Uniform Protocols for Imaging in Clinical Trials – UPICT

Clinical and Translational Science Awards Imaging Working Group: Clinical Trials Committee

CTSA CLINICAL & TRANSLATIONAL SCIENCE AWARDS

Background

Imaging is used in clinical trials for a variety of purposes, (e.g., determining eligibility, triage for subgroup analyses, response assessment, and endpoint measurements). Variance in imaging-derived data in clinical trials detracts from the value that imaging might contribute. Multiple factors other than biology contribute to this variance, such as technical differences among vendor platforms, machine drift over time, and changes introduced by services calls and system upgrades.

Imaging biomarkers (quantitative whenever possible) could contribute to decreased sample size through enrichment of the accrued cohort and to shortening the clinical trial's duration through the use of imaging as an early predictive surrogate endpoint. In order for imaging to fulfill this promise, non-biologic variance (noise) must be reduced so that signal is 1) sufficiently conspicuous and 2) a consequence of the intervention under investigation in the trial rather than to some artifact of the manner in which the imaging is conducted.

In order to improve the reliability of imaging in clinical trials, the CTSA Imaging Working Group (CTSA-IWG) promulgates Uniform Protocols for Imaging in Clinical Trials (UPICT).

UPICT Concept and Goals:
To facilitate the development and maintenance of consistent imaging protocols (including imaging quality control procedures) for use in clinical trials:

•to "improve" the contribution of imaging data, including increased statistical power,
•while supporting robust case accrual,
•and decreasing time to study initiation and site activation;

•while facilitating image data aggregation across trials and
•supporting the development, optimization, validation, and qualification of imaging biomarkers;

•through the participation of imaging scientists and clinical trialists drawn from the broad range of interested constituencies.

In addition, UPICT provides an impetus to improve the consistency of imaging performed during routine clinical care (thereby increasing the chances that pre-enrollment imaging might be used as the "baseline" study for clinical trials). Furthermore, as interventions translate from clinical trials to clinical care so too will the standardized imaging protocols translate from a supporting role in trials to clinical practice.

In order to actualize the UPICT concept and goals, the CTSA-IWG has established and implemented specific objectives, strategies, and activities (see next panel).

Objectives

UPICT has established the following objectives:

•Provide a standardized template to facilitate the authoring of, comparison among, and use of imaging protocols for clinical trials
•Provide a searchable library of imaging protocols that have been used in single- and multi-site clinical trials
•Provide a searchable library of consensus protocols that are endorsed by pertinent experts and organizations
•Provide a forum for clinical trialists and imaging scientists to collaborate on improving the value of imaging protocols in clinical trials
•Ensure that UPICT is transparent and inclusive
•Avoid duplication of other clinical trial imaging protocol development efforts (but instead include their work products within the UPICT infrastructure)

Strategies / Activities

UPICT has implemented the following strategies and activities:

•Inclusion of CTSA and non-CTSA representation in all UPICT activities including monthly web-based meetings (i.e., imaging device industry, PhRMA, BIO, federal agencies, CROs, academia, and clinical imaging practices)
•Formal workflow for UPICT Processes
•Invite contribution of clinical trial imaging protocols from academia (single- and multi-site) and industry (device, PhRMA, BIO, CRO) trials (Proffered Protocols)
•Engagement of the QIBA Technical Committees which are also contributing Proffered Protocols)
•Established UPICT web site / wiki under the CTSA-IWG with specific workspaces for the authoring, vetting, annotation, and editing of protocols –
http://upictwiki.ctsa-imaging.org
•Finalized UPICT Template v1.0
•Writing groups authoring Consensus Protocols using the UPICT Template for posting in the Consensus Library:
- Oncologic FDG-PET
- Oncologic vCT
- MRI for AD / MCI
- COPD / Asthma CT
•Currently extracting Proffered Protocols into the UPICT Template for posting in the Proffered Protocol Library:

- ACRIN
  - vCT
  - FDG-PET
  - MRI
- ACOSOG
  - DCE-CT
- ADNI and ADNI II
  - MRI
  - FDG and βAmyloid-PET
- QIBA
  - Oncologic vCT
  - Oncologic FDG-PET
  - DCE-MRI
  - COPD / Asthma CT
- CALGB
  - various
- Netherlands and EANM
  - Whole-body FDG-PET

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UPICT Template v1.0

Imaging Protocol

0. Executive Summary

1. Context of the Imaging Protocol within the Clinical Trial
   - 1.1. Utilities and Endpoints of the Imaging Protocol
   - 1.2. Timing of Imaging within the Clinical Trial Calendar
   - 1.3. Management of Pre-enrollment Imaging
   - 1.4. Management of Protocol Imaging Performed Off-schedule
   - 1.5. Management of Protocol Imaging Performed Off-specification
   - 1.6. Management of Off-protocol Imaging
   - 1.7. Subject Selection Criteria Related to Imaging
     - 1.7.1. Relative Contraindications and Remediations
     - 1.7.2. Absolute Contraindications and Alternatives
     - 1.7.3. Imaging-specific Inclusion Criteria

2. Site Selection, Qualification and Training
   - 2.1. Personnel Qualifications
     - 2.1.1. Technical
     - 2.1.2. Physics
     - 2.1.3. Physician
     - 2.1.4. Other (*e.g., radiochemistry, radiobiologist, pharmacist, etc.*)
   - 2.2. Imaging Equipment
   - 2.3. Infrastructure
   - 2.4. Quality Control
     - 2.4.1. Procedures
     - 2.4.2. Baseline Metrics Submitted Prior to Subject Accrual
     - 2.4.3. Metrics Submitted Periodically During the Trial
   - 2.5. Protocol-specific Training
     - 2.5.1. Physician
     - 2.5.2. Physics
     - 2.5.3. Technician

