Data Support Document
cIMT Measurement

This document includes information on the carotid intima-media thickness (cIMT) measurement that was initially applied for Baseline (BL) images and repeated for Follow-up 1 (FUP1), Follow-up 2 (FUP2), and Follow-up 3 (FUP3). All acquired images are assessed for quality. Each image is given a rating of 1) good quality images but do not require reanalysis; 2) good quality images but require reanalysis; and 3) poor quality images that cannot be analysed. The images that were rated as good quality but required reanalysis from baseline were reanalysed centrally.

The baseline data set will include two sets of cIMT values. These values will represent 1) original cIMT value that was derived in real time at the time of data collection and 2) re-analysis of the right-side images. The description of methods for original analysis and reanalysis are provided below.

I-   THE ORIGINAL cIMT MEASUREMENT (BL and FUP1)

1.0   PURPOSE AND SCOPE

Carotid ultrasound has been routinely used for the evaluation of ischemic cerebrovascular signs and symptoms. In the utilization of carotid ultrasound in the context of risk stratification, the carotid intima-media thickness (cIMT) is measured for the objective of detecting preclinical or subclinical cardiovascular disease. Measurement of the cIMT is considered a surrogate marker for the measurement of carotid artery atherosclerosis, which correlates with the presence of coronary atherosclerosis. This procedure measures the thickness of the carotid artery wall (between the innermost layer of the artery, the intima, and the middle layer of the artery, the media)[1].

The cIMT and plaque scans were collected in the Canadian Longitudinal Study on Aging (CLSA) Comprehensive cohort, comprised of more than 30,000 participants from across Canada, who were 45-85 years old at recruitment[2,3]. Image files and raw data from the carotid ultrasound scanners may be available on special request. For more information on the CLSA, data previews, and on how to request data through the CLSA, refer to the CLSA website, at www.clsa-elcv.ca.

2.0   INSTRUMENTS AND METHODOLOGY

2.1   Data Collection

To ensure consistency across all Data Collection Sites (DCS) the CLSA developed the standard operating procedure: *SOP_DCS-0011 – Carotid Intima-Media Thickness*[4].

The cIMT measurement was performed at the DCS on participants who were able to stand without the assistance of another person. The measurement was completed using the GE VIVIDi machine (model number 905521), three Meditrace Foam 230 electrodes, and Aquasonic Ultrasound gel. (*Note: CLSA was provided 20 cases (600/case) of IVY ECG Electrodes (Item number E8007RG) in kind from our VIVIDi equipment supplier; these electrodes were used to complete approximately the first 4,000 participant measurements.*) The participant was required to lie on the exam bed for at least 5 minutes before the measurement was taken.

All contraindications for a participant not being eligible to take a cIMT ultrasound measurement were detailed in *SOP_DCS-0011 – Carotid Intima-Media Thickness*[4] and the CLSA Interpretation and Contraindications Questionnaire (Comprehensive) document[5].

All changes to the collection of the measurement were detailed in *SOP_DCS-0011 – Carotid Intima-Media Thickness* revision history[4].

2.2   Available Data Overview

The following images and data were captured[6]:
- Right & left cIMT (carotid intima media thickness)
  - Cineloop (3 consecutive cardiac cycles)
  - Still image (1 per side) with cIMT measurement tracing
  - Structured Report (SR) file (1 per side)
- Right & left plaque sweep

The following baseline data are available to researchers:
- Exam time, data and side
- The cIMT image(s)
- The CLSA Quality Control (QC) rating for the still IMT image used for analysis
- Plaque sweep(s)
- Measurements:
  - IMT posterior wall measurement number the number of discrete intima media thickness measures
  - IMT posterior standard deviation (SD): SD of the measurements (mm)
  - IMT posterior min: minimum measurement value (mm)
  - IMT posterior max: maximum measurement value (mm)
  - IMT posterior average: average of the posterior wall measurements (mm)

An overview and summary of alphanumeric variables for the cIMT measurement can be found on the Data Preview Portal (DPP) at https://datapreview.clsa-elcv.ca/. The DPP also contains information on the total number of participants who completed, skipped or were contraindicated for the measurement.

