defining, achieving, and assessing patient representativeness for each engagement. This will help in articulating their rationale and ensure processes are understandable to others. Documentation should include any limitations, missing data, challenges, or barriers anticipated or experienced (e.g., individuals or sub-groups that the stakeholder cannot reach). Stakeholders should focus on documenting those gaps and learnings that were not initially planned or expected. It is important that patients are engaged in this work and their perspectives are considered. The organization attempting to engage should try to document the challenges encountered, and efforts made to overcome or mitigate them. Stakeholders can utilize this process to not only identify unexpected gaps, but also to understand why they occurred. This does not need to be an overly extensive or onerous effort. It is simply good practice to document actions and rationale.

### ***Need for Training***

The Roundtable participants also discussed one aspect of representativeness where there is an important gap. A need exists for training all stakeholders on patient representativeness – both patients and those who engage them. This includes education to understand what patient representativeness means and how it can be achieved and assessed as a part of patient engagement, and training to provide skill sets needed by different stakeholders in patient engagement. For example, it may be necessary to establish training for patient readiness, including how a single patient can act effectively as a “patient representative” (i.e., representing a broader community versus speaking to their own experiences). In addition, participants identified a need to train people who are engaging with patients, because they need to know effective engagement methods, including the impact of patient representativeness, and how to define, achieve, assess, and document it in a transparent way.

## **Conclusion**

The NHC’s May 8, 2017 Roundtable brought together key stakeholders from across the health care ecosystem to discuss patient representativeness and reach consensus on considerations for defining, achieving, and assessing representativeness as part of patient engagement efforts. The Roundtable participants considered many issues related to patient representativeness, and this white paper captures the key principles from the discussion.

Participants strongly agreed that a single target for patient representativeness cannot fit every patient engagement situation. Instead, context, including the objective of the engagement, must influence how patient representativeness is defined for any engagement activity. Moreover, the variability of patient interactions requires that stakeholders address representativeness as a process with a minimum target, rather than a fixed standard.

This work represents an important first step in advancing the discussion and enhancing stakeholders’ ability to meet a high target of patient representativeness for each patient engagement activity. The NHC, along with other stakeholders, will continue to contribute to this discussion and develop tools to advance the understanding and achievement of patient representativeness in engagements across health care contexts, including in drug development, product review, and value assessment. While greater representativeness improves any engagement effort, the quality of the engagement interaction is often more important. A focus on the quantity and representativeness of patients involved must never detract from the quality of the interaction.

## Appendix A

### Patient Representativeness Roadmap and Rubric

*To guide decision-making on representativeness for each patient-engagement activity, establish the following, prior to initiation of engagement and with patient input:*

	Guiding Questions to Consider	Good Process	Poor Process
<b>1. Define – Clearly define the objective(s) for each engagement effort.</b>			
	<ul style="list-style-type: none"> <li>What is the objective(s) of the engagement activity?</li> <li>What information or learning is desired from the activity?</li> <li>Have patients been involved in crafting the objective?</li> </ul>	<ul style="list-style-type: none"> <li>Objective for engagement is clearly articulated with patient input and guidance.</li> <li>The process to define engagement objective is documented and transparent.</li> </ul>	<ul style="list-style-type: none"> <li>Objective for engagement is unclear or not articulated at all.</li> <li>Processes to define the objective are not documented or transparent.</li> <li>Effort appears to be a “fishing expedition” to gather data to support an activity that has already transpired.</li> </ul>
<b>2. Understand – Understand as much as possible about the full population and subpopulations and challenges to reaching them.</b>			
	<ul style="list-style-type: none"> <li>What is known about the full patient population of interest?</li> <li>What sources of information about this population are available?</li> <li>Are the sources outdated or inaccurate?</li> <li>Have discussions occurred with patient(s)/patient group to best understand the</li> </ul>	<ul style="list-style-type: none"> <li>All publicly available sources of information about the population are identified through literature review, opinions from specialists, and patient input.</li> <li>Patients are engaged in helping describe the full patient population, subgroups, and anticipated challenges and burdens.</li> <li>Issues with feasibility or</li> </ul>	<ul style="list-style-type: none"> <li>There is a poor understanding of the full and target populations.</li> <li>Sources of information on the full population were not tapped or were ignored.</li> <li>Patients were not consulted when trying to understand the full and target populations</li> <li>Feasibility for reaching the target population was not considered.</li> <li>Challenges were poorly understood and not considered.</li> </ul>

