U.S. FOOD & DRUG ADMINISTRATION

PATIENT-FOCUSED DRUG DEVELOPMENT
GUIDANCE PUBLIC WORKSHOP

Methods to Identify What is Important to Patients & Select, Develop or Modify Fit-for-Purpose Clinical Outcomes Assessments

Workshop Date: October 15-16, 2018

Attachment to Discussion Documents for Patient-Focused Drug Development Public Workshop on Guidance 2 and 3:

METHODS TO IDENTIFY WHAT IS IMPORTANT TO PATIENTS AND SELECT, DEVELOP OR MODIFY FIT-FOR-PURPOSE CLINICAL OUTCOME ASSESSMENTS

LEGISLATION BACKGROUND (APPENDIX 1) and GLOSSARY

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APPENDIX 1. Legislation Background

A. Overview of the Series of FDA Guidance for Enhancing the Incorporation of the Patient's Voice in Drug[1] Development and Regulatory Decision Making

This series of guidance documents builds on learnings from the disease-specific PFDD meetings[2] that FDA conducted under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) as an enhancement of the Agency's implementation of a more structured approach to ***benefit-risk assessment***.[3] The PFDD meetings conducted to date have given FDA a deeper appreciation for the expertise that patients and caregivers can bring to the process and the value of incorporating their voice. This series of guidance documents is intended to facilitate the advancement and use of systematic approaches to collect and use robust and meaningful patient and caregiver input that can better inform medical product development and regulatory decision making.

Focusing on practical approaches and methods, this series will inform stakeholders of FDA's current thinking about methods that could be used bridge from important early-stage efforts to gain patients' narrative perspectives on the clinical context (e.g., meetings with patients), to development and use of ***methodologically-sound*** data collection tools in clinical trials. These guidance documents will also address Agency expectations regarding what sort of analyses might be conducted as part of this work and what sort of documents might be produced, and when appropriate, submitted to FDA.

The topics and questions that each guidance document will address are described below.

Guidance 1: Whom do you get input from, and why? How do you collect the information?

Guidance 1 will discuss sampling methods that could be used when planning to collect patient input. It will also provide a general overview of the relationship between potential research question(s) and method(s) when deciding from whom to get input (including defining the target population and development of the sampling strategy).

Guidance 2: What do you ask, and why? How do you ask non-leading questions that are well-understood by a wide range of patients and others?

Guidance 2 will discuss methods for eliciting information from individuals identified in Guidance 1, gathering information about what aspects of symptoms, impacts of their disease, and other issues are important to patients. It will discuss best practices in how to do qualitative research including conducting interviews, development of interview guides, selection of types of survey questions, and considerations for collecting demographics and survey information. It will also discuss survey methods and qualitative research topics to help avoid misleading

[1] For the purposes of this document, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.
[2] https://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/ucm347317.htm
[3] https://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/ucm326192.htm

results such as inadvertently priming patients in ways that can lead to results that poorly represent what is important to patients.

Guidance 3: How do you decide what to measure in a clinical trial and select or develop ***fit-for-purpose clinical outcome assessments (COAs)***[4]?

Guidance 3 will address refining the list of important impacts and concepts from patients to develop potential study instruments. Given that not everything identified as important by patients, caregivers, and clinicians can demonstrate change in a specific treatment trial or is measurable, how will you select what to measure in a medical product development program to show clinical benefit? How will you identify or develop fit-for-purpose COAs to assess outcomes of importance to patients?

Guidance 4: Once you have a COA measurement tool and a way to collect data using it, what is an appropriate clinical trial endpoint?

Guidance 4 will address topics related to COA-related endpoint development and interpretation, including topics related to instrument administration and meaningful within-patient score changes.

B. Patient Experience Data

Patient experience data. Patient experience data is defined in Title III, Section 3002(b) of the 21st Century Cures Act as data intended to provide information about impact (including physical and psychosocial impacts) of a disease or condition, or a related therapy or clinical investigation. Patient experience data can be interpreted as including (but is not limited to) the experiences, perspectives, needs and priorities of patients related to: 1) the symptoms of their condition and its natural history; 2) the impact of the conditions on their functioning and quality of life; 3) their experience with treatments; 4) input on which outcomes are important to them; 5) patient preferences for outcomes and treatments; and 6) the relative importance of any issue as defined by patients. For additional details on patient experience data, please refer to **Guidance 1**.[5] The following subsections will discuss patient experience data related to burden of disease and treatment and benefits and risks in management of the patient's disease.