3. Subject Scheduling
   - 3.1. Timing Relative to Index Intervention Activity
   - 3.2. Timing Relative to confounding Activities *(to minimize "impact")*
   - 3.3. Scheduling Ancillary Testing

4. Subject Preparation
   - 4.1. Prior to Arrival
   - 4.2. Upon Arrival
     - 4.2.1. Confirmation of subject compliance with instructions
     - 4.2.2. Ancillary Testing
     - 4.2.3. Preparation for Exam

5. Imaging-related Substance Preparation and Administration
   - 5.1. Substance Description and Purpose
   - 5.2. Dose Calculation and/or Schedule
   - 5.3. Timing, Subject Activity Level, and Factors Relevant to Initiation of Image Data Acquisition
   - 5.4. Administration Route
   - 5.5. Rate, Delay and Related Parameters / Apparatus
   - 5.6. Required Visualization / Monitoring, if any
   - 5.7. Quality Control

6. Individual Subject Imaging-related Quality Control

7. Imaging Procedure
   - 7.1. Required Characteristics of Resulting Data
     - 7.1.1 Data Content
     - 7.1.2. Data Structure
     - 7.1.3. Data Quality
   - 7.2. Imaging Data Acquisition
     - 7.2.1. Subject Positioning
     - 7.2.2. Instructions to Subject During Acquisition
     - 7.2.3. Timing/Triggers
     - 7.2.4. Model-Specific Parameters
     - 7.2.5. Archival Requirements for Primary Source Imaging Data
   - 7.3. Imaging Data Reconstruction
     - 7.3.1. Model-Specific Parameters
     - 7.3.2. Archival Requirements for Reconstructed Imaging Data
     - 7.3.3. Quality Control

8. Image Post-processing
   - 8.1. Input Data to Be Used
   - 8.2. Methods to Be Used
   - 8.3. Required Characteristics of Resulting Data
   - 8.4. Platform-specific Instructions
   - 8.5. Archival Requirements
   - 8.6. Quality Control

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9. Image Analysis
   - 9.1. Input Data to Be Used
   - 9.2. Methods to Be Used
   - 9.3. Required Characteristics of Resulting Data
   - 9.4. Platform-specific Instructions
   - 9.5. Archival Requirements
   - 9.6. Quality Control

10. Image Interpretation
   - 10.1. Input Data to Be Used
   - 10.2. Methods to Be Used
   - 10.3. Required Characteristics of Resulting Data
   - 10.4. Platform-specific Instructions
   - 10.5. Reader Training
   - 10.6. Archival Requirements
   - 10.7. Quality Control

11. Archival and Distribution of Data
   - 11.1. Central Management of Imaging Data
   - 11.2. De-identification / Anonymization Schema(s) to Be Used
   - 11.3. Primary Source Imaging Data
   - 11.4. Reconstructed Imaging Data
   - 11.5. Post-Processed Data
   - 11.6. Analysis Results
   - 11.7. Interpretation Results and Reporting

12. Quality Control
   - 12.1. QC Associated with the Site
     - 12.1.1. Quality Control Procedures
     - 12.1.2. Baseline Metrics Submitted Prior to Subject Accrual
     - 12.1.3. Metrics Submitted Periodically During the Trial
   - 12.2. QC Associated with Imaging-related Substance Preparation and Administration
   - 12.3. QC Associated with Individual Subject Imaging
     - 12.3.1. Phantom Imaging and/or Calibration
     - 12.3.2. Quality Control of the Subject Image and Image Data
   - 12.4. QC Associated with Image Reconstruction
   - 12.5. QC Associated with Image Processing
   - 12.6. QC Associated with Image Analysis
   - 12.7. QC Associated with Interpretation

13. Imaging-associated Risks and Risk Management
   - 13.1. Radiation Dose and Safety Considerations
   - 13.2. Imaging Agent Dose and Safety Considerations
   - 13.3. Imaging Hardware-specific Safety Considerations
   - 13.4. Management and Reporting of Adverse Events Associated with Imaging Agent and Enhancer Administration
   - 13.5. Management and Reporting of Adverse Events Associated with Image Data Acquisition

Appendix A. Acknowledgements and Attributions
Appendix B. Background Information
Appendix C. Conventions and Definitions
Appendix D. Documents included in the imaging protocol (e.g., CRFs)
Appendix E. Associated Documents (derived from the imaging protocol or supportive of the imaging protocol; e.g., Imaging Charter, Site Manual, SOPs)
Appendix F. TBD
Appendix G. Model-specific Instructions and Parameters

Considerations

UPICT Consensus Protocols should 1) account for variations in current technology and 2) accommodate continued technological evolution 3) while maintaining protocol stability using versioning; 4) provide detail sufficient to ensure consistency and reproducibility while 5) incorporating placeholders for trial / disease-specific parameters; 6) accommodate standard of care imaging to the extent possible; 7) facilitate accrual; and 8) support the needs of academia, agencies, and industry.

UPICT Proffered and Consensus Protocols recognize the variable capabilities of clinical trial imaging sites worldwide by incorporating Acceptable, Target, and Ideal parameters to which participating sites adhere.