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Assessments and Endpoints

Demonstrating Effectiveness

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Clinical Evaluation of a Treatment

• MID
  ➢ What is the MID?
    ❖ Not the primary question, nor
      • How do we determine the MID?
      • Is the MID good enough?
  ➢ The MID of What?
  ➢ Initial question is
    ❖ What assessments will be useful?
    ❖ What is the endpoint that should be used?
  ➢ Evaluation of MID
    ❖ Suited to the type of assessment
    ❖ May follow reasoning that led to selection of assessment
What is an Endpoint?

- Study endpoint consists of
  - A specific clinical outcome assessment
    - Evaluated at specific time(s) & circumstances
  - Analyzed in a specified manner
  - Both aspects effect the utility of the endpoint

- Careful selection of the study endpoint is important to an efficient and successful clinical development program
  - Endpoint is an aspect of the program; not just the study
  - Previously emphasized that many features of the disease and patient population, and early attention to these, are important to understand
Utility of a study endpoint derives from

- Ability to convincingly show a treatment effect in a clinical study
- Ability to interpret that effect as *effectiveness*
  - A tangible benefit to the patient

Marketing approval for a drug based on demonstrating that:

- The drug is effective
- The benefits outweigh the risks
Selecting a Clinical Outcome Assessment (COA) (1)

• Comprehensive consideration of all the different effects of the disease on the patients
  ➢ Activities affected
  ➢ Body elements impaired producing the disability
  ➢ Prevalence of each aspect
  ➢ Concordance of impairment patterns across patients
  ➢ Range of severity
  ➢ Rate of worsening
  ➢ Within patient variability (day to day, wk to wk)
  ➢ Identifiable phenotype categories

• Select the aspect(s) of patient clinical status best suited to be the objective for measurement and evaluation of treatment effects
Selecting a COA (2)

- Are there any existing well described COAs that measure or relate to that clinical aspect?
  - What are the measurement characteristics of those tools?
    - Coarse vs fine gradations
    - Intra-patient, inter-evaluator reliability
    - Burden to obtain measurement
    - Range of measurement relative to this patient population (floor, ceiling limitations)
  - Are any well-suited?
- Alternative is create a new COA
  - Designed to suit this disorder
Types of COAs

• Direct observation, recording of patient’s typical daily functioning
  ➢ Self or observer or interview with clinician

• Report of activities or events in usual daily life that are thought to be due to the selected impaired functions but not directly meaningful
  ➢ E.g., record of as-needed pain medication use

• Measurement of an activity not a part of usual daily life
  ➢ E.g., *Artificial procedure* performed in clinic
  ➢ Thought to be evaluating impaired abilities that are used to perform daily life activities
  ➢ Clear articulation of related usual daily life activities that are intended; Often are not self-evident
Artificial Procedure COA

• Can be uniformly applicable to all study patients
• Can be administered in a consistent manner.
• May be structured to stress-test the isolated basic actions
  ➢ The normal daily life activity might not push the body-function to maximal functional ability
  ➢ May be very sensitive to changes in functional ability of a patient
  ➢ Over-stressing can introduce non-meaningful variability (noise)
Artificial Procedure COAs (2)

- They are _indirect measures_ of a meaningful aspect of the disease’s effects on the patient
  - The patient does not usually perform these procedures in daily life
    - E.g., 6-minute walk, ETDRS visual acuity tests
  - Are meant to imply some functional ability of the patient in daily life
  - Measurements cannot be intrinsically interpreted as to clinical meaning

- Prospective planned efforts enable linkage to ‘real’ daily activities, interpretability

- Development of new tests, qualification of existing tests in new a patient group initiated in advance of A&WC study
Selecting a COA (3)

• Construction of new COA with consideration of natural history (slide 3) may be needed
  ➢ Existing, but ill-suited, COAs for other disorders may impair sensitivity to treatment effects

• Disease expression between patients important
  ➢ Uniform vs. variable?
  ➢ If variable a single feature-focused assessment may not detect benefit to patients where the selected feature is not (presently) prominently affected
Selecting a COA (4)

• Consider using multiple assessments when expression variability present
  ➢ Can ensure all patients have at least one substantially affected ability included among the assessments
    ❖ Enables detecting treatment’s benefit in each patient
  ➢ Combine the multiple assessments in endpoint
    ❖ Multiple analytic methods available to combine
    ❖ Interpretability of endpoint can be differently affected by different analysis methods
  ➢ Some multi-domain PROs may be intended, in part, to employ this approach
Analysis and Interpretability (1)

