**X. Imaging Protocol**

0. Executive Summary
   *Provide a brief (less than 250 words) synopsis to let readers quickly determine if this imaging protocol is relevant to them. Sketch key details such as the primary utility, imaging study design, specific aims, context, methods, expected results, risks, and deliverables.*

1. Context of the Imaging Protocol within the Clinical Trial
   *Describe how this imaging protocol interfaces with the rest of the clinical trial.*

   1.1. Utilities and Endpoints of the Imaging Protocol
   *Describe one or more utilities or endpoints this Imaging Protocol could serve in a Clinical Trial. (e.g. to determine eligibility of potential subjects in the clinical trial; to triage eligible subjects into cohorts based on stage or severity of disease; to assess response to treatment; to establish the presence of progression for determining TTP, PFS, etc.; to monitor for adverse events; to establish a database for the development, optimization, and validation of imaging biomarkers, etc.)*

   1.2. Timing of Imaging within the Clinical Trial Calendar
   *Describe for each discrete imaging acquisition the timing that will be considered "on-schedule" preferably as a "window" of acceptable timing relative to other events in the clinical trial calendar. Consider presenting the information as a grid which could be incorporated into the clinical trial calendar.*

   1.3. Management of Pre-enrollment Imaging
   *Describe the evaluation, handling and usage of imaging performed prior to enrollment. Clearly identify purposes for which such imaging may be used: eligibility determination, sample enrichment, stratification, setting the measurement base-line, etc.*
   *(e.g. What characteristics or timing will make the imaging acceptable for the purpose?*
   *Will digitized films be accepted?*
   *Will low-grade images be annotated and/or excluded from parts of the trial?*
   *Is there normalization that should be done to improve low-grade priors?*
   *How should such imaging be obtained, archived, transferred, etc.)*

   1.4. Management of Protocol Imaging Performed Off-schedule
   *Describe the evaluation, handling and usage of imaging performed according to the Procedure below but not within the "on-schedule" timing window described in Section 1.2.*
   *(e.g. For what purpose(s) may such imaging be used (for clinical decision-making; for data analysis; for primary endpoints; for secondary endpoints; for continued subject eligibility evaluation; to supplement but not replace on-schedule imaging, etc.)?*
   *What characteristics or timing will make the imaging acceptable for the purpose?*
   *Is there normalization that should be done to account for the schedule deviation?*
   *What is the expected statistical impact of such imaging on data analysis?*
   *How should such imaging be recorded, archived, etc.)*

1.5. Management of Protocol Imaging Performed Off-specification
*Describe the evaluation, handling and usage of imaging described below but not performed completely according to the specified Procedure. This may include deviations or errors in subject preparation, the acquisition protocol, data reconstruction, analysis, interpretation, and/or adequate recording and archiving of necessary data.*
*(e.g. For what purpose(s) may such imaging be used (for clinical decision-making; for data analysis; for primary endpoints; for secondary endpoints; for continued subject eligibility evaluation; to supplement but not replace on-schedule imaging, etc.)?*
*What characteristics or timing will make the imaging acceptable for the purpose?*
*Is there normalization that should be done to account for the schedule deviation?*
*What is the expected statistical impact of such imaging on data analysis?*
*How should such imaging be recorded, archived, etc.)*

1.6. Management of Off-protocol Imaging
*Describe the evaluation, handling and usage of additional imaging not described below. This may include imaging obtained in the course of clinical care or potentially for research purposes unrelated to the clinical trial at the local site.*
*(e.g. For what purpose(s) may such imaging be used (for clinical decision-making; for data analysis; for primary endpoints; for secondary endpoints; for continued subject eligibility evaluation; to supplement but not replace on-schedule imaging, etc.)?*
*What characteristics or timing will make the imaging acceptable for the purpose?*
*Is there normalization that should be done to account for the schedule deviation?*
*What is the expected statistical impact of such imaging on data analysis?*
*How should such imaging be recorded, archived, etc.)*

1.7. Subject Selection Criteria Related to Imaging
1.7.1. Relative Contraindications and Remediations
*Describe criteria that may require modification of the imaging protocol.*
*(e.g. subjects with kidney insufficiency are contraindicated for Contrast CT in this protocol, at the physicians discretion, kidney function may be re-evaluated prior to imaging to see if the insufficiency has resolved, or the subject may be evaluated for dialysis, etc.)*
1.7.2. Absolute Contraindications and Alternatives
*Describe criteria that may fully disqualify the subject for the imaging protocol.*
*If possible, identify possible alternative imaging protocols.*
*(e.g. subjects with pacemakers are disqualified for this MRI protocol. Consider using CT protocol UPICT-31254 instead)*
*These alternatives may also be useful for relative contraindications if remediations described in 1.7.1 are not possible or successful.*
1.7.3. Imaging-specific Inclusion Criteria
*Describe inclusion criteria that are specifically related to the imaging portion of the study.*

2. Site Selection, Qualification and Training

**Full document**

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
*List required equipment and software packages, such as CT scanners, image processing workstations, and analysis packages. Specific capabilities of the equipment are described in later sections of this document.*
*Consider discussing the trade-off between accrual rates and the "bullseye rings of compliance" described in Section 7.2.*
2.3. Infrastructure
*List required infrastructure, such as subject management capabilities, internet capability, image de-identification and transmission capability.*

2.4. Quality Control
    2.4.1. Procedures
        See 12.1.1.
    2.4.2. Baseline Metrics Submitted Prior to Subject Accrual
        See 12.1.2.
    2.4.3. Metrics Submitted Periodically During the Trial
        See 12.1.3.

    *Additional task-specific Quality Control is described in sections below.*

2.5. Protocol-specific Training
    2.5.1. Physician
        See 10.5, …
    2.5.2. Physics
        See …
    2.5.3. Technician
        See …

3. Subject Scheduling
*Describe requirements and considerations for the physician when scheduling imaging and other activities, which may include things both related and unrelated to the trial.*

3.1. Timing Relative to Index Intervention Activity
3.2. Timing Relative to confounding Activities *(to minimize "impact")*
*(e.g. Avoid scheduling a biopsy on a tumor within X days prior to the FGD-PET scan to evaluate tumor viability; Avoid scheduling the MRI scan within X hours following administration of TPA (for stroke) to the subject.)*
3.3. Scheduling Ancillary Testing
*(e.g. order a blood draw to occur within X hours preceding the imaging procedure.)*

4. Subject Preparation
   4.1. Prior to Arrival
       *Describe the presence/absence/timing of subject activities that may impact the procedure or results. These items should typically result in instructions for the subject at time of scheduling, or reminders sent to the subject shortly prior to imaging.*
       *(e.g. oral and/or IV intake, vigorous physical activity, non-protocol-related medical interventions, etc.)*

   4.2. Upon Arrival
       4.2.1. Confirmation of subject compliance with instructions
           *(e.g. instructions to the admitting nurse/tech to confirm with the subject upon arrival that they have complied with each of the instructions in 4.1.)*
       4.2.2. Ancillary Testing
           *(e.g. blood draws, weight/blood pressure measurement, etc. associated with the imaging and downstream actions relative to such testing)*
       4.2.3. Preparation for Exam
           *(e.g. empty bladder, removal of metal objects, etc.)*

5. Imaging-related Substance Preparation and Administration
   *(e.g. Contrast agents, radiopharmaceuticals or stress agents intended to directly affect the imaging process.  Does not include therapeutic drugs/agents unless they are also imaging agents.)*

   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
       See 12.2.

6. Individual Subject Imaging-related Quality Control
   See 12.3.

7. Imaging Procedure
   *When the imaging procedure involves acquisition of multiple series, Section 7 may be repeated (7a, 7b) as necessary to describe each acquisition.*

   7.1. Required Characteristics of Resulting Data
       *Describe the characteristics of the imaging data resulting from acquisition and reconstruction that are relevant to its use in the clinical trial.  This description is generally independent of the vendor, platform, and version of the imaging equipment.*
       7.1.1. Data Content
           *Describe what the acquired images should contain/cover.*

4

*(e.g. Anatomic Coverage, Field of View)*

    7.1.2.  Data Structure
*Describe how the data should be organized/sampled.*
*(e.g. Spatial Resolution, Collimation Width, Slice Interval, Temporal Resolution, Framing Rates)*

    7.1.3.  Data Quality
*Describe any needed measurements of quality.*
*(e.g. Image Quality, Noise Levels, Motion Artifacts, Radiation Dose)*

7.2.  Imaging Data Acquisition

    7.2.1.  Subject Positioning

    7.2.2.  Instructions to Subject During Acquisition
*(e.g., breath hold, etc.)*

    7.2.3.  Timing/Triggers
*(e.g., relative to administration of imaging agents; inter-time point standardization)*

    7.2.4.  Model-Specific Parameters
*Appendix G.1 lists acquisition parameter values for specific models/versions that can be expected to produce data meeting the requirements of Section 7.1 while also complying with the radiation dosimetry specified in Section 13.*

    7.2.5.  Archival Requirements for Primary Source Imaging Data
See 11.3.

7.3.  Imaging Data Reconstruction
*Describe the data reconstruction process including any inherent data correction, smoothing, etc. This may conceivably be performed on a different system than acquisition, and occasionally at a later time, particular for supplementary reconstructions.*