1. Burden of Disease and Treatment

A disease or condition (hereon referred to as disease) generally has:

- a core set of distinctive signs and symptoms;
- affects specific groups of people; and
- follows a characteristic course.

[4] Words or phrases found in the Glossary appear in bold italics at first mention within the body of text in this document.
[5] *Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders: Patient-Focused Drug Development: Collecting Comprehensive and Representative Input*

Diseases can be complex and have various consequences for patients which can affect its measurement (Jones, Podolsky & Greene, 2012). For regulatory decision-making, there is a need to understand the determinants of disease and treatment's impact in patients' lives to ensure that the most meaningful outcomes are being measured in clinical trials.

Burden of disease and treatment. The burden of disease can be viewed as the impact of disease on patients' lives, from the onset of disease to the outcome of interest (e.g., disease severity, disease improvement (recovery), or death). It may involve assessing the potential of treatment (i.e., medical products) to change the disease course and future outcomes. For regulatory purposes, FDA will view the burden of disease and treatment as the patient's experience with the disease and treatment from the patient's perspective.

To evaluate the burden of disease and treatment, information should be gathered about how diseases and treatments affect patients to provide a complete picture of the patient experience (National Collaborating Centre for Infectious Diseases, 2016). Refer to **Section II** of the Guidance 2 discussion document for details on the different methods on how to gather this information.

Important aspects of burden that can characterize the patient's experience, include but are not limited to:

- the symptoms of patients' disease and its natural history;
- the impact of the disease on their functioning and quality of life;
- patients' experience with treatments;
- patient input on which outcomes are important to them;
- patient preferences for outcomes and treatments; and
- the relative importance of any issue as defined by patients.

2. Benefits and Risks in Management of the Patient's Disease

Patient Engagement in Regulatory Benefit-Risk Assessments. To fully characterize patients' experience with disease and treatment, it is important to understand how patients manage their disease and their perspective on the benefits and risks in disease management.

Within medical product development, evidence should support that the benefits of using a medical product for its intended use outweigh the potential risks. Weighing benefits and risks of medical products requires the assessment of scientific evidence but also patient judgments about the relative importance of benefits and risks.

To evaluate the patient's perspective on benefits and risks in their disease management, information should be gathered about what benefits or risks of are of interest to patients, including degree of tolerability of adverse events to integrate patient concerns into regulatory benefit-risk evaluations and complements the totality of impacts of disease and treatment. Refer to **Section II of the Guidance 2 discussion document** for details on different methods on how to gather this information.

GLOSSARY

As appropriate, definitions from existing federal resources (e.g., BEST (Biomarkers, Endpoints, and Other Tools) Resource) have been incorporated into this glossary. External resources were also utilized to define terms and have been cited.

1. **Ability to detect change:** Evidence that a COA can identify differences in scores over time in individuals or groups who have changed with respect to the measurement concept.

2. **Assent:** A child's affirmative agreement to participate in research capture through verbal and written acknowledgement. Mere failure to object should not, absent affirmative agreement, be construed as assent.

3. **Benefit:** Benefits are the favorable effects of a medical product. Types of benefit include clinical benefit *(see definition below)*. Benefits may also include important characteristics of the medical product, such as convenience (e.g., a more convenient dosing regimen or route of administration) that may lead to improved patient compliance, or benefits that affect those other than the patient. (*Source: International Conference on Harmonisation (ICH) Guidelines – Efficacy M4E(R2); ANSI/AAMI/ ISO 14971: 2007/(R)2016 Medical devices—Application of risk management to medical devices*)

4. **Benefit-risk assessment:** Evaluation of the demonstrated benefits and risks of a medical product and making a judgment as to whether the expected benefits outweigh the potential risks associated with its expected use.

5. **Caregiver:** 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, and who understands the patient's health-related needs. This person may or may not have decision-making authority for the patient and is not the patient's healthcare provider.

6. **Ceiling effect:** A ceiling effect can occur at the item level or at the scale score level. An item level ceiling effect is observed when a large concentration of participants endorses the highest response category within an item. A scale score level ceiling effect is observed when a large concentration of participants' scores fall at or near the upper limit of the scale score of the instrument. Either situation may occur when the upper extreme of the concept(s) assessed by item response categories or by the scale score of the instrument does not sufficiently match the level of the upper extreme of the target patient population.

