ETCTN – Image-Guided Biopsy Standard Operating Procedure (Final Version – 10.26.2018)

1. PURPOSE

1.1. To delineate a standard operating procedure for the acquisition of image-guided biopsies performed by Interventional Radiologists (IR) within the Experimental Therapeutics Clinic Trials Network (ETCTN). For this document, Interventional Radiologists are defined as those Radiologists responsible for the acquisition of biopsy samples.

2. SCOPE

2.1. This SOP provides a general framework for image-guided biopsies within ETCTN trials.

2.2. In addition to this general framework, each ETCTN protocol will include trial-specific requirements for the acquisition and processing of biopsy samples. The trial-specific requirements will be summarized within the protocol.

3. ABBREVIATIONS

3.1. CRF – Case Report Form

3.2. CTEP – Cancer Therapy Evaluation Program

3.3. ETCTN – Experimental Therapeutics Clinical Trials Network

3.4. IR – Radiologist(s) responsible for the acquisition of biopsy samples

3.5. SOP – Standard Operating Procedure

3.6. PD - Pharmacodynamic

4. DEFINITIONS:

4.1. Biomarker Definitions [adapted from Dancey, et al., Clin Cancer Res. 2010 Mar 15;16(6):1745-55]

4.1.1. Known valid biomarker – A biomarker for which there is widespread agreement about the physiologic or clinical significance

4.1.2. Probable valid biomarker – A biomarker for which there is scientific framework or body of evidence that suggests physiologic or clinical significance

4.1.3. Exploratory biomarker - A biomarker that does not meet the criteria for probable or known valid biomarker

4.1.4. Integral role– Biomarker tests that are done for the trial to proceed; Integral studies are inherent in the design of the trial from the onset and are done in real time for the conduct of the trial.

4.1.5. Integrated role – Biomarker tests that are intended to identify or validate assays or markers that are planned for use in future trials. Trials are designed to test a hypothesis and include complete plans for specimen collection, laboratory measurements, and analysis. Statistical design and analysis should be prespecified.

4.2. MediData Rave – Centralized NCI Clinical Information Technology system.

5. OPERATING PROCEDURES

5.1. Biopsy Purpose:

5.1.1. IRs, as co-investigators on each ETCTN protocol, will participate in defining the requirements for each biopsy procedure. The purpose of each biopsy in the protocol will be defined as follows:

5.1.1.1. Research-Clinical Impact:

- One or more cores from a single biopsy procedure will be used for **integral biomarker(s),** used to directly impact patient care. Integral biomarkers are defined as essential for conducting the study as they define eligibility, stratification, disease monitoring or study endpoints.

- Additional cores from that single biopsy procedure may be used for **integrated and/or exploratory biomarkers**, which are research assays that do not directly benefit the patient. Integrated biomarkers are defined as assays that are clearly identified as part of the clinical trial from the outset and are intended to identify or validate assays or markers that are planned for use in future trials. Exploratory biomarkers are designed for research purposes, may not be performed on all subjects in a trial, and collection of these exploratory markers by investigators participating in the trial may be voluntary.

5.1.1.2. Research-No Clinical Impact:

- All cores from a single biopsy procedure impact research goals, but do not directly impact patient care or benefit the patient.

- All cores will only be used for **integrated and/or exploratory biomarkers**.

5.2. Pre-Biopsy Assessment:

5.2.1. Purpose. A pre-biopsy lesion assessment can increase trial safety and efficiency. By agreement between all investigators, an attempt at biopsy will be made if the clinical trial team determines that a biopsy poses minimal relative risk, provides potential clinical gain to the participant, and will likely yield sufficient tissue for analysis.

5.2.1.1. Institutional Process for Pre-Biopsy Assessment. The clinical trial team at each Institution will establish a process to determine whether to attempt a biopsy in individual patients. The clinical trial team at each Institution will:

- Determine the pre-biopsy assessment communication process (face-to-face, electronic, frequency of communications, etc.).

- Follow the Institutional clinical reporting/billing requirements for the pre-biopsy consultation.