- Analysis method of COA impacts the intrinsic interpretability of the endpoint’s observed treatment difference
- There is a tension between sensitivity of the endpoint and interpretability
  - Finely gradated continuous scale COAs analyzed in that form may be sensitive to small differences
  - Often easier to judge meaning of larger differences in measured values
  - Consider when specifying endpoint
    - Endpoint = COA + analysis
• Some COAs have natural analysis method
  ➢ Clinical Event endpoints
    ❖ Difference or ratio of rates
    ❖ Time to event

• Continuous scale COA
  ➢ Analyze in continuous form
  ➢ Analyze after changing into some categorized form
    ❖ Categorization by outcome measurement
    ❖ Categorization by change from baseline
    ❖ Less sensitivity traded for greater interpretability
Interpretation

• General clinical meaningfulness of a COA
  ➢ Does not establish clinical meaningfulness of any particular observed treatment difference

• Understanding the meaning of an observed treatment difference essential
  ➢ Value of observed treatment effect is treatment’s benefit

• Approval based on judgment that benefits outweigh risks
Interpretation

• MID: Minimum effect size with value to the patient
  ➢ Effect size with minimal value to the patient
• Relative value of larger effect sizes also useful to understand
  ➢ Differences with minimum, moderate, large importance
    ❖ Especially when risks are not minimal
  ➢ MID not important if observed treatment effect can be interpreted without precisely knowing MID
  ➢ Smallest confidently-affirmed important difference
    ❖ May be larger than the unknown MID
    ❖ Difficulty of achieving high precision in interpretability or
    ❖ Difficulty from reliability of the instrument
Interpretation

• Clinical meaning is not a purely statistical evaluation of the COA
  ➢ E.g., 2 sd of intra-patient variability may identify a reliably detectable difference
    ❖ Does not establish that it is a meaningful difference
  ➢ ‘True’ MID may be greater or less than reliably determined difference

• For continuous scale or interval COAs, the value to the patient of small changes may not be the same at different locations in the scale
  ➢ E.g. 5 pt difference from baseline 42 may not mean the same as from baseline 87 or 23
Achieving Interpretability

• Different categories of COAs will have different approaches
  ➢ Types of information and relative weights

• Naturalistic COAs
  ➢ May be able to rely heavily on face validity for assurance of broad meaningfulness
    ❖ E.g., pain VAS, individual sub-elements of a questionnaire
  ➢ Psychometric properties when combined into complex tool
  ➢ Contains directly meaningful items that aid establishing interpretation of indirectly-meaningful reports
Achieving Interpretability

- Artificial procedure measurement COA
  - More complex to establish meaningfulness
  - Specify the normal life aspect it is intended to represent
  - How are COA measurements related to reports of those activities

- FDA Guidance on PRO tools
  - Specifically for creation and qualification of PROs
  - Conceptual elements of guidance also relevant for other tools
  - Will be discussed later talks in this conference
Achieving Interpretability

- Information basis for determining meaningfulness of a COA / endpoint
  - Relevant to specific type of patients in the intended clinical trial
  - Might not be all patients with any form / stage of the disease
  - Same disease or, possibly, an adequately similar different disease
Endpoint Effect and Interpretation

• Does clinical meaning of the effect need to be an intrinsic part of the endpoint?
  ➢ Not necessarily

• Interpretation easier if meaningfulness is an intrinsic part of the endpoint
  ➢ E.g., difference in percentage of patients experiencing a change that is confidently meaningful (responder type of endpoint)
  ➢ Statistically significant difference is automatically clinically significant
Endpoint Effect and Interpretation

• Not doing so has program risks
  ➢ Study primary endpoint result may leave uncertainty whether there is tangible benefit
  ➢ Benefit-risk comparison may be uncertain
    ❖ Potential for critical differences in judgment of favorable vs unfavorable
    ❖ May prevent or delay marketing approval
  ➢ Tension between high sensitivity vs clarity of meaning should be considered

• Separate conclusions feasible
  ➢ Well-planned, prospective approach as to how meaningfulness of observed effect is established
  ➢ Study, other data, planned to be persuasive