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1. Overview

This document describes the standard operating procedures for central adjudication of patient outcomes in TRACER. Adjudication will be performed by the multiple principal investigator (MPI) team or MPI-designated clinicians. Necessary infrastructure and data management for adjudication will be provided by the Data Management and Coordinating Center (DMCC). Results of central adjudication will not be reported back to study sites unless requested.

2. Adjudication of Hepatocellular Carcinoma

2.1. Classification of Liver Lesions on Diagnostic Imaging

Prerequisites: For liver lesions categorized as LR-3 (1cm or greater), LR-4, LR-5, LR-TIV, LR-M, or indeterminate, DICOM image files and redacted radiology reports will be uploaded to CDMS according to the TRACER Imaging SOP. The DMCC may review uploaded files to confirm de-identification.

Blinding: Only de-identified images and imaging reports will be viewed by imaging adjudicators. The following information specifically will be concealed: study participant IDs, the patient's study arm assignment, indication, the site where the imaging was performed. Prior imaging from the same patient may be viewed for comparison, provided that it was uploaded for central adjudication.

Each lesion will be reviewed by at least one study radiologist and interpreted for presence vs. absence of liver cancer according to LI-RADS (Liver Imaging Reporting and Data System) v2018. Lesion interpretation should be recorded in order of decreasing concern (LR-TIV > LR-5 > LR-M > LR-4 > LR-3. The review should be completed within 1 month after images are uploaded. The DMCC will notify the radiologists when imaging is ready to review.

Review by a second study radiologist may be requested. The adjudication system in CDMS will be set up to allow for multiple reviews of each imaging exam.

2.2. Final Determination

For patients who have liver imaging or histology consistent with or concerning for liver cancer during the Surveillance Follow-up portion of their study participation, presence vs. absence of HCC or other liver cancer will be centrally adjudicated.

Prerequisites: The final adjudication of HCC for a patient will require all central adjudication of the patient's liver imaging to be complete. Additionally, AFP test results and liver histology findings from biopsies or liver transplantation should be entered into Rave EDC. If additional documentation (e.g., pathology reports) is required, the DMCC will issue a request to the patient's recruiting site. Sites are then responsible for uploading de-identified documents to Medidata Rave or submitting them through CDMS Issue Tracking. Typically, patients needing HCC adjudication will be selected, and their relevant data compiled for adjudication, after they have been recorded as Off Study or Off Surveillance Follow-up.

Blinding: No patient-identifying information may be provided to the MPI adjudicator. In addition, the MPI adjudicator will be blinded to the patient's study arm assignment and the originating site's name and site ID for all submitted data.

An MPI will be assigned to make an overall assessment of 1) malignancy not definite for HCC, 2) definite HCC, 3) indeterminate for HCC, or 4) not HCC. The final adjudication will be based on central imaging interpretation, biopsy results (if available), and tumor markers (AFP as available). Uncertainty about overall patient-level HCC status will be resolved through discussion with other study MPIs. The final adjudication should be done within three months of completion of imaging adjudication, but ideally within one month. The adjudication result will be recorded in CDMS.