7. **Clinical benefit:** A positive clinically meaningful effect of an intervention, i.e., a positive effect on how an individual feels, functions, or survives. *(Source: BEST (Biomarkers, Endpoints and Other Tools) Resource)*

8. **Clinical outcome:** An outcome that describes or reflects how an individual feels, functions or survives. *(Source: BEST (Biomarkers, Endpoints and Other Tools) Resource)*

9. **Clinical outcome assessment (COA):** Assessment of a clinical outcome can be made through report by a clinician, a patient, a non-clinician observer or through a performance-

based assessment. Types of COAs include: patient-reported outcome (PRO) measures, clinician-reported outcome (ClinRO) measures, observer-reported outcome (ObsRO) measures, and performance outcome (PerfO) measures. *(Source: BEST (Biomarkers, Endpoints and Other Tools) Resource)*

10. **Clinician-reported outcome (ClinRO):** A measurement based on a report that comes from a trained health-care professional after observation of a patient's health condition. Most ClinRO measures involve a clinical judgment or interpretation of the observable signs, behaviors, or other manifestations related to a disease or condition. ClinRO measures cannot directly assess symptoms that are known only to the patient (e.g., pain intensity). *(Source: BEST (Biomarkers, Endpoints and Other Tools) Resource)*

11. **Cognitive interviewing:** A qualitative research process used to determine whether concepts and items are understood by respondents in the same way that instrument developers intend. Cognitive interviews involve incorporating follow-up questions in a field test interview to gain a better understanding of how respondents interpret questions/tasks asked of them. In this method, respondents are often asked to think aloud and describe their thought processes as they answer the instrument questions. Respondents should reflect the target population who will be responding to the instrument during the study.

12. **Concept (also referred to as concept of interest):** In a regulatory context, the concept is the aspect of an individual's clinical, biological, physical, or functional state, or experience that the assessment is intended to capture (or reflect). *(Source: BEST (Biomarkers, Endpoints and Other Tools) Resource)*

13. **Concept elicitation:** A process or method to collect a holistic set of relevant concepts (i.e. disease and treatment symptoms and associated impacts) that are important to patients from relevant stakeholders (e.g., patients, experts, caregivers).

14. **Concept saturation:** When interviewing patients, caregivers, and/or experts, the point when no new relevant or important information emerges and collecting additional data will not add to the understanding of how patients perceive the concept of interest and the items in a questionnaire.

15. **Conceptual framework:** An explicit description or a diagram for an instrument showing the relationships between items (i.e., questions/tasks included in the instrument), domains (sub-concepts), and concepts measured and the scores produced by a COA. The conceptual framework of a COA evolves over the course of instrument development as empiric evidence is gathered to support item grouping and scores.

16. **Construct validity:** Evidence that relationships among items, domains, and concepts conform to a priori hypotheses concerning logical relationships that should exist with other measures or characteristics of patients and patient groups.

17. **Content validity:** Evidence from qualitative research demonstrating that the instrument measures the concept of interest including evidence that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept,

population, and use. Testing other measurement properties will not replace or rectify problems with content validity.

18. **Context of use:** A statement that fully and clearly describes the way the medical product development tool is to be used and the medical product development-related purpose of the use. *(Source: BEST (Biomarkers, Endpoints and Other Tools) Resource)*

19. **Criterion validity:** The extent to which the scores of a COA are related to a known gold standard measure of the same concept. For most COAs, criterion validity cannot be measured because there is no gold standard.

20. **Data analysis plan:** A roadmap for how the data will be organized and analyzed and how results will be presented. A data analysis plan should be established when planning a research study (i.e., before data collection begins). Among other things, the data analysis plan should describe: (a) the data to be collected; (b) the analyses to be conducted to address the research objectives, including assumptions required by said analyses; (c) data cleaning and management procedures; (d) data transformations, if applicable; and (e) how the study results will be presented (e.g., graphs, tables).

21. **Data management plan (DMP):** A written document that describes the data you expect to acquire or generate during the course of your research study; how you intend to manage, describe, analyze, and store said data; and what mechanisms you will use at the end of your study to preserve and share your data. (*Source: Stanford University Libraries n.d.(b)*)

22. **Disease burden:** The impacts, direct and indirect, of the patient's health condition that has a negative effect on his or her health, functioning, and overall well-being. Disease burden includes (but is not limited to): the physical and physiologic impacts of the disease and its symptoms; co-morbidities; emotional and psychological effects of the disease, its management, or prognosis; social impacts; effects on relationships; impacts on the patient's ability to care for self and others; time and financial impacts of the disease and its management; and considerations on the impacts on the patient's family.

