Considerations in Characterizing the Diagnostic Performance of a Device

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FDA Draft Guidance

Design Considerations for Pivotal Clinical Investigations for Medical Devices issued on August 15, 2011
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm265553.htm

- 2 broad device categories:
  - Therapeutic and aesthetic devices
  - Diagnostic devices

Diagnostic Device Study Design Considerations

- Indications for use important to:
  - Define study design
  - Select performance measures
  - Choose study population (subjects and sites)
- Device should be evaluated in the context of its indications for use

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Context of Indications for Use

- What device measures, identifies, or detects, and what anatomical structures are being examined
- How device is used (per instructions for use)
- When device is used (conditions of use)
- For what (target condition)
- On whom (target population)
- By whom device (operator or target user)
- What device reports (output)

Examples of Indications for Use

- Imaging only (qualitative)
- Measurement (quantitative), but does not mention specific disease
- Aid in the diagnosis of a specific disease
- Diagnosis of a specific disease
- Screening

Diagnostic Device Study Design Considerations *Imaging only (qualitative)*

- Masked graders
- Pre-establish assessment criteria
- Images obtained with both predicate & subject device – same eye, same location, equivalent parameters – numerous pairs across the typical intended population (various pathologies and free of disease)
- Assessment of image quality and identification of relevant structures/pathology

Diagnostic Device Study Design Considerations *Measurement (Quantitative)*

- Covered in Gene Hilmantel's presentation

Diagnostic Device
Study Design Considerations
Aid in the Diagnosis of a Specific Disease

- Not the only information used for diagnosis
- Sample size of subjects with specific disease should be large enough to characterize the precision
- Measurements not negatively affected by particular disease state and variability not significantly affected
- May include normative database (NDB)

Diagnostic Device Study Design Considerations *Diagnosis of a Specific Disease*

- May include NDB
- Establish *clinical decision limits* (not just normative limits)
- Pivotal diagnostic performance study comparing reported diagnosis with clinical reference standard must use different population than was used to determine clinical decision limits
- No ophthalmic OCTs currently cleared or approved for this type of indication

Diagnostic Device Study Design Considerations *Screening*

- Defined intended population for referral for further workup
- Clinical decision limit - clear cut-off for referral
- Pivotal diagnostic performance study must use different population than was used to determine clinical decision limit
- No ophthalmic OCTs currently cleared or approved for this type of indication

Diagnostic Clinical Performance Study

- A type of "Pivotal" clinical study design for diagnostics
- Goal:
  - » Characterize diagnostic clinical performance of device
  - » Support a favorable benefit/risk analysis related to the diagnostic clinical performance

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Diagnostic Clinical Performance Study

- Diagnostic device is characterized by clinical performance measures that quantify how well the diagnostic device output agrees with a subject's 'true status' as determined by a *clinical reference standard*
  - » Determine appropriate clinical reference standard
  - » Validate *clinical decision limits* for the device output

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Clinical Reference Standard

- Best available method for establishing a subject's true status with respect to a target condition
- Can be a single method or a combination of methods and techniques, including clinical follow-up
- Can evolve over time
- The one used for a particular study always needs to be defined when reporting performance measures

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Clinical Reference Standard *(cont.)*

What constitutes "best available method" / reference standard?

- Opinion and practice within the medical and regulatory community
- Several possible methods could be considered
- Maybe no consensus reference standard exists

Development of Clinical Decision Limits

- Cross-sectional study of known normal and known diseased subjects of varying severity can provide preliminary information about possible decision limits
  - » Can provide distribution of measurements in known normal and known diseased subjects
  - » The distributions should demonstrate some separation
  - » Possible decision limits are between these two distributions

Example of Diagnostic Clinical Performance Study

- Prospective longitudinal study
  - » Goal: evaluation of Predictive Utility of Clinical Decision Limits
  - » Requires a clinical reference standard for the disease or condition of interest
  - » Enroll representative subjects from the intended use population (e.g., glaucoma suspects)
  - » Follow subjects over time

FDA Questions related to Diagnostic Performance Studies

- For a cross-sectional study describing the distribution of measurements in known normal and known diseased subjects (excluding suspects):
  - How should the diseased subject population be defined? What clinical work-up should be done to establish these populations?
  - Can the diseased population be further divided by severity of disease using a clinical reference method (e.g. perimetry)? If so, should the clinical performance of the imaging device be characterized separately for each severity group?

FDA Questions related to Diagnostic Performance Studies (cont.)

- For a longitudinal diagnostic performance study where the structural measurement is taken at baseline and the clinical reference standard consists of a baseline assessment with follow-up:
  - » What subjects should be included in the study population (including glaucoma suspects)?
  - » What is an appropriate clinical reference standard?
  - » What minimum follow-up period would provide assurance that the subject has been appropriately classified?

Thank you!