# Final Study Report (Non-CTIMP)

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|---|---|---|---|
| **Study Title:** | Development of a new approach to measure the volume of breast tissue removed during wide local excision using specimen weight and mammographic density | | |
| **Local Study Reference:** | UHDB/2019/088 | **IRAS ID:** | 325661 |
| **Chief Investigator:** | Mr Emanuele Garreffa | | |
| **Sponsor:** | University Hospitals of Derby and Burton NHS Foundation Trust | | |
| **Funder:** | UHDB Small Research Grants Scheme funding 2023 | | |
| **Start Date:** | 10/10/2023 | **Number of Participating Organisations/Sites:** | 1 |
| **Planned End Date:** | 31/01/2025 | **Actual End Date:** | 31/01/2025 |
| **Planned Number of Participants:** | 365 | **Actual Number of Participants Recruited:** | 370 |


**Lay Summary:**

**What was the study about?**

This study aimed to understand how accurately the size (volume) of breast tissue removed during surgery can be estimated. We wanted to find out whether a new calculation method could estimate tissue volume more accurately than the method currently used in clinical practice. This matters because accurate volume estimates can influence treatment decisions and help ensure patients receive the most appropriate care.

**What did we do?**

We studied breast tissue samples from women undergoing wide local excision surgery for breast cancer. Tissue samples were collected as part of routine care and no additional procedures were required. We measured the actual volume of the tissue samples and compared these measurements with volumes estimated using the current method and a new method developed using study data. We also looked at whether factors such as tissue weight and density could improve volume estimates.

**What did we find?**

We found that when compared using the complete dataset the new (phase 1) calculation method was no more accurate than the method already in use. Both methods tended to overestimate or underestimate tissue volume for many samples, and only around one quarter of samples were estimated accurately by either method. Overall, the new method did not provide a meaningful improvement compared to current practice.
An additional analysis was undertaken in which estimate of the tissue sample densities were included with the other explanatory variables included in the phase 1 analysis. This also failed to produce more accurate estimates than the current method.

However, the accuracy of the estimation methods appears to be related to the weight of the tissue sample. For samples weighing between 2 and 17g, the method developed in phase 1 (phase1 method) was inclined to be more accurate than the current method. For

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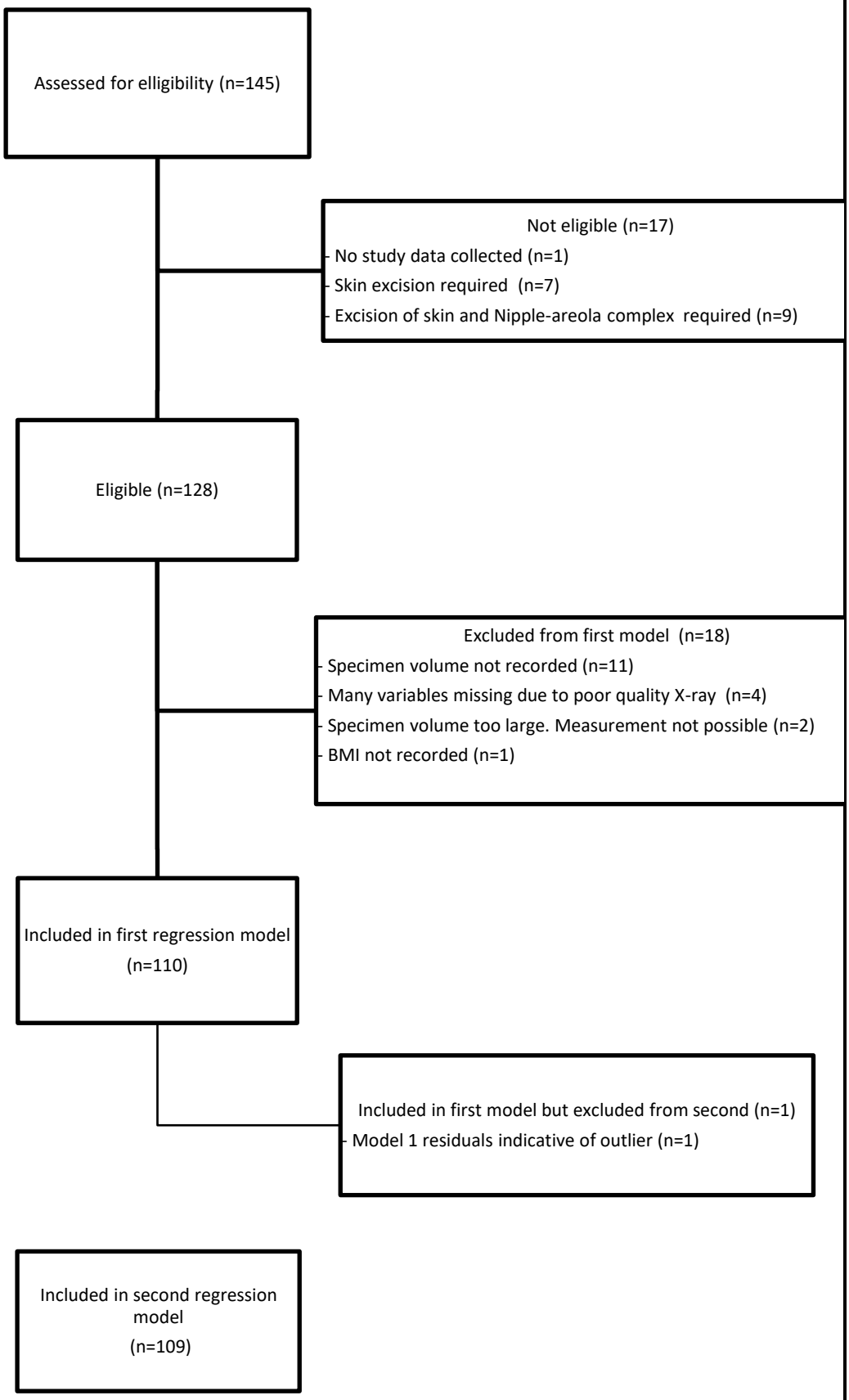