23. **Domain:** A subconcept represented by a score of an instrument that measures a larger concept comprised of multiple domains. For example, psychological function is the larger concept containing the domains subdivided into items describing emotional function and cognitive function

24. **Endpoint:** A precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question. A precise definition of an endpoint typically specifies the type of assessments made, the timing of those assessments, the assessment tools used, and possibly other details, as applicable, such as how multiple assessments within an individual are to be combined. *(Source: BEST (Biomarkers, Endpoints and Other Tools) Resource)*

25. **Fit-for-purpose:** A conclusion that the level of validation associated with a tool is sufficient to support its context of use. (*Source: BEST (Biomarkers, Endpoints and Other Tools) Resource*)

26. **Floor effect:** A floor effect can occur at the item level or at the scale score level. An item level floor effect is observed when a large concentration of participants endorses the lowest response category within an item. A scale score level floor effect is observed when a large concentration of participants' scores fall at or near the lower limit of the scale score of the instrument. Either situation may occur when the lower extreme of the concept(s) assessed by item response categories or by the scale score of the instrument does not sufficiently match the level of the lower extreme of the target patient population.

27. **Generalizability:** The extent to which study findings can be reliably extended to the target population of interest.

28. **Instrument or tool:** An assessment system comprising three essential components: 1) materials for measurement; 2) an assay for obtaining the measurement; and 3) method and/or criteria for interpreting those measurements. *(Source: BEST (Biomarkers, Endpoints and Other Tools) Resource)*

29. **Intended use:** The specific clinical circumstance or purpose for which a medical product or test is being developed. In the regulatory context, "intended use" refers to the objective intent of the persons legally responsible for the labeling of medical products. *(Source: BEST (Biomarkers, Endpoints and Other Tools) Resource)*

30. **Item:** An individual question, statement, or task (and its standardized response options) that is evaluated or performed by the patient to address a particular concept.

31. **Item tracking matrix:** A record of the development (e.g., additions, deletions, modifications, and the reasons for the changes) of items or tasks used in an instrument.

32. **Health literacy:** The degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions. (*Source: U.S. Department of Health and Human Services Quick Guide to Health Literacy)* Health literacy also includes numeracy skills—such as calculating cholesterol and blood sugar levels, measuring medication doses, and understanding nutrition labels—and knowledge of health topics.

33. **Informed Consent:** The act of participants providing both verbal and written agreement to participate in a research study. In order to facilitate the informed consent process, potential participants must be provided with adequate information regarding the research study in an understandable way that permits them to make an informed and voluntary decision about whether or not to participate. The amount of information and the manner of presentation will vary depending on the complexity and risk involved in the research study. Informed consent is an ongoing educational interaction between the investigator and the research participant that continues throughout the study. The requirement for informed consent is one of these central protections defined by the:

- Department of Health & Human Services (HHS) regulations at 45 CFR part 46
- Food and Drug Administration (FDA) regulations at 21 CFR part 50

34. **Labeling claim:** A statement of clinical benefit. A claim can appear in any section of a medical product's FDA-approved labeling or in advertising and promotional labeling of prescription drugs, biologics, and devices.

35. **Literacy:** A person's ability to read, write, speak, and compute and solve problems at levels necessary to: (a) function on the job and in society; (b) achieve one's goals; and (c) develop one's knowledge and potential. (*Source: U.S. Department of Health and Human Services Quick Guide to Health Literacy*)

36. **Measurement properties:** All the attributes relevant to the application of a COA including the content validity, construct validity, reliability, and ability to detect change. These attributes are specific to the measurement application and cannot be assumed to be relevant to all measurement situations, purposes, populations, or settings in which the instrument is used.

37. **Methodologically sound:** Assurance that the methods and processes used to obtain and analyze patient experience data are rigorous, robust, and adhere to scientifically established principles and best practices for method development or implementation. Evidence generated by methodologically sound methods and processes increases confidence that the results can be trusted, interpreted, and support the intended regulatory uses.

38. **Mixed methods research:** Research that uses both qualitative and quantitative research methods. See definitions for qualitative and quantitative research methods.

39. **Observer-reported outcome (ObsRO):** A measurement based on a report of observable signs, events or behaviors related to a patient's health condition by someone other than that patient or a health professional. Generally, ObsROs are reported by a parent, caregiver, or someone who observes the patient in daily life and are particularly useful for patients who cannot report for themselves (e.g., infants or individuals who are cognitively impaired). An ObsRO measure does not include medical judgement or interpretation. *(Source: BEST (Biomarkers, Endpoints and Other Tools) Resource)*

40. **Patient:** Any individual with or at risk of a specific health condition, whether or not he or she currently receives any therapy to prevent or treat that condition. Patients are the individuals who directly experience the benefits and harms associated with medical products.