    7.3.1.  Model-Specific Parameters
*Appendix G.2 lists reconstruction parameter values for specific models/versions that can be expected to produce data meeting the requirements of Section 7.1.*

    7.3.2.  Archival Requirements for Reconstructed Imaging Data
See 11.4.

    7.3.3.  Quality Control
See 12.4.

8.  Image Post-processing
*Describe subsequent modification of the reconstructed image pixels prior to analysis. This is often performed on a different platform than the acquisition system.*
*(e.g. spatial registration, spatial re-orientation, re-slicing, feature enhancement, 3D view generation)*

8.1.  Input Data to Be Used

*Describe required input data and any necessary validation or adjustments which should be performed on it.*
*(e.g. particular image series or views; raw, processed, both)*

8.2. Methods to Be Used
*Describe how the analysis should be performed.*
*(e.g. algorithms to be used; where measurements should be taken; definition of key anatomical points or pathology boundaries; related annotations)*

8.3. Required Characteristics of Resulting Data

8.4. Platform-specific Instructions
*Appendix G.3 lists parameter values and/or instructions for specific models/versions that can be expected to produce data meeting the requirements of Section 8.3.*

8.5. Archival Requirements
See 11.5.

8.6. Quality Control
See 12.5.

9. Image Analysis
*Describe the generation of new data/information based on the images. This may be performed by an automated program, a semi-automated program, or entirely by a human.*
*(e.g. organ segmentation, size or volume measurement, flow rate calculation, tissue characterization, observation of the presence/absence/degree of features such as edema)*

9.1. Input Data to Be Used
*Describe required input data and any necessary validation or adjustments which should be performed on it.*
*(e.g. particular image series or views; raw, processed, both)*

9.2. Methods to Be Used
*Describe how the analysis should be performed.*
*(e.g. algorithms to be used; where measurements should be taken; definition of key anatomical points or pathology boundaries; scoring scales and criteria, related annotations)*

9.3. Required Characteristics of Resulting Data

9.4. Platform-specific Instructions
*Appendix G.4 lists parameter values and/or instructions for specific models/versions that can be expected to produce data meeting the requirements of Section 9.3.*

9.5. Archival Requirements
See 11.6.

9.6. Quality Control
See 12.6.

10. Image Interpretation
*Describe the diagnostic conclusions of interest to be drawn from the images.*
*(e.g. progression of disease, presence/absence/degree of pathology, viable tumor vs. necrotic)*

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*While Analysis is primarily about computation; Interpretation is primarily about judgment. Interpretation may be performed at both the lesional / target level and in the aggregate at the subject level (e.g., in an oncology study each index lesion may be measured in longest diameter during the analysis phase, but in this phase a judgment may be made as to whether there is a new "non-index" lesion; the aggregation of the measured lesions with comparison to previous studies coupled with the judgment as to the presence or absence of a new lesion will result in the RECIST classification at the subject level).*

10.1. Input Data to Be Used
*Describe required input data and any necessary validation or adjustments which should be performed on it. May also specify data which should not be used until after the clinical trial interpretation is recorded.*
*(e.g. particular image series or views; before and after processing versions of images to evaluate/validate the effects of processing; analysis results)*

10.2. Methods to Be Used
*Describe how the interpretation should be performed.*
*(e.g. definition of key anatomical points or pathology boundaries; scoring scales and criteria such as BIRADS, interpretation schema such as RECIST, related annotations)*

10.3. Required Characteristics of Resulting Data

10.4. Platform-specific Instructions
*Appendix G.5 provides instructions for specific models/versions that can be expected to produce data meeting the requirements of Section 10.3.*

10.5. Reader Training

10.6. Archival Requirements
See 11.7.

10.7. Quality Control
See 12.7.

11. Archival and Distribution of Data
*Describe the required data formats, transmission methods, acceptable media, retention periods, …*
*(e.g. Is the site required to keep local copies in addition to transmitting to the trial repository? Must all intermediate data be archived, or just final results? At what point may various data be discarded?)*

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

12. Quality Control

12.1. QC Associated with the Site

12.1.1. Quality Control Procedures

*Describe required procedures and documentation for routine and periodic QC for the site and various pieces of equipment.*

12.1.2. Baseline Metrics Submitted Prior to Subject Accrual
*List required baseline metrics and submission details.*

12.1.3. Metrics Submitted Periodically During the Trial
*List required periodic metrics and submission details.*

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

*Full document*

**Appendix A:     Acknowledgements and Attributions**

**Appendix B:     Background Information**

**Appendix C:     Conventions and Definitions**

**Definitions**
*Review this document and define relevant terms and notations here.*

**Acquisition vs. Analysis vs. Interpretation**
This document organizes acquisition, reconstruction, post-processing, analysis and interpretation as steps in a pipeline that transforms data to information to knowledge.

Acquisition, reconstruction and post-processing are considered to address the collection and structuring of new data from the subject.  Analysis is primarily considered to be computational steps that transform the data into information, extracting important values.  Interpretation is primarily considered to be judgment that transforms the information into knowledge.

*(The transformation of knowledge into wisdom is beyond the scope of this document.)*

**Bulls-eye Compliance Levels**
Acquisition parameter values and some other requirements in this protocol are specified using a "bullseye" approach.  Three rings are considered from widest to narrowest with the following semantics:

> ACCEPTABLE: failing to meet this specification will result in data that is likely unacceptable for the intended use of this protocol.

> TARGET: meeting this specification is considered to be achievable with reasonable effort and equipment and is expected to provide better results than meeting the ACCEPTABLE specification.

> IDEAL: meeting this specification may require unusual effort or equipment, but is expected to provide better results than meeting the TARGET.

An ACCEPTABLE value will always be provided for each parameter.  When there is no reason to expect better results (e.g. in terms of higher image quality, greater consistency, lower dose, etc.), TARGET and IDEAL values are not provided.

Some protocols may need sites that perform at higher compliance levels do so consistently, so sites may be requested to declare their "level of compliance".  If a site declares they will operate at the TARGET level, they must achieve the TARGET specification whenever it is provided and the ACCEPTABLE

specification when a TARGET specification is not provided.  Similarly, if they declare IDEAL, they must achieve the IDEAL specification whenever it is provided, the TARGET specification where no IDEAL level is specified, and the ACCEPTABLE level for the rest.

## Appendix D:   Documents included in the imaging protocol (e.g., CRFs)

*(Material the site needs to submit)*

*Subject preparation*

*Imaging agent dose calculation*

*Imaging agent*

*Image data acquisition*

*Inherent image data reconstruction / processing*

*Image analysis*

*Interpretation*

*Site selection and Quality Control*

*Phantom Imaging and Calibration*

## Appendix E:   Associated Documents (derived from the imaging protocol or supportive of the imaging protocol)

*e.g. the Imaging Charter, Site Manual, Standard Operating Procedures, etc.*

## Appendix F:   TBD

## Appendix G:   Model-specific Instructions and Parameters

The presence of specific product models/versions in the following tables should not be taken to imply that those products are fully compliant with the QIBA Profile.  Compliance with a profile involves meeting a variety of requirements of which operating by these parameters is just one.  To determine if a product (and a specific model/version of that product) is compliant, please refer to the QIBA Conformance Document for that product.

G.1.  Image Acquisition Parameters

The following technique tables list acquisition parameter values for specific models/versions that can be expected to produce data meeting the requirements of Section 7.1.

These technique tables may have been prepared by the submitter of this imaging protocol document, the clinical trial organizer, the vendor of the equipment, and/or some other source.  (Consequently, a given model/version may appear in more than one table.)  The source is listed at the top of each table.

Sites using models listed here are encouraged to consider using these parameters for both simplicity and consistency.  Sites using models not listed here may be able to devise their own acquisition parameters that result in data meeting the requirements of Section 7.1 and conform to the considerations in Section 13.

In some cases, parameter sets may be available as an electronic file for direct implementation on the imaging platform.

*UPICT Template V1.0*

*Full document*

**Table G.1a**

Model X: <description of manufacturer, model, version, etc.>
Model Y: <description of manufacturer, model, version, etc.>
Model Z: <description of manufacturer, model, version, etc.>

Source: *<submitted by who>*                    Date: *<submitted when>*

| Parameter | Level* | Model X | Model Y | Model Z |
|---|---|---|---|---|
| **Parameter A** | Acceptable | | | |
| | Target | | | |
| **Parameter B** | Acceptable | | | |
| | Target | | | |
| | Ideal | | | |
| **Parameter C** | Acceptable | | | |
| **Parameter D** | Acceptable | | | |
| | Target | | | |

* See Appendix C for a discussion of the Levels of Compliance

## UPICT Template V1.0

### Full document

### Table G.1b

Model A1: <description of manufacturer, model, version, etc.>
Model A2: <description of manufacturer, model, version, etc.>

Source: *<submitted by who>*                    Date: *<submitted when>*

| Parameter | Level* | Model A1 | Model A2 |
|---|---|---|---|
| **Parameter A** | Acceptable | | |
| | Target | | |
| **Parameter B** | Acceptable | | |
| | Target | | |
| | Ideal | | |
| **Parameter C** | Acceptable | | |
| **Parameter D** | Acceptable | | |
| | Target | | |

* See Appendix C for a discussion of the Levels of Compliance

G.2.  Image Reconstruction Parameters

G.3.  Post-Processing Instructions

G.4.  Analysis Instructions

G.5.  Interpretation Instructions