3.0   DATA PREPARATION

Alphanumeric data were reviewed for completeness and compatibility and formatted into a .csv file format. An indicator variable was added indicating whether the extraction of alphanumeric data attached to the still image was possible for each identifier. Impossible 0 values of measurements were replaced by missing value codes.

4.0   QUALITY

4.1   Quality Assurance

The CLSA Data Curator along with members of the Quality Assurance Committee performed a monthly review of the sizes of all cIMT image files collected. The purpose of the review was to identify anomalies such as unusually small or exceedingly large image files, which could suggest problems with image quality or the VIVIDi configuration. The reviewer notified the National Coordinating Centre (NCC) Comprehensive Research Coordinator of any file size anomalies. They discussed these issues with the DCS Coordinators, the IT specialists and the expert reviewers to identify the source(s) of the anomalies and then implemented corrective actions.

As part of the CLSA quality assurance (QA) process, a team of experts reviewed approximately ten images per DCS, randomly selected, on a monthly basis. These images were rated for quality as described in the *Quality Check for cIMT Scans information document [internal CLSA document]*. DCSs were provided feedback regarding the quality of the scans reviewed and further individual staff training was provided, when required. Review of the images was conducted via remote access to an image review and rating software program (Alder) developed in-house. By means of a MySQL database backend, all images and their rating data are tracked by participant and interview identifier information.

Some of the errors identified by the QA process include:
- Good image, with analysis box(es) in the wrong spot(s)
- Clear image of the artery but no IMT present
- Interviewers were not analyzing the best frame:
  - Frozen single frame (not analyzed) was different than the single frame analyzed
  - Unanalyzed frame should have been analyzed
- The focus point needed to be moved to the far wall of the cIMT in the image
- Contrast needed to be adjusted to ensure that the cIMT was clearly visible

NOTE: Requests for a copy of the *Quality Check for cIMT Scans* document can be sent to access@clsa-elcv.ca if required upon receipt of data.

Please note that only the cIMT still images were reviewed by the QC team. The plaque sweep images were not reviewed. Furthermore, plaque sweep images were not collected beyond the baseline visit.

4.2   Quality Control

All baseline cIMT still images had a QA rating, on a scale of one to five and based on an agreed set of fault codes (ref. *Quality Check for cIMT Scans information document)*, completed prior to releasing the data to researchers. Based on the fault codes, a simplified quality grade determined categorically if an image was good, re-analyzable or not usable. The fault codes, rating and grade are provided to approved users along with the image data. FUP1 quality assessment checks (QAC) are currently in progress.

4.3 Pre-release Data Preparation

Still images, cineloops and structured report files were retrieved in their native dicom format from the CLSA data repository for identity verification and laterality correction. Given that ultrasound is a gantryless imaging modality, the onus is on the operator to correctly identify to the system the side of the anatomy for local storage archiving as well as for transmission to the CLSA data repository. In some cases, the eight-digit unique interview identifier was entered incorrectly, or the data was attributed to the incorrect participant during the export procedure. A master list of participant identifiers, interview identifiers, machine serial numbers and the visit datetimes allows for the formation of unique keys that can be compared with the embedded dicom tags (e.g., PatientID, StationName, StudyDate, etc.) in the files. Such comparison affords correct identification in terms of participant as well as anatomical side. Additional dicom tags (e.g., InstanceNumber, SeriesNumber, AcquisitionDatetime) allow for consistent grouping of a participant's files to a particular anatomical side.

All images and structured report files were downloaded to one location, had pertinent dicom tags retrieved and compared to a master list of unique keys, accepted or rejected as valid and then further grouped by participant into left and right sides. Structured report files were further processed to extract sets of one or more IMT measurements per participant side (i.e., minimum, maximum, average, standard deviation and number of thickness samples).

All QAC data – fault codes, rating values and quality grades – derived as per items 4.1 and 4.2, were verified and correctly attributed by side to participant and interview identifiers.

II- REANALYSIS OF THE RIGHT-SIDE cIMT IMAGES (BL)

At baseline, 14,885 participants, out of the 29,000 participants who performed the test, had good quality image at the right side of which 12,934 had cIMT values. To increase this number, CLSA decided to reanalyse all images that were deemed analyzable.

