Regulatory Considerations for Imaging Biomarkers in Clinical Trials

• Requirements for use in regulated trials:
  1. Imaging biomarker validated
  2. Software FDA 21 CFR Part 11 compliant (both in terms of development and usage in the trial)
1. Imaging Biomarker Validation

• Imaging Biomarker – quantitative measurement of biological property
• Two phases of validation: “Test / Analytic Validation” and “Clinical Validation”
  • First phase includes accuracy and reproducibility of the measure/classifier against a reference standard (as we typically do for journal publications)
  • Second phase is prospective use in clinical trials (this is much less commonly done)
• FDA Biomarker qualification is available
  • Not a requisite for use in clinical trials (commonly used techniques, e.g., RECIST, have not been qualified, but are validated as described above)
Omics-Based Test Development Process

Discovery and Test Validation Stage

- Discovery Phase
  - Candidate Test Developed on Training Set, Followed by Lock-Down of All Computational Procedures
  - Confirmation of Candidate Omics-Based Test Using:
    1. An Independent Sample Set If Available (Preferred); OR
    2. A Subset of the Training Set NOT Used During Training (Less Preferred)

- Test Validation Phase
  - Define Clinical Test Method
  - Analytical Validation
  - Clinical/Biological Validation Using Blinded Sample Set
  - Defined, Validated, and Locked Down Test (Intended Use, Assay, Computational Procedures, and Interpretation Criteria)

Evaluation for Clinical Utility and Use Stage

Three Potential Pathways (IRB Approval and FDA Consultation)

- Prospective/Retrospective Study with Archived Specimens
- Prospective Clinical Trial; Test Does NOT Direct Patient Management
- Prospective Clinical Trial; Test Directs Patient Management

IDE Needed? (Investigational device exemption)

- No
- No
- Yes

Additional High-Quality Evidence to Evaluate Clinical Utility of the Test

Practice Guidelines and Reimbursement

Clinical Use

Evolution of Translational OMICS lessons learned and the path forward (March 2012) by IOM (Institution of Medicine) report
2. FDA 21 CFR Part 11 compliant software

• Three major elements to achieve compliance:
  1. Requirements on system/data controls
  2. Software validation
  3. Procedural controls on use of software
FDA 21 CFR Part 11 – system data controls

• System security with user authentication and authorization (for specific data access and functionality)
• Use of electronic signatures which lock data (regulations provide details on database fields required to record a valid electronic signature)
• Audit trail that records original measurements and reason for change if a measurement needs to be unlocked and updated (e.g., following a QC check)
FDA 21 CFR Part 11 – software validation

• Software validation must be performed and documented to demonstrate that the system fulfills its intended use

• Software development must be governed by Standard Operating Procedures (SOPs), e.g.,
  • System Development Life Cycle
  • Change Control
  • Test Execution/ Fault Investigation
  • Risk Management

• These procedures are similar to those required for development of 510(k) cleared products
  • 510(k) clearance is generally not required for use in a therapeutic clinical trial, but it can be made a requisite if the therapy relies on the software, e.g., for patient selection
FDA 21 CFR Part 11 – software validation

• The following documents are typically generating in the course of validating a computer system (which following the SOPs)
  • Requirements Specification
  • Design Specification
  • Validation Plan
  • Test installation Qualification
  • Operational Qualification (test results)
  • Traceability Matrix (confirming all requirements covered by tests)
  • Production Installation Qualification
  • Performance Qualification
  • Validation Summary
FDA 21 CFR Part 11 – procedural controls

• The following SOPs are also prepared
  • Administration SOP (for use by system administrators maintaining the system)
  • Operation SOP (for system users)

• Confirming of training and adherence to these procedures are required to ensure ongoing compliance

• If software is updated, re-validation is required according to a Change Control SOP
Summary

• Biomarker and software validation are important regulatory (FDA) requirements

• Engagement of appropriate support is necessary to support algorithm developers and software engineers
  • e.g., biostatisticians for biomarker validation
  • e.g., quality assurance specialists for software validation