PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Bragatston study protocol: a multicenter cohort study on automated quantification of cardiovascular calcifications on radiotherapy planning CT-scans for cardiovascular risk prediction in breast cancer patients
AUTHORS	Emaus, Marleen; Išgum, Ivana; van Velzen, Sanne; van den Bongard, Desirée; Gernaat, Sofie; Lessmann, Nikolas; Sattler, Margriet; Teske, Arco; Penninkhof, Joan; Meijer, Hanneke; Pignol, Jean-Philippe; Verkooijen, Helena

VERSION 1 - REVIEW

REVIEWER	Nobuo Tomizawa New Tokyo Hospital, Japan
REVIEW RETURNED	12-Apr-2019

GENERAL COMMENTS	1. Page 8, line 55. Please show why the case-to-control ratio was set as 1:3. 2. Page 9, line 9. Please clarify the slice thickness and increment of the evaluated images. 3. Page 9, line 55. Please describe the specific calculation method of the modified Agatston score. 4. Page 10, line 44. The criteria for HT, DL, DM should be cited. 5. Page 10, line 44. Why is RA a risk factor for CVD? If possible family history of CVD should be included. 6. How will the data be evaulated? Will the data be transfered to a data center? Please clarify. 7. Figure. Please add some more figures showing the calcium of valves and aorta.

REVIEWER	Sophie Jacob IRSN, France
REVIEW RETURNED	07-May-2019

GENERAL COMMENTS	The manuscript addresses a relevant topic that is the issue to consider baseline CVD risk factor to properly evaluate the risk of RT-induced CVD.

	This is a well written manuscript describing the Bragatston study protocol that was designed in order to answer 3 main points: validation of an automated quantification of calcifications on RT planning CT-scan without having to perform another CT-scan dedicated to CAC scoring; impact of CAC scoring on the mid-term risk of CVD after BC RT; interest of considering this CAC scoring as compared with other know CVD risk factors in the prediction of the risk of CVD. I only have few minors comments and questions: In the paragraph on Reference library of manual calcification quantification, it is not clear how the last step for calcium scoring is performed. Is it performed the same way as with the automatic calcification quantification once the atherosclerotic calcifications have been detected with the 2 CNN ? Is it again a “modified Agatston score” ? Moreover, it would be interesting to precise how many patients will be included in this part, as 16 000 with manual calcium scoring is probably not feasible in a reasonable delay. Is it more than the 561 UMBRELLA patients? This figure should also be clarified in the statical analysis WP1 paragraph. In the paragraph on tumor and breast cancer treatment, a list (maybe not exhaustive) of the collected variables in the NCR is missing. It would help to understand which variables will be tested in WP2. This is shortly detailed in the statistical analysis part, but would help comprehension if the list of variable was detailed earlier.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 Nobuo Tomizawa

1. Page 8, line 55. Please show why the case-to-control ratio was set as 1:3.

We rephrased this paragraph (section ‘Study design and population’): “To increase statistical power, a case-to-control ratio of 1:3 will be applied leading to a random sample of approximately 600 patients. The power gained by including more than three controls to one case is little.”

2. Page 9, line 9. Please clarify the slice thickness and increment of the evaluated images.

We added this information to the revised manuscript (section ‘Study design and population’): “The RT planning CT-scans that will be collected are acquired as part of clinical routine (no contrast enhancement, no ECG-triggering, 120 kVp, in-plane resolution 0.78-1.37 mm, 3.0 mm slice thickness, 3.0 mm increment).”

3. Page 9, line 55. Please describe the specific calculation method of the modified Agatston score.

We described this calculation method in section ‘Automatic calcification quantification’: “These modified Agatston scores will be calculated by multiplying the calcification area (in mm2) by the density score (1, 130–199 Hounsfield Units (HU); 2, 200–299 HU; 3, 300–399 HU; 4, > 399 HU) of the area (calcification density) and summing the lesion scores, in which a minimal lesion definition of 1.5 mm3 will be maintained to eliminate noise.”

4. Page 10, line 44. The criteria for HT, DL, DM should be cited.

We added this information into the revised manuscript (section 'Tumor and treatment characteristics and CVD risk factors'): "Regarding hypertension, hypercholesterolaemia, diabetes and smoking, a patient will be scored positive when the risk factor is documented in the hospital medical record or reported by the GP by means of a questionnaire."

5. Page 10, line 44. Why is RA a risk factor for CVD? If possible family history of CVD should be included

Thank you very much for correcting the error regarding RA. We removed from the manuscript 'rheumatoid arthritis' as risk factor.

We restricted our traditional CVD risk factor data collection to those factors that are included in the traditional CVD risk calculators like Framing risk. Family history of CVD is only used in a very few calculators. In addition, there is variation in the definition of a positive family history of CVD. Therefore, we decided to not include this risk factor.

6. How will the data be evaulated? Will the data be transfered to a data center? Please clarify.

We clarified this issue (section 'Ethics and dissemination'): "All data, with the exception of data provided by Statistics Netherlands, will be stored centrally at the University Medical Center Utrecht. This dataset will be sent to Statistics Netherlands for additional linkage."

7. Figure. Please add some more figures showing the calcium of valves and aorta.

We added three figures: one showing calcifications in the thoracic aorta (figure 3), one showing mitral valve calcifications (figure 4) and one showing aortic valve calcifications (figure 5).

Reviewer: 2 Sophie Jacob

1. In the paragraph on Reference library of manual calcification quantification, it is not clear how the last step for calcium scoring is performed.

a. Is it performed the same way as with the automatic calcification quantification once the atherosclerotic calcifications have been detected with the 2 CNN ?

Yes.

b. Is it again a "modified Agatston score" ?

Yes.

To be more clear about this issue we added the following information (section 'Reference library of manual calcification quantification'): "In line with the automatic calcification quantification, CAC, TAC, AVC and MVC will be expressed in volume scores (in mm3). The modified Agatston scores will be calculated as described in the previous section."

2. Moreover, it would be interesting to precise how many patients will be included in this part, as 16 000 with manual calcium scoring is probably not feasible in a reasonable delay. Is it more than the 561 UMBRELLA patients? This figure should also be clarified in the statistical analysis WP1 paragraph.

We agree with you and added the missing information to the revised manuscript:

- Section 'Reference library of manual calcification quantification': "Manual calcium scoring will be done in a subset of planning CT-scans randomly selected per hospital (UMC Utrecht: n=500; the Erasmus MC Cancer Institute: n=300; Radboudumc: n=200)"

- Section 'Statistical analysis': "Results will be presented for the total sample of 1,000 manually and automatically assessed planning CT-scans. In addition, results will be stratified by participating hospital."

3. In the paragraph on tumor and breast cancer treatment, a list (maybe not exhaustive) of the collected variables in the NCR is missing. It would help to understand which variables will be tested in WP2. This is shortly detailed in the statistical analysis part, but would help comprehension if the list of variable was detailed earlier.

We agree with you and added the following information to the paragraph on tumor and breast cancer treatment (section 'Tumor and treatment characteristics and CVD risk factors'): "Tumor data variables include tumor stage, grade and receptor status and treatment data variables include type of surgery (breast conserving therapy, mastectomy), radiotherapy (laterality and radiation fields (if available)), chemotherapy (yes, no), hormonal therapy (yes, no) and immunotherapy (yes, no)."