During a project to determine distensibility of the carotid artery from the baseline right carotid artery cineloops, cIMT values were generated in parallel with the distensibility analysis. This reanalysis was completed using Artery Measurement Software (AMS) whereas original baseline analysis was done with GE cIMT software. The reanalysed cIMT value was the average cIMT value determined from three end-diastolic frames[7]. In contrast, the cIMT value generated during the original CLSA data collection is the average IMT value for a single still frame end diastolic frame (IMT posterior average).

There are UIDs without an original IMT value inputted from the CLSA. Participants without a cineloop will never have an IMT. Since images can fail the distensibility analysis but still have a passable IMT, we are analyzing them exclusively for passable IMT.

In the IMT reanalysis, at least one IMT value was generated from the UIDs classified as re-analyzable. The IMT value was taken across 1 cm on analyzable end-diastolic frames (this will result in ~100 individual IMT measures being analyzed per frame).

Reanalysis from the Echopac Carotid IMT UIDs is ongoing. As such, the number of valid IMT values will go up. So far 23,000 participant images were re-analyzed and 15,800 cIMT values were extracted. The images for the remaining 6,000+ participants are being processed.

An additional variable "cIMT value arising from reanalysis" is released to researchers.

III-   USE OF cIMT BASELINE VALUES: ORIGINAL MEASUREMENT VERSUS REANALYSIS

Given that different methods were used to capture cIMT measures at baseline and at reanalysis, values from each method were compared across 9,211 good quality right-side images. The average cIMT value in the two methods differed slightly; overall ICC is 0.76 and mean IMT value are 0.72193 (SD=0.15297) and 0.68025 (SD=0.16594) respectively. New values are always lower compared to our original value.

The CLSA team will be investigating the difference between the two methods to identify if there are any systematic errors. If there are no systematic errors, new cIMT values could be adjusted by using single or age-sex correction factors. Researchers will be provided the results and clear guidance once the analysis is finalized.

For now, both measurements at baseline are released to the researcher. It is up to the researcher to decide which data they want to use. For baseline cross-sectional analysis, the reanalyzed cIMT values (15,800+) from right-side images could be used; however, for longitudinal analysis, the original cIMT values should be used to compare with other waves that used the same methods. Please note in that case only cIMT original values with good quality images are valid.

IV-   CONDITIONS OF USE

Conditions of use for alphanumeric data are described in the CLSA Access Agreement[8].

V-   REFERENCES

1. Cigna Medical Coverage Policy: Carotid Intima-Media Thickness Measurement. Available at: https://cignaforhcp.cigna.com/public/content/pdf/coveragePolicies/medical/mm_0475_cover agepositioncriteria_carotid_intima_media_thickness.pdf. (Accessed: Sept. 25, 2023)

2. Canadian Longitudinal Study on Aging: Canadian Longitudinal Study on Aging Protocol. Available at: https://www.clsa-elcv.ca/doc/511. (Accessed: Sept. 25, 2023)

3. Canadian Longitudinal Study on Aging: CLSA Follow-Up 1 Renewal Protocol. Available at: https://www.clsa-elcv.ca/doc/519. (Accessed: Sept. 25, 2023)

4. Canadian Longitudinal Study on Aging: SOP_DCS_0011 Carotid Intima Media Thickness. Available at: https://www.clsa-elcv.ca/doc/522. (Accessed: Sept. 25, 2023)

5. Canadian Longitudinal Study on Aging: Data Collection Site Questionnaires (Comprehensive). Available at: https://clsa-elcv.ca/doc/1122. (Accessed: Sept. 25, 2023)

6. Canadian Longitudinal Study on Aging: Physical assessments collected in the Canadian Longitudinal Study on Aging (CLSA). Available at: https://www.clsa-elcv.ca/doc/3653. (Accessed: Sept. 25, 2023)

7. Shenouda N, Proudfoot NA, Currie KD, Timmons BW, MacDonald MJ. Automated ultrasound edge-tracking software comparable to established semi-automated reference software for carotid intima-media thickness analysis. *Clin Physiol Funct Imaging*, 2018, 38 (3): 396-401. doi: 10.1111/cpf.12428

8. Canadian Longitudinal Study on Aging: CLSA Access Agreement. Available at: https://www.clsa-elcv.ca/doc/2841. (Accessed: Sept. 25, 2023)