	<p>full population?</p> <ul style="list-style-type: none"> <li>• Is the target patient population for the engagement activity the full population or a subpopulation?</li> <li>• What is the degree of heterogeneity in the full or subpopulation?</li> <li>• Have you considered viewpoints from a diverse number of patient groups or patients? How will you balance perspectives?</li> <li>• Is the target population easily identifiable?</li> <li>• Are there any anticipated challenges to reaching the target population?</li> </ul>	<p>lack of resources to get to the target are considered.</p> <ul style="list-style-type: none"> <li>• The process to define the target population is documented and transparent.</li> </ul>	
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<p><b>3. Specify – Develop a description of the minimum target(s) for representativeness for the engagement activity.</b></p>			
	<ul style="list-style-type: none"> <li>• Has patient input been incorporated to define the minimum representativeness target(s)?</li> <li>• What is the minimum target(s) of patient representativeness for this interaction?</li> <li>• What are the target patient characteristics sought?</li> <li>• What are the target patient numbers sought?</li> <li>• Are the patients desired for</li> </ul>	<ul style="list-style-type: none"> <li>• Clearly defined minimum target(s) for patient representativeness are established including the specific patient characteristics sought.</li> <li>• Patients are ready to engage.</li> </ul>	<ul style="list-style-type: none"> <li>• No targets were established in terms of patient characteristics or numbers.</li> <li>• Targets were established but the rationale for them is unclear.</li> <li>• Processes are unclear.</li> </ul>

	the engagement ready to contribute in a meaningful way?		
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<b>4. Plan – Develop a plan to achieve the minimum target(s) defined.</b>			
	<ul style="list-style-type: none"> <li>• Have patients contributed to defining plans to achieve and assess patient representativeness target(s)?</li> <li>• Do the engagement plans articulate the patient responsibilities?</li> <li>• Are there power imbalances inherent in the plans? Are there ways to mitigate these?</li> <li>• What burdens to patient exist with this target? Are there plans to minimize burdens?</li> <li>• Are your plans defensible?</li> </ul>	<ul style="list-style-type: none"> <li>• The plan for achieving representativeness includes appropriate and feasible efforts not just those that are convenient.</li> <li>• Patient responsibilities are clearly articulated.</li> <li>• The plans and processes are transparently documented with rationale.</li> </ul>	<ul style="list-style-type: none"> <li>• There is no plan to meet representativeness targets.</li> <li>• Plans are poorly described or not feasible.</li> <li>• No rationale for plans are described.</li> </ul>

<b>5. Evaluate – Develop an evaluation plan to assess progress on achieving target(s) or if they need to be adjusted based on new information.</b>			
	<ul style="list-style-type: none"> <li>• Has a reasonable effort been made to achieve patient representativeness?</li> <li>• Have patient representativeness target(s) been reached (or as close as possible)?</li> <li>• How will target(s) be refined throughout the engagement effort?</li> <li>• At what points in the</li> </ul>	<ul style="list-style-type: none"> <li>• Every reasonable effort is made to achieve patient representativeness targets in the plan.</li> <li>• A plan is created to assess patient representativeness throughout the engagement.</li> <li>• As part of the assessment, plans to meet the target(s) are refined throughout the engagement effort.</li> </ul>	<ul style="list-style-type: none"> <li>• No assessment plan exists, no evaluation is conducted.</li> <li>• Targets are not met but it unclear why.</li> <li>• Challenges were encountered, but limitations and learnings are not documented or shared.</li> </ul>

	<p>engagement efforts is patient representativeness assessed? Is that often enough?</p> <ul style="list-style-type: none"> <li>• Are engagement plans flexible enough to incorporate new information throughout the project?</li> <li>• What is the rationale for what actions were or were not taken to ensure representativeness?</li> <li>• What insights are documented on barriers encountered?</li> </ul>	<ul style="list-style-type: none"> <li>• Issues and challenges are addressed as best possible and not avoided.</li> <li>• When target patient representativeness could not be achieved, there is clear documentation of limitations, challenges, and barriers.</li> <li>• All work is transparently documented to share learnings.</li> </ul>	
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<b>6. Document – Record how patient representativeness was defined, targeted, achieved, and assessed.</b>			
	<ul style="list-style-type: none"> <li>• Does complete documentation exist on the process and rationale for why decisions were made?</li> <li>• Have the plans considered limitations, missing data, challenges, and barriers, innovative techniques, and explained them in the documentation?</li> </ul>	<ul style="list-style-type: none"> <li>• All processes and decisions (including rationale) to create plans, revise plans are transparently documented.</li> <li>• Limitations, missing data, challenges, and barriers are documented and explained.</li> <li>• The documentation uses clear and easily understandable language.</li> <li>• Key learnings and best practices are being shared publically.</li> </ul>	<ul style="list-style-type: none"> <li>• Documentation does not exist or is incomplete, unclear, and/or not transparent.</li> <li>• Learnings are not shared.</li> </ul>

## Appendix B. Case Examples

The Patient Representativeness Roadmap and Rubric is intended to guide decision-making on representativeness for a given patient engagement activity. The Roadmap and Rubric consist of six guiding principles with examples of what “good” and “poor” processes look like.