41. **Patient advocate:** An individual or group of individuals, who may or may not be part of the target patient population, who has a role in promoting an interest or cause to influence policy with respect to patients' health or healthcare.

42. **Patient-centered:** See ***patient-focused***

43. **Patient-centered outcome:** 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. (*Source: ISPOR Plenary*, Patrick 2013)

44. Patient engagement: Activities that involve patient stakeholders sharing their experiences, perspectives, needs, and priorities that help inform FDA's public health mission. Such activities may include (but are not limited to): testimony at Advisory Committee meetings, submission to regulations.gov public docket; meetings attended by patients, FDA, and other stakeholders; other correspondence with FDA; interactions through social media; and interactions with or information from patient representatives or patient advocates.

45. Patient experience data: Defined in Title III, Section 3001 of the 21st Century Cures Act of 2016, as amended by section 605 of the Food and Drug Administration Reauthorization Act (FDARA) of 2017,[6] and includes data that are collected by any persons and are intended to provide information about patients' experiences with a disease or condition. Patient experience data can be interpreted as information that captures patients' experiences, perspectives, needs, and priorities related to (but not limited to): 1) the symptoms of their condition and its natural history; 2) the impact of the conditions on their functioning and quality of life; 3) their experience with treatments; 4) input on which outcomes are important to them; 5) patient preferences for outcomes and treatments; and 6) the relative importance of any issue as defined by patients.

46. Patient-focused (also referred to as ***patient-centered*****):** Ensuring that patients' experiences, perspectives, needs, and priorities are meaningfully incorporated into decisions and activities related to their health and well-being.

47. Patient-focused drug development (PFDD) (also referred to as ***patient-focused medical product development*****:** A systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into the development and evaluation of medical products throughout the medical product life cycle.

48. Patient input: Information that captures patients' experiences, perspectives, needs, and priorities. See *Patient Experience Data.*

49. Patient partner: An individual patient, caregiver or patient advocacy group that engages other stakeholders to ensure the patients' wants, needs and preferences are represented in activities related to medical product development and evaluation. (*Source:* Wilson *et al*, 2018)

50. Patient perspective: A type of patient experience data that specifically relates to patients' attitudes or points of view about their condition or its management. Patient perspectives may

[6] "PATIENT EXPERIENCE DATA.—For purposes of this section, the term 'patient experience data' includes data 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 (including physical and psychosocial impacts) 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." This definition is found in section 569C(c) of the FD&C Act (codified at 21 U.S.C. § 360bbb–8c), and is referred to in section 3002 of the 21st Century Cures Act, which directed FDA to issue certain guidance documents regarding the collection of patient experience data, see section 3002(b).

include (but are not limited to): perceptions, goals, priorities, concerns, opinions, and preferences.

51. **Patient preference:** A statement of the relative desirability or acceptability to patients of specified alternatives or choice among outcomes or other attributes that differ among alternative health interventions. *(Source: FDA Guidance on PPI for medical devices)*

52. **Patient-reported outcome (PRO): A** measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a 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 response. Symptoms or other unobservable concepts known only to the patient (e.g., pain severity or nausea) can only be measured by PRO measures. PROs can also assess the patient perspective on functioning or activities that may also be observable by others. *(Source: BEST (Biomarkers, Endpoints and Other Tools) Resource)*

53. **Patient representative:** An individual, who may or may not be part of the target population, who has direct experience with a disease or condition (e.g., a patient or caregiver) and can provide information about a patient's experience with the disease or condition.

54. **Performance outcome (PerfO):** A measurement based on a standardized task performed by a patient that is administered and evaluated by an appropriately trained individual or is independently completed.

55. **Qualitative research methods:** Methods associated with the gathering, analysis, interpretation, and presentation of narrative information (e.g., spoken or written accounts of experiences, observations, and events). Qualitative research methods may also include direct observations (e.g., non-verbal communication and behaviors).

56. **Quantitative research methods:** Methods associated with the gathering, analysis, interpretation, and presentation of numerical information.

57. **Recall period:** The period of time patients, caregivers, or clinicians are asked to consider in responding to a COA item or task. Recall can be momentary (real time) or retrospective of varying lengths.

58. **Reliability:** The ability of a COA to yield consistent, reproducible estimates of true treatment effect.