5.2.1.2. Individual Patient Pre-Biopsy Assessment. IR co-investigators are encouraged to apply this pre-biopsy scoring and correlation system to assist in the determination of biopsy appropriateness.

- IR co-investigators assign a subjective score of 1-3 based on likelihood of success due to lesion characteristics. (see attached "MATCH biopsy guide book.pptx" for reference)

    1 - Biopsy should not be done
    A. Due to safety concerns
    B. Due to lack of suitable lesion for biopsy

    2 - Uncertainty about success

    A. Due to access path to lesion
    B. Due to lesion characteristics

    3 - Likely successful

- Lesion characteristics to be considered

    - Size (small) (<2 cm)
    - Location/path to lesion
    - Morphologic features (necrosis, sub-solid, sclerosis, ill-defined/infiltrative)
    - PET (+/-), avidity
    - Organ/site (sclerotic bone is low yield; fine needle aspiration to be used)

- Pre-biopsy assessments will be reported and tracked through a trial-specific CRF within the CTEP Medidata Rave system.

5.3. Pre-Biopsy Patient Communication and Consent Procedures:

5.3.1. The Image-Guided Biopsy consent procedures will depend on the type of biopsy being performed and will follow Institutional clinical trials guidelines.

5.4. Biopsy Instructions - Percutaneous biopsy with local anesthetic.

5.4.1. These instructions will be protocol-specific and will depend on the location of the lesion and patient safety considerations. Sample biopsy instructions may include the following:

5.4.1.1. Local anesthesia to be administered as needed.

- Sedation may be used for comfort, if considered safe for the patient and allowed by the protocol.

5.4.1.2. Contraindications to percutaneous biopsy:

- Significant coagulopathy that cannot be adequately corrected.
- Severely compromised cardiopulmonary function or hemodynamic instability.
- Lack of a safe pathway to the lesion.
- Inability of the patient to cooperate with, or to be positioned for, the procedure.

5.4.1.3. Complications of biopsy will be reported and tracked as required in the protocol and defined by Common Terminology Criteria for Adverse Events (CTCAE).

5.5. Imaging Procedures.

5.5.1. The use of imaging to facilitate biopsies will be decided by members of the Radiology team at the clinical site and may include ultrasound, CT, or MRI.

5.5.2. Biopsy Sample Acquisition Goal: This goal will be protocol-specific and will depend on the location of the lesion and patient safety considerations. An example of a biopsy acquisition goal may include the following:

5.5.2.1. Four (4) core biopsies

5.5.2.2. Each core should be at least 10mm in length

5.5.2.3. Each core should be largest gauge that is clinically acceptable

5.6. Post-Biopsy Sample Processing:

5.6.1. Sample processing will be protocol-specific and provided to each clinical trial team.

5.6.2. A designated member of the pathology research staff will be responsible for transport of the core biopsy samples from the radiology suite to the pathology laboratory for processing.

5.6.3. The protocol pathology staff will then be responsible for the shipping of the samples to the appropriate laboratory for analysis as determined in the protocol.

5.7. Biopsy Core Adequacy Determination:

5.7.1. The adequacy of each biopsy core will be determined by the pathologists on the Institutional clinical trial team. The biopsy adequacy definitions are as follows:

5.7.1.1. Nucleic Acid assays: Adequacy is defined as >20% tumor cells with minimal necrosis and stromal tissue.

5.7.1.2. Pharmacodynamic (PD) assays: Adequacy will be defined in the protocol, using these guidelines (see attached "NCI – Biopsy Core Adequacy.pdf" as reference":

Viable Tumor Content	Suitability for PD Assay
>50%	Optimal for Slide-Based and Extraction-Based Assays
25-50%	Adequate for Slide-Based Assays; Marginal for Extraction-Based Assays
5-25%	Marginal for Slide-Based Assays; Not Adequate for Extraction-Based Assays
<5%	Not Adequate for Slide- or Extraction-Based Assays

5.7.2. Biopsy Core Adequacy will be reported and tracked when possible.