The six key principles are:

1. *Define* – Clearly define the objective(s) for each engagement effort.
2. *Understand* – Understand as much as possible about the full population and subpopulations and challenges to reaching them.
3. *Specify* – Develop a description of the minimum target(s) for representativeness for the engagement activity.
4. *Plan* – Develop a plan to achieve the minimum target(s) defined.
5. *Evaluate* – Develop an evaluation plan to assess progress on achieving target(s) or if they need to be adjusted based on new information.
6. *Document* – Record how patient representativeness was defined, targeted, achieved, and assessed.

The following four case examples are organized to demonstrate alignment with each of the six key principles of the Roadmap and Rubric.

Key Principles	Case Study #1	Case Study #2	Case Study #3	Case Study #4
<p><b>1. <u>Define</u> engagement activity objective:</b></p>	<ul style="list-style-type: none"> <li>• A biopharmaceutical company wants to engage patients in <b>interviews</b> to understand the impact of a rare disease on patients’ lives.</li> <li>• The company has little experience with the disease or therapeutic area.</li> <li>• This is early-stage engagement, pre-clinical work.</li> </ul>	<ul style="list-style-type: none"> <li>• A biopharmaceutical company wants to engage patients through <b>a survey</b> to understand the impact of different disease symptoms and treatment side effects as they relate to treatment decision making.</li> <li>• This engagement is intended to augment other data obtained through clinical trials and literature review.</li> </ul>	<ul style="list-style-type: none"> <li>• A biopharmaceutical company wants to engage patients through <b>a survey</b> to understand the emerging needs of both people living with a disease and their partners.</li> </ul>	<ul style="list-style-type: none"> <li>• A patient advocacy organization wants to engage its members by developing a <b>leadership council</b> to understand patient perspectives on a variety of issues related to the organization’s disease focus.</li> </ul>

<p><b>2. <u>Understand the full population:</u></b></p>	<ul style="list-style-type: none"> <li>• There are only case reports.</li> <li>• The population is estimated to be approximately 50,000 children in the US.</li> <li>• Two small patient advocacy groups exist. Interviews were conducted with the lead person from each.</li> <li>• One of the patient groups has a publicly accessible blog. Qualitative data was reviewed collaboratively with the patient group.</li> <li>• A clinical specialist was identified by both patient groups as the leading expert.</li> <li>• A local patient, a child, and his family were recruited to be advisors.</li> <li>• It is difficult to have a complete understanding of the full population due to the nature of this rare disease. However, symptoms change over time.</li> <li>• It was recommended the researchers consider population fatigue, impact of the disease on the family and siblings, and difficulty in getting an accurate</li> </ul>	<ul style="list-style-type: none"> <li>• The patient population has known cognitive impairments, which necessitate specific approaches to get meaningful feedback.</li> <li>• Advocacy organization reach is limited to high-functioning and highly motivated patients/ caregivers.</li> <li>• Thus, outreach is needed beyond those patients involved in advocacy organizations to get a full picture of the population.</li> </ul>	<ul style="list-style-type: none"> <li>• The demographic profile of patients has changed over time and by geography, making multinational representation important.</li> <li>• The disease also covers a wide age range.</li> <li>• The survey was developed in collaboration with an external, multinational Steering Committee of patients/ representatives.</li> <li>• A preliminary phase of qualitative research was carried out with 24 patients across four countries to help understand the key areas of focus.</li> <li>• It was decided to concentrate on adults, so the survey was designed for patients 18 years and older.</li> </ul>	<ul style="list-style-type: none"> <li>• The disease of interest has many different forms.</li> <li>• The organization had the goal of engaging people that encompassed the variety of diagnoses and experiences.</li> <li>• Candidates for the Council were “scored” based on criteria created to highlight the array of perspectives ranging from one disease form to another, and to capture greatest likelihood of success in promoting the goals of the council.</li> <li>• After this initial research, discussion and considerable thought the organization arrived at the specific criteria needed.</li> </ul>
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	<p>diagnosis due to lack of clinicians' familiarity with the disease.</p> <ul style="list-style-type: none"> <li>The number or percent of undiagnosed cases is difficult to determine; impacts on minority and under-served populations are not well understood.</li> </ul>			
<p><b>3. Specify target (based on information learned from #2):</b></p>	<ul style="list-style-type: none"> <li>Recruit 10 child/parent dyads for interviews, to get patient and parent perspectives.</li> <li>Be sure to include children with a range of ages from 2 to 12 years, to capture changes over time.</li> <li>Structure interviews to be by telephone (to capture geographic range) and for no more than one half-hour with the child due to fatigue from the illness. Parent interviews can be longer. Multiple interviews with the child, in half-hour, increments may be needed if acceptable to patients and families.</li> <li>Strive for racial and cultural diversity as much as possible in recruitment with the understanding this may be limited.</li> </ul>	<ul style="list-style-type: none"> <li>Recruit patients through a partnership with a community clinic group.</li> <li>The clinic group covers a large geographically and socially-economically diverse, real-world patient population.</li> <li>Strive for racial and cultural diversity as much as possible in recruitment with the understanding this may be limited at this point.</li> </ul>	<ul style="list-style-type: none"> <li>An in-depth quantitative survey was carried out in nine countries.</li> <li>Patient respondents were sought worldwide.</li> <li>A plan was created to gather diversity by geography, disease history, sexual orientation, gender, co-morbidities and age.</li> </ul>	<ul style="list-style-type: none"> <li>Twelve Council members were identified with a pre-specified range of diversity in perspectives (to encompass different forms of the disease), commitment to the disease community and the likelihood of a successful, robust role on the council.</li> </ul>

<p>4. <b>Plan for achieving targets:</b></p>	<ul style="list-style-type: none"> <li>• A partnership is formed with both patient groups and the leading clinical expert to recruit the patient/parent dyads from both the academic setting, and through both patient groups' websites.</li> <li>• A plan is put into place to capture target characteristics.</li> </ul>	<ul style="list-style-type: none"> <li>• The survey was kept purposely short, to be completed without the assistance of clinic staff.</li> <li>• All patients with the condition and their caregivers were asked to complete the survey with no exclusions.</li> <li>• The survey was co-developed with advocacy partners who helped "test" the instrument with patients to refine test questions, language, length and format. This confirmed that to reach the most diverse patient population the final survey needed to be simple, short and use parallel question formats to meet the cognitive needs of the patient population (e.g., a caregiver questionnaire also developed).</li> </ul>	<ul style="list-style-type: none"> <li>• Participants were recruited in multiple ways, including: working with the Steering Committee members (who supported recruitment via their own connections and networks), collaborating with charities, patient support organizations, non-governmental organizations, disease-related online communities, and promoting the research via social media.</li> </ul>	<ul style="list-style-type: none"> <li>• The twelve top-scoring candidates were placed in a matrix that noted how each person's qualities and characteristics matched up with the key domains.</li> <li>• The organization examined how well the domains were represented by the top-scoring candidates, and then iteratively added and removed candidates until we achieved the desired coverage across the pre-specified criteria was achieved.</li> </ul>
<p>5. <b>Evaluate progress:</b></p>	<ul style="list-style-type: none"> <li>• It is expected that recruitment will be completed in a one-month period. Interviews should be completed within two weeks of recruitment.</li> </ul>	<ul style="list-style-type: none"> <li>• Due to significant work at the outset to define the research goal, identify limitations of different research methods, and gather input from both patient organizations and individual patients no changes were required.</li> </ul>	<ul style="list-style-type: none"> <li>• When it was noted that the response rate was greater in some countries than others, efforts were made to increase outreach to the patient groups and online support groups in those countries.</li> </ul>	<ul style="list-style-type: none"> <li>• Duplicates (meaning two candidates with identical domain profiles) were re-evaluated for relative strengths and weaknesses. One of was tentatively removed and placed on the standby list.</li> </ul>

	<ul style="list-style-type: none"> <li>• Each week, recruitment and completion status were evaluated. Barriers and challenges encountered were minimal and documented.</li> <li>• No change to the plan was required.</li> </ul>			<ul style="list-style-type: none"> <li>• As gaps were filled, additional duplicates were created; and as duplicates were removed, new gaps opened. The exercise took many rounds before landing on the best slate possible per the criteria.</li> </ul>
<p><b>6. <u>Document</u> each step:</b></p>	<ul style="list-style-type: none"> <li>• All steps and decisions were documented with rationale for each decision.</li> </ul>	<ul style="list-style-type: none"> <li>• All steps and decisions were documented with rationale for each decision.</li> </ul>	<ul style="list-style-type: none"> <li>• All steps and decisions were documented in a report with rationale.</li> <li>• Survey results were posted.</li> <li>• The results have been presented at medical conferences. The data is available on a public website designed to be a quality of life resource for patients.</li> </ul>	<ul style="list-style-type: none"> <li>• All steps and decisions were documented throughout the process with rationale for each decision.</li> <li>• The criteria for selection were publicly announced prior to the call for nominations.</li> </ul>