

1 PROTOCOL AND QUALITY ASSURANCE FOR CAROTID IMAGING IN 100,000

2 PARTICIPANTS OF UK BIOBANK: DEVELOPMENT AND ASSESSMENT

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Funding

UK Biobank has received funding from the UK Medical Research Council, Wellcome Trust, Department of Health, British Heart Foundation, Diabetes UK, Northwest Regional Development Agency, Scottish Government, and Welsh Assembly Government. SC was supported by the UK Engineering and Physical Sciences Research Council (EPSRC) (Impact acceleration award EP/K503769/1) and Heart Research Australia. The QA tool was developed as part of the InnovateUK and EPSRC funded AQABUS project (EP/L505316/1). RC is supported by a BHF personal Chair. PL is supported by the British Heart Foundation FS/11/65/28865.

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1 **Word count, including references: 3938**

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Abstract

Background - Ultrasound imaging is able to quantify carotid arterial wall structure for assessment of cerebral and cardiovascular disease risks. We describe a protocol and quality assurance process to enable carotid imaging at large scale that has been developed for the UK Biobank Imaging Enhancement Study of 100,000 individuals.

Design - An imaging protocol was developed to allow measurement of carotid intima-media thickness (CIMT) from the far wall of both common carotid arteries. Six quality assurance criteria were defined and a web-based interface (Intelligent Ultrasound) was developed to facilitate rapid assessment of images against each criterion.

Results and Conclusions – Excellent inter- and intra-observer agreements were obtained for image quality evaluations on a test dataset from 100 individuals. The image quality criteria then were applied in the UK Biobank Imaging Enhancement Study. Data from 2560 participants was evaluated. Feedback of results to the imaging team led to improvement in quality assurance (QA), with QA failures falling from 16.2% in the first two-month period examined to 6.4% in the last. 80% had all CIMT images graded as of acceptable quality, with at least one image acceptable for 98% of participants. CIMT measures showed expected associations with increasing age and gender.

Carotid imaging can be performed consistently, with semi-automated quality assurance of all scans, in a limited time frame within a large scale multimodality imaging assessment. Routine feedback of quality control metrics to operators can improve the quality of the data collection.

Abstract word count: 239

Keywords: Carotid, UK Biobank, Ultrasound, Carotid Intima Media Thickness, Carotid IMT, Quality Assurance

INTRODUCTION

UK Biobank is a prospective study of 500,000 people aged between 40 and 69 years at recruitment between 2006 and 2010.¹ An initial feasibility assessment (pilot phase) was initiated in 2014, to evaluate the feasibility of conducting a multi-modal imaging study in 100,000 participants over 6 years, including MRI scans of the brain, heart and body, a dual-energy X-ray absorptiometry (DEXA) scan and a carotid ultrasound.² The large scale and the richness of the phenotyping in UK Biobank allows researchers to examine aspects of cardiovascular epidemiology that previously would not have been possible.

Imaging of the carotid vessels can provide information on the thickness of the carotid vessels, expressed as the carotid intima media thickness (CIMT), and the presence of carotid plaque. Information concerning both has been associated with incident cardiovascular events.³⁻⁵ Use of ultrasound to image the carotids has the advantage of being relatively low-cost, fast, free of ionizing radiation, and requiring relatively little training to use,⁶ leading to its successful use in a number of large population-based cohort studies.^{4,5,7,8} Good reproducibility is seen even among relatively inexperienced operators under routine clinical conditions.⁶ However, imaging on the scale of UK Biobank is unprecedented and requires adaptation of usual approaches that allow both efficient data acquisition and exceptional attention to quality assurance, to avoid bias and minimise measurement variation over time. Previous publications have described the UK Biobank in general,¹ and the imaging substudies involving cardiac MRI,^{2,9} liver MRI,¹⁰ and brain MRI.¹¹ In this article, we describe the carotid ultrasound scanning protocol used within the UK Biobank Imaging Enhancement study and the development of a quality assurance process. We also report an evaluation of this process based on carotid ultrasound scans from the first 2,560 participants.

