



U.S. Food and Drug Administration

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**Measurement in Clinical Trials: Review and Qualification of  
Clinical Outcome Assessments; Public Workshop  
October 19, 2011—White Oak, MD**

## **Glossary**

NOTE: This terminology is for purposes of aiding clear discussion at this workshop. It is not meant to be all encompassing or necessarily precisely applicable in regulatory discussions outside of this workshop.

**Assessment (measure)** — An evaluation of some aspect of a patient that results in a recorded datum.

**Biomarker** — A patient characteristic that is measured as an indicator of biologic processes; normal, pathogenic, or response to a therapeutic intervention. Patient characteristics that are classified as biomarkers are those that are not significantly influenced by rater judgment or patient motivation and effort (e.g., not a measure of a patient's volitional performance of some defined procedure). Measurements that can (and therefore, should) have a sufficiently well defined procedure for measurement so that minor aspects of rater or technician involvement have no impact on the measurement are included within the category of biomarkers. Biomarkers are not *psychomodulated* measures.

**Clinician-reported outcome (ClinRO) assessment** — An assessment that is determined by an observer with some recognized professional training that is relevant to the measurement being made.

**Concept** — The *thing* being directly measured by an assessment. Assessments that are categorized as *direct* are evaluating a concept that is a meaningful aspect of how a patient *feels* or *functions*. Assessments that are categorized as *indirect* are evaluating a concept that is not itself a meaningful aspect of how a patient *feels* or *functions*. For indirect assessments there will also be an intended ultimate-concept that is meaningful, and which is proposed as related to the indirect concept.

**Context of Use** — A complete and precise statement of what circumstances are appropriate for use of the outcome assessment, and how they are applied in the drug development and approval process.

**Direct assessment (of treatment benefit)** — A measure that is directly evaluating a meaningful aspect (the intended *concept*) of how a patient feels or functions. Survival is also a direct assessment of treatment benefit.

**Drug** — For purposes of this discussion the term drug includes both human drugs and human biological products.

**Drug development tool (DDT)** — a method (and associated materials) that aids drug development. DDTs include, but are not limited to, biomarkers and clinical trial outcome assessments. DDTs suitable for the CDER DDT *Qualification* process are a subset of all types of DDTs, and should be intended for potential use, over time, in multiple drug development programs. Some DDTs used as clinical trial outcome assessments may sometimes be called an *instrument*. The term “instrument”, or “tool”, refers to the means to capture data plus all the information and documentation that support its use within the intended context of use.

**Effectiveness** — An essential component of the basis for marketing approval of a drug; drugs must be safe and effective to justify approval. Within usage by FDA according to statute and regulations, effectiveness and efficacy are synonymous. Effectiveness is defined as a benefit to

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the patient in how they feel, function or survive due to treatment with the drug. Effectiveness can be demonstrated with assessments that are categorized as either direct or indirect when those assessments are appropriately supported. Note that *treatment benefit* is a broader term, and includes a comparative safety type of benefit.

**Endpoint** — The way an assessment will be used as a study result and statistically compared among treatment groups to assess the effect of treatment. Endpoints are often named by the assessment measured, but a complete statement of the endpoint should include a full description of what data are collected, and how they are analyzed to support a specific study objective.

**Feels** — A patient's physical sensation or perceived mental state. A patient may feel pain, feel feverish, or perceive a severely low mood (as with depression). Note that measurement of the ability to feel physical sensations absent the sensation itself (e.g., the ability to sense physical pain in peripheral neuropathy) is a measure of *functions*, not feels.

**Function** — A patient's ability to perform specified activities that are a meaningful (to the patient), part of typical (e.g., daily) life. Direct evidence of treatment benefit can be supported by demonstration of the impact of treatment on the patient's performance of activities of value in his or her daily life. Functioning does not refer to, and is not directly demonstrated by effects on, isolated physiologic process (e.g., liver metabolic capacity) that the patient is not consciously directly aware of, the ability to perform activities not meaningful to the patient, nor the ability to perform activities that are not part of typical daily life. A benefit in function can be shown by an *indirect* assessment, however, when there is a relationship between the concept evaluated by the assessment and a meaningful functional ability.

**Indirect assessment (of treatment benefit)** — A measure that can be used to infer a specified aspect of how a patient *feels*, *functions* or survives but is not directly evaluating that aspect. Indirect measures of treatment benefit are used when direct assessment of the impact of treatment on how a patient feels, functions or survives is infeasible. Examples include the use of observer assessment to detect behavior thought to be associated with infant symptoms, or the ability to perform activities that are not part of typical daily life.

**Observer-reported outcome (ObsRO) assessment** — An assessment that is determined by an observer who does not have a background of professional training that is relevant to the measurement being made, i.e., a non-clinician observer such as a teacher or caregiver. This type of assessment is often used when the patient is unable to self-report (e.g., infants, young children). An ObsRO should only be used in the reporting of observable concepts (e.g., signs or behaviors); ObsROs cannot be validly used to directly assess symptoms (e.g., pain) or other unobservable concepts.

**Outcomes** — The benefits or harms to a patient who receives an intervention. Outcomes are represented by concepts and can be core, proximal, or distal to the disease or condition treated.

**Patient-reported outcome (PRO) assessment** — A measurement based on a report that comes directly from the patient (i.e., study subject) about the status of particular aspects of a patient's health condition. PROs are recorded without amendment or interpretation of the patient's response by a clinician or other observer. A PRO measurement can be recorded by the patient directly, or recorded by an interviewer provided that the interviewer records exactly the patient's response.

**Psychomodulated measure** — An assessment that, of necessity, requires rater judgment and/or patient cooperation and motivation (e.g., to perform a defined activity) in the process of making

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the measurement. All PRO, ClinRO, and ObsRO assessments are psychomodulated. A psychomodulated measure is not a *biomarker*.

**Qualification** — A regulatory conclusion that within the stated *context of use*, the results of assessment with a *drug development tool* (DDT) can be relied upon to have a specific interpretation and application in drug development and regulatory decision-making and labeling.

**Treatment benefit** — The effect of treatment on how a patient survives, feels, or functions. Treatment benefit can be demonstrated by either an effectiveness or safety advantage. For example, the treatment effect may be measured as an improvement or delay in the development of symptoms or as a reduction or delay in treatment-related toxicity.

**Sign** — An observable indicator of a disease or health condition. Signs are usually observed by a clinician but may be noticed and reported by the patient. Some signs require interpretation (judgment) to report and therefore are psychomodulated measures and not biomarkers (e.g., degree of breathlessness, edema, ). Other signs can be measured and recorded without rater judgment and are biomarkers (e.g., resting blood pressure, body temperature).

**Surrogate endpoint** — An *indirect* outcome measure that is used as a substitute for a *direct* measurement of how a patient feels or functions. All biomarkers used as a clinical trial outcome assessment are surrogate endpoints or proposed as surrogate endpoints. The acceptability of a surrogate endpoint is dependent upon a demonstration that it can be used to reliably infer treatment benefit. The term is also sometimes applied to indirect psychomodulated measures to emphasize that they are indirect, and a substitute (replacement) for a direct measure of how a patient *feels* or *functions*.

**Symptom** — Any subjective indicator of a disease, health condition, or treatment-related effect that the patient is aware of and can be noticed and known only by the patient.