59. **Representativeness:** Confidence that a sample from which evidence is generated is sufficiently similar to the intended population. In the context of patient experience data, representativeness includes the extent to which the elicited experiences, perspectives, needs, and priorities of the sample are sufficiently similar to those of the intended patient population.

60. Research protocol: A document that describes the background, rationale, objectives, design, methodology, statistical considerations, and organization of a clinical research project. (*Source: UCSF Clinical Research Resource HUB*) A research protocol guides the study and associated data collection and analysis in a productive and standardized manner.

61. Response scale: The system of numbers or verbal anchors by which a value or score is derived for an item. Examples include Likert scales, rating scales, visual analog scale (VAS).

62. Risk: Risks are adverse events and other unfavorable effects associated with a medical product. Risks include drug interactions, risks identified in the non-clinical data, risks to those other than the patient (e.g., fetus, those preparing and administering the medical product), and risks based on pharmacologic class or current knowledge of the product. Factors such as potential misuse, abuse, or diversion of the product may also be considered. (*Source: International Conference on Harmonisation Guidelines – Efficacy M4E(R2), ANSI/AAMI/ ISO 14971: 2007/(R)2016 Medical devices— Application of risk management to medical devices)*

63. Risk tolerance: The degree to which a patient would accept increased probability or severity of a harm in exchange for a specific expected benefit. *(Source: Medical Device Innovation Consortium (MDIC) Patient Centered Benefit-Risk Project Report)*

64. Science of patient input: Methods and approaches of systematically obtaining, analyzing, and using information that captures patients' experiences, perspectives, needs, and priorities in support of the development and evaluation of medical products.

65. Score: A number derived from a patient's, caregiver's, or clinician's response to items or tasks in an instrument. A score is computed based on a prespecified, appropriate scoring algorithm and is subsequently used in statistical analyses of clinical trial results. Scores can be computed for individual items, domains, or concepts, or as a summary of items, domains, or concepts.

66. Scoring algorithm: A set of pre-specified rules to assign numerical value or values to quantify the responses to the instrument. A scoring algorithm may create a single score from a single item or multiple items (e.g., domain score).

67. Sign: Any objective evidence of a disease, health condition, or treatment-related effect. Signs are usually observed and interpreted by the clinician but may be noticed and reported by the patient.

68. Social Media: Web-based tools that are used for computer-mediated communication. Social media may include but is not limited to: (1) blogs, (2) microblogs, (3) social networking sites, (4) professional networking sites, (5) thematic networking sites, (6) wikis, (7) mashups, (8) collaborative filtering sites, (9) media sharing sites, and others. (*Source: Grajales III et al. 2014*)

69. Subgroup: A subset of the study population or study sample defined by specific baseline characteristics. For example, demographic subgroups are commonly defined by subject sex,

race, and age.

70. **Symptom:** Any subjective evidence of a disease, health condition, or treatment-related effect that can be noticed and known only by the patient.

71. **Target population** (also referred to as the *target patient population*, the *underlying population*, or *intended population*)**:** The group of individuals (patients) about whom one wishes to make an inference.

72. **Target product profile (TPP):** A clinical development program summary in the context of labeling goals where specific types of evidence (e.g., clinical trials or other sources of data) are linked to the targeted labeling claims or concepts.

73. **Task:** See ***item***

74. **Treatment burden:** The impacts of a specific treatment or treatment regimen that have a negative effect on the patient's health, functioning, or overall well-being. Treatment burden includes (but is not limited to): side effects, discomfort, uncertainty about treatment outcomes, dosing and route of administration, requirements, and financial impacts.

75. **Treatment effect:** The amount of change in a disease/condition, symptom, or function that results from a medical intervention (as compared to not receiving the intervention or receiving a different intervention).

76. **Treatment outcome:** The benefits or harms to a patient who receives an intervention; the impact on a patient's health, function, or well-being—or on a clinical indicator thereof—that is assumed to result from an intervention. *(Source: Patient-Centered Outcomes Research Institute (PCORI) Methodology Report)*

77. **Usability testing:** A formal evaluation with documentation of respondents' abilities to use the instrument, as well as comprehend, retain, and accurately follow instructions.

78. **User acceptance testing (UAT):** One aspect of an extensive system/ software validation process designed to determine whether the software complies with the written system specification or user requirements document. It is not intended solely to determine if respondents like or can use the system.

79. **Validation:** A process to establish that the performance of a test, tool, or instrument is acceptable for its intended purpose. Elements of validation include but are not limited to the following: construct validation, content validation, criterion validation, analytical validation, clinical validation.