METHODS

Protocol Development

A protocol was developed based on reported guidelines for carotid image acquisition^{12,13} that took account of the practical aspects of space for equipment, time available and the limited experience of the technicians. In addition, the requirement for potential future analysis of raw ultrasound data was considered in acquisition of images. The protocol was devised to operate alongside the other planned assessments for the Imaging Enhancement of UK Biobank (cardiovascular, brain and abdominal magnetic resonance imaging, DEXA, as well as a repeat of the study's baseline measures, which incorporate a comprehensive computer-based questionnaire with interview, physical measures, and blood and urine sampling).

The flowchart for the protocol developed is shown in Figure 1. An abbreviated version of the UK Biobank Standard Operating Protocol is available from <http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=511>. In the pilot phase, imaging was performed solely at the UK Biobank imaging facility at Cheadle, Stockport, UK. In brief, a CardioHealth Station (Panasonic Healthcare Corporation of North America, Newark, NJ, USA) was used, with a 9MHz linear array transducer. The carotid study was performed in a darkened room and participants lay supine supported by a triangular pillow. Initially, a 2D sweep of both carotids was performed along the short-axis (transverse plane) from low in the neck up to the jaw, at least to the level of the carotid bifurcation, with the right carotid scanned first. The conventionally configured CardioHealth Station user interface software allows these sweeps to be performed but not stored. To meet the needs of the UK Biobank, this interface was modified prior to commencement of the study to allow cine image loop

storage. The sweep was repeated in the long-axis (longitudinal plane) and stored. These longitudinal images were also used to identify the bifurcation for measurement of CIMT. This was performed at two angles for each carotid, giving a total of four CIMT measurements, which when measured from the vertical axis were 150° and 120° on the right carotid, and 210° and 240° on the left carotid. Automated position location identification provided a real-time readout of the transducer angle to the technician. The CIMT was measured at time of acquisition using the semi-automated CardioHealth Station hardware and software, with 'Auto ROI' and 'Auto Freeze' enabled. The CHS software places a marker on the screen to guide the user in alignment of the flow divider and a 10mm region-of-interest box to facilitate CIMT measurement. The far-wall of the common carotid was then automatically tracked by the region-of-interest box. When three consecutive cardiac cycles met internal quality thresholds, the image auto-froze in end-diastole, giving the mean, maximum and minimum of the CIMT tracking. Manual override of the automatically derived CIMT boundaries was performed in cases where the detected boundaries did not align with the underlying B-mode image, and manual override of the auto-freeze feature was performed if auto-freeze was not invoked after prolonged period of scanning. The technician also had the facility to adjust the image to ensure the CIMT measurement was not taken at sites of focal plaque, defined based on the Mannheim Consensus as: "a focal structure that encroaches into the arterial lumen of at least 0.5mm or 50% of the surrounding IMT value or demonstrates a thickness >1.5mm as measured from the media-adventitia interface to the intima-lumen interface".¹²

Quality Assurance

Development of Quality Criteria - To develop quality assurance (QA) processes for carotid imaging, we reviewed available literature on protocols used in previous studies and also criteria described for carotid image quality.^{5,12-15} No specific guidelines for quality assurance for a study of this size (i.e. for 100,000 participants) were identified in literature review. Thus, we defined six QA criteria based on how a technician is trained to handle the probe and identify the region of interest when acquiring a carotid image, as described below:

1. **Horizontal.** The whole carotid (not just at the location of the box) lies approximately horizontal on the image, with >75% of the long axis of the carotid < 15 degrees above or below the horizontal.
2. **Oblique** (also referred to as **arterial misalignment**). The section obtained should be along the long-axis of the carotid, with >80% of the visualised common carotid showing parallel near and far carotid walls.
3. **Box location.** The distal edge of the box for automated CIMT measurement should be positioned 1cm proximal to the flow divider of the carotid bulb, and there should be no focal plaque within the box.
4. **White-black-white.** The CIMT should have distinct borders that define a clear “white-black-white” pattern on the monitor.
5. **CIMT tracking.** The automated CIMT measurement was recorded at the correct time in the cardiac cycle (end-diastole) and > 50% of the CIMT within the measurement box has been tracked. All areas of CIMT tracked should accurately align with the B-mode image.
6. **Angle.** The acquisition angle of the image should have been recorded within 30 degrees of the selected angle category (i.e., for images selected to represent 120 degrees, the acceptable range is 90-150 degrees).

Based on these six quality criteria, we developed a single Pass/Fail QA flag for images. For an image to pass the overall QA, an image needed to pass *all* of the individual criteria of box position and CIMT tracking, but could fail *one* of horizontal, oblique or white-black-white criteria. For each participant, a carotid study consisted of four images showing the CIMT measurement acquired at predefined angles of acquisition (i.e., right 150°, right 120°, left 210°, and left 240°). A separate QA flag was generated for each angle of acquisition.

Assessment of Quality Criteria - To evaluate our approach, we used a test dataset of 100 carotid studies to estimate both inter and intra-observer reproducibility of the quality criteria, after which we evaluated the process as a whole in the Pilot Phase (2567 subjects, of whom 2560 had a QA assessment at each angle of acquisition). To ensure consistency in application of these criteria, we developed a web-based interface to allow the rapid semi-automated review of images. The images were loaded into a simple custom designed grading tool (Intelligent Ultrasound Ltd, Abingdon, United Kingdom), and each image was assessed twice (on separate occasions) by three clinicians experienced in grading carotid ultrasound images, henceforth called graders. When assessing inter- and intra-observer reliability or agreement, measures that adjust the raw percentage agreement by that expected due to chance are used, such as Cohen's kappa. However, Cohen's kappa and its direct extensions tend to show paradoxical behaviour at the extremes of prevalence (for example, as in our case, if a large majority of images passed QA assessment), with very high agreement between observers sometimes even leading to negative kappas.^{16,17} We therefore used Gwet's first order agreement coefficient, referred to as the AC1 statistic, to assess reliability. This, like Cohen's kappa, is 0 in cases of no agreement and 1 in cases of perfect agreement, but incorporates observer uncertainty into the model and tends to be less affected by prevalence.^{17,18}

Application of Quality Assurance and Quality Audit in Pilot Phase - Participant age was provided and analysed according to decade of birth, with age groups of ≤50, 51-60, 61-70,

and ≥ 71 years at the time of carotid ultrasound. Once the QA criteria were finalised, all studies acquired were reviewed for quality assurance (QA) purposes by a trained UK Biobank senior radiographer and information fed back to the sonographers on a weekly basis. Images from each of the four acquired angles were graded as Pass/Fail, according to the developed criteria and based on an overall assessment of each image. A random selection of approximately 10% of these images, as well as any borderline images, were reviewed by expert staff in the Oxford Cardiovascular Clinical Research Facility. Results from the external review were fed back to the imaging centre on a monthly basis to complete the audit cycle, with teleconferences as required to discuss any specific issues.

Statistical Analysis - At the end of the pilot phase, we used the available data on CIMT, quality assurance and the age and sex of participants to investigate the overall validity of the acquired carotid measurements. Specifically, we studied associations between CIMT and age and sex, reasoning that measured CIMT should be higher in older age groups and in male participants. We used multivariate linear regression, with predictor variables of age (as an ordered categorical variable based on decade) and sex. We then assessed the impact of the quality assurance process on carotid measures by studying how the model fit varied if images that failed QA were excluded. We did this based on exclusion of all studies in which one image failed QA. All statistical analyses were performed using R version 3.2.2.¹⁹

RESULTS

Assessment of Quality Criteria - 588 images from 100 participants acquired during the pilot phase of the UK Biobank Imaging Enhancement were graded in the semi-automated tool (Figure 2A) by three graders on two separate occasions. More than one image from each angle of acquisition was eligible for assessment during this phase of the QA process. Overall, there was a very good agreement between evaluations performed by different graders

(Supplementary Figure 1, Supplementary Table 1). All criteria showed excellent intra-observer reliability (minimum Gwet AC1 88%), with good inter-observer reliability (minimum Gwet AC1 78%). Examples of images passing and failing QA are shown in Figure 2B-G.

Application of Quality Assurance and Quality Audit - Images from the first 2567 participants after implementation of the QA protocol were evaluated. Pass/Fail QA flags for all four angles of acquisition were available for 2560 participants, and, of these, 2519 (98%) had at least one image passing QA. 523 (20%) studies had at least one image failing QA but the proportion of images failing QA decreased over time, with an average across views of 16.2% failing QA in the first two month period compared to 6.4% failing in the last two month period analysed (Supplementary Figure 2).

Evaluation of validity of carotid datasets

Data for evaluation of associations were available for 2558 of the 2567 participants. Based on the entire dataset, mean CIMT was higher in older, compared with younger, age groups and was higher in men than in women (Table 1, Supplementary Figure 3). A linear regression model (Table 2) showed a 61 μ m (95% CI: 55-67 μ m) increase in CIMT per decade, and a 48 μ m (95% CI: 39-57 μ m) increase in male compared to female participants compared to the average CIMT of 553 μ m (95% confidence interval (95% CI): 542-564 μ m) in 45-50 year old females in the model (adjusted R^2 0.191, $p < 2 \times 10^{-16}$). Studies with one image that failed QA tended to have on average a 46 μ m greater CIMT (Supplementary Figure 3) and a linear regression model with a QA flag (indicating any image failing QA) had slightly higher adjusted R^2 than the model without the QA flag (Table 2). However, the confidence interval for reference CIMT in younger females, as well as those of older age and male sex, was very

similar under both models, suggesting that the impact of including ‘failed’ images on the overall assessment is small.

DISCUSSION

We describe a protocol for carotid image acquisition and semi-automated measurement of carotid IMT within a limited timeframe for application within a large cohort study.

Furthermore, we describe development of quality assurance criteria to allow evaluation of quality of images and audit control. Application of these procedures reduced the number of quality fails within scans and helped to ensure that 98% of participants had at least one CIMT measure. Analysis of the dataset confirms that the CIMT measures within the UK Biobank Imaging Enhancement pilot phase associate with age and sex in the expected way, implying face validity of the measures.

A key feature of the UK Biobank imaging protocol is that it needs to be performed within a limited time frame in participants who also undergo abdominal, cardiac and brain magnetic resonance imaging, dual energy X-ray absorptiometry (DEXA), blood sampling and an extensive questionnaire. During the study visit, only 10 minutes is available for carotid imaging, including time for patient registration. In addition to this time constraint, we expect that data acquisition will be performed by multiple technicians at three separate imaging assessment centres over the course of the Imaging Enhancement Study (which will take 6-7 years). Our protocol was therefore developed to achieve a relatively detailed image acquisition in a highly reproducible manner. A recent meta-analysis highlights the variability in CIMT measurements across studies.²⁰ The use of semi-automated measurement techniques is recommended in international consensus statements to reduce inter-observer variability,^{12,13} and we therefore chose an ultrasound system that implements these. In addition, the

1 CardioHealth Station system we used has been shown to have excellent reproducibility even
2 in less-experienced users.^{6,21,22}

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4 A potential limitation of the protocol at this time is the lack of quantification of the plaque
5 that may be present in the images. Focal plaque has been shown to provide additional
6 discrimination above that provided by CIMT measurement alone.^{23,24} However, the additional
7 discrimination is modest (area under the receiver operating curve 0.64 for plaque vs 0.61 for
8 CIMT as a predictor of myocardial infarction over an average of eight years in a large meta-
9 analysis).²⁴ As the assessment of plaque is much more subjective, it is both operator
10 dependent and time consuming. Therefore it was not considered practical to provide
11 evaluation of plaque at the time of image acquisition. However, the image acquisition
12 protocol provides both a short axis 2D sweep along the length of the carotid as well as
13 longitudinal views to above the bifurcation. Retrospective evaluation of stored image datasets
14 will therefore be possible to assess plaque characteristics and other novel carotid parameters.
15 These images will be available to external researchers. In addition, these stored raw image
16 datasets have the potential to be used for future novel metric evaluations including, for
17 example, assessment of geometric variation or measurements of intima media thickness in
18 other locations within the vessel. By linking these measures to the available imaging
19 modalities or later clinical outcomes, potentially new carotid biomarkers of cerebral or
20 cardiovascular health could be identified.

21
22 The within and between rater reliability of our QA criteria suggest they can be applied with
23 little inter- or intra-observer variability. A number of these criteria, such as the “White-Black-
24 White” criterion, are integral to CIMT measurement, while others, such as the exclusion of

focal plaque from the measurement box, were chosen to increase reproducibility. The “Angle” criterion has relatively relaxed requirements for the angle of acquisition, as we decided that the exact angle of acquisition was not as important as repeated measurements of the two carotids in this single time point study, and therefore should not lead to failure of the entire carotid study. With the development of a standardised interface for grading the quality of the images acquired and a larger number of studies acquired it may be possible to develop image analysis techniques that would automate the QA process further.

The impact of inclusion or exclusion of QA criteria on the model fit was very small and therefore data released by UK Biobank includes all CIMT measures irrespective of the QA flag. There was a higher rate of QA fails with older age, and the provision of QA flag may therefore be of scientific interest. There is a distinct possibility that future analyses will reveal that images that fail QA have predictive value in themselves. For example, it is possible that highly tortuous carotid arteries would be more likely to fail QA, and that the tortuosity is predictive of future cardiovascular events. The QA flag for each image is therefore provided along with the CIMT measure on the UK Biobank data showcase (available at biobank.ctsu.ox.ac.uk/showcase).

A major advantage of the QA process is that real-time feedback is possible during training. The number of images failing QA during the course of the pilot phase more than halved following such feedback based on QA measures, with a rapid fall on implementation of the QA audit process and maintenance of lower levels thereafter. Interestingly, both left sided angles of acquisition had a higher failure rate initially, and appeared to have a more rapid improvement compared to right sided angles of acquisition. As we did not record handedness

1 of operators, we were unable to investigate this further. The audit process involved feedback
2 to the technicians of both number of image fails and reasons for image quality failures.
3 Furthermore, as each image could be identified by time and operator, the advice could be
4 personalised for individual technicians to improve their carotid imaging technique. Several
5 operators performed carotid imaging during the pilot phase and new operators started during
6 that period. The QA criteria were introduced as part of the training for new technicians and
7 each was required to show competency against the QA criteria in test cases before being
8 allowed to scan participants. Therefore the maintenance of a low failure rate provides
9 reassurance that the use of the QA criteria within training processes was also robust.

10 In summary, carotid images and semi-automated CIMT measures are now available from the
11 UK Biobank Imaging Enhancement Study. This is the first published description of the
12 protocol used for acquisition of these images and the rationale for the design. Furthermore,
13 we provide a detailed evaluation of the quality assurance process, description of a semi-
14 automated online tool for rapid image evaluation and demonstrate that the data generated fits
15 expected patterns of association with age and gender.

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Conflicts of interest

SL is an employee of, and RB and RM are consultants to Panasonic Corporation. JP is an employee of, and AN, MY and PL are consultants to Intelligent Ultrasound Ltd. SG, NA, CS, RC, PM, and PL are employees of or have received support from UK Biobank.

Authorship

AJL, SG, RM, SL, RB, JAN, SN, SEP, NA, CS, RC, PMM, PL contributed to the conception or design of the work. SC, AJL, SG, RM, RB, JP, MY, NA, CS, RC, PMM, PL contributed to the acquisition, analysis or interpretation of data for the work. SC drafted the manuscript. SC, AJL, SG, RM, SL, RB, JP, MY, JAN, SN, SEP, NA, CS, RC, PMM, PL critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Table 1. Carotid intima-media thickness by age.

Age (years)	n	Overall mean (sd)	Female n (%)	Female mean (sd)	Male mean (sd)	Poor QA n (%)
≤ 50	170	588 (84)	95 (56%)	578 (76)	600 (93)	23 (14%)
51-60	787	628 (107)	451 (57%)	607 (83)	657 (126)	119 (15%)
61-70	1180	701 (123)	596 (51%)	675 (104)	728 (134)	238 (20%)
≥ 71	421	763 (145)	175 (42%)	739 (126)	781 (155)	143 (34%)

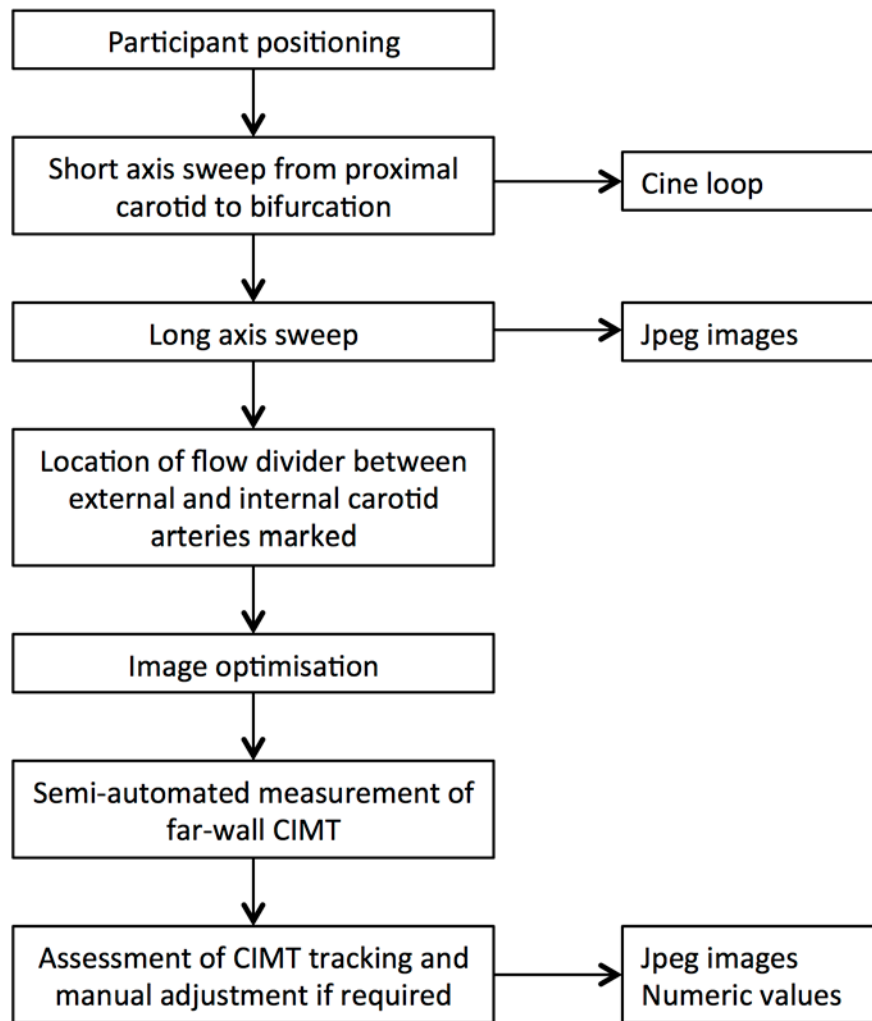
“Poor QA” refers to studies where at least one of the four angles of acquisition was deemed to not pass quality assurance criteria. CIMT is measured in micrometres. Abbreviations: CIMT, carotid intima-media thickness; sd, standard deviation.

Table 2. Linear regression, with carotid intima media thickness as outcome variable.

	Basic model	Incorporating QA
n	2558	2558
Adjusted R ²	0.19	0.21
Average CIMT for ≤ 50 year old females	553 (542 - 564)	551 (539 - 562)
Increase per decade	61 (55 - 67)	58 (52 - 63)
Increase in males	48 (39 - 57)	45 (36 - 54)
Increase if study had any image failing QA		46 (35 - 57)

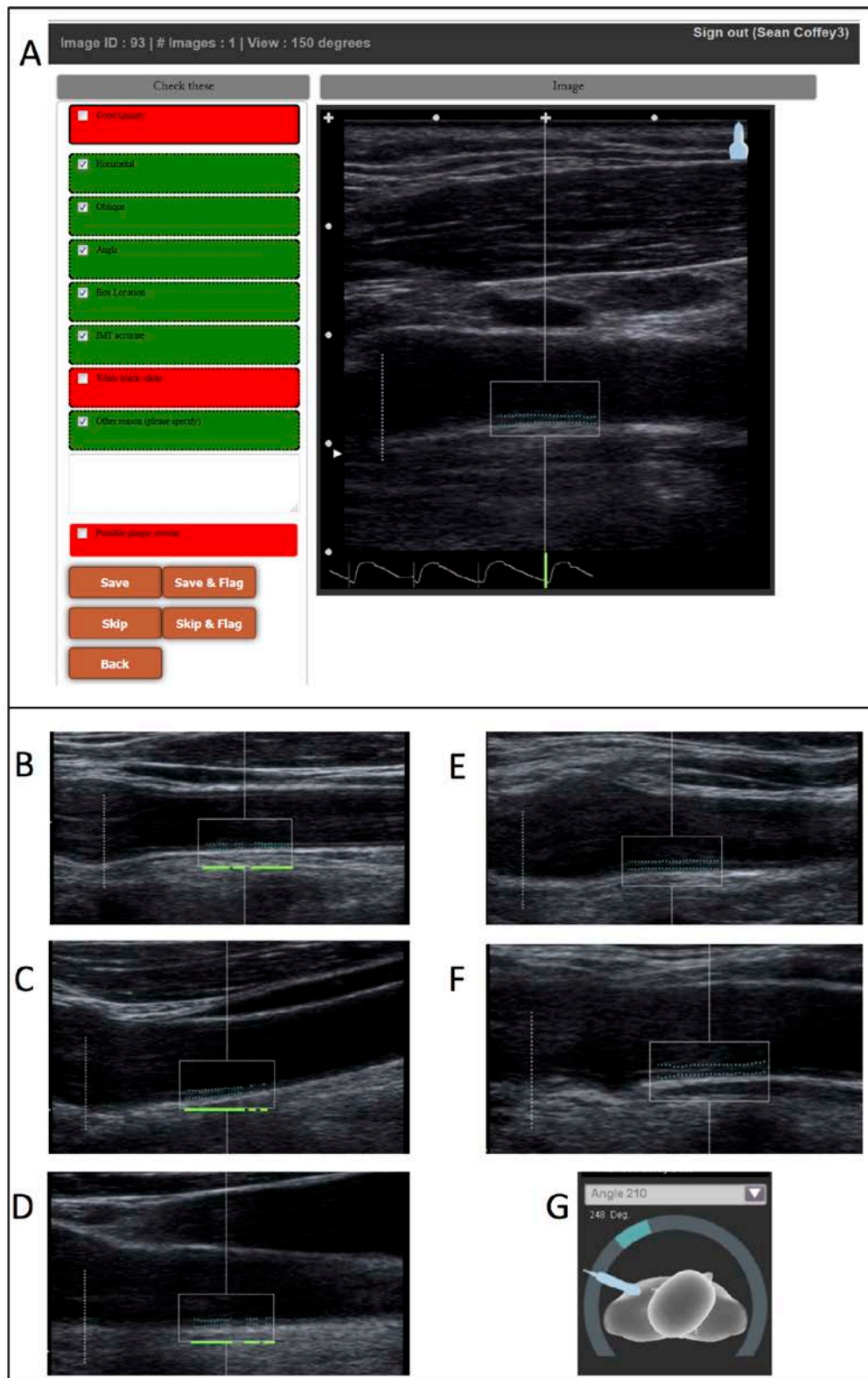
CIMT is measured in μm , with the 95% confidence interval shown in brackets. The average CIMT for ≤ 50 year old females is based on the linear regression model intercept. Abbreviations: CIMT, carotid intima media thickness; QA, quality assurance.

Figure 1. Overview of UK Biobank carotid ultrasound protocol.



Outputs from the protocol are shown on the right of the figure. Four separate sets of CIMT measurements were obtained: right carotid at 150°, right carotid at 120°, left carotid at 210°, and left carotid at 240°. Numeric values stored were maximum, mean, and minimum CIMT. Abbreviations: CIMT, carotid intima-media thickness.

1 **Figure 2. Quality assurance grading process.**



2
3 Figure showing the grading interface (A) and example images (lower panel). The grading
4 interface shows an image not meeting the “White-black-white” quality assurance (QA) criterion
5 (indicated by the lack of a tick in this box). The example images show a good quality image (B),

- 1 and images failing quality assurance criteria: Horizontal (C), Oblique (D), Box location (E), CIMT
- 2 tracking (F), and Angle (G). Assessment of the Angle criterion was facilitated by the use of an
- 3 automated transducer position identifier, as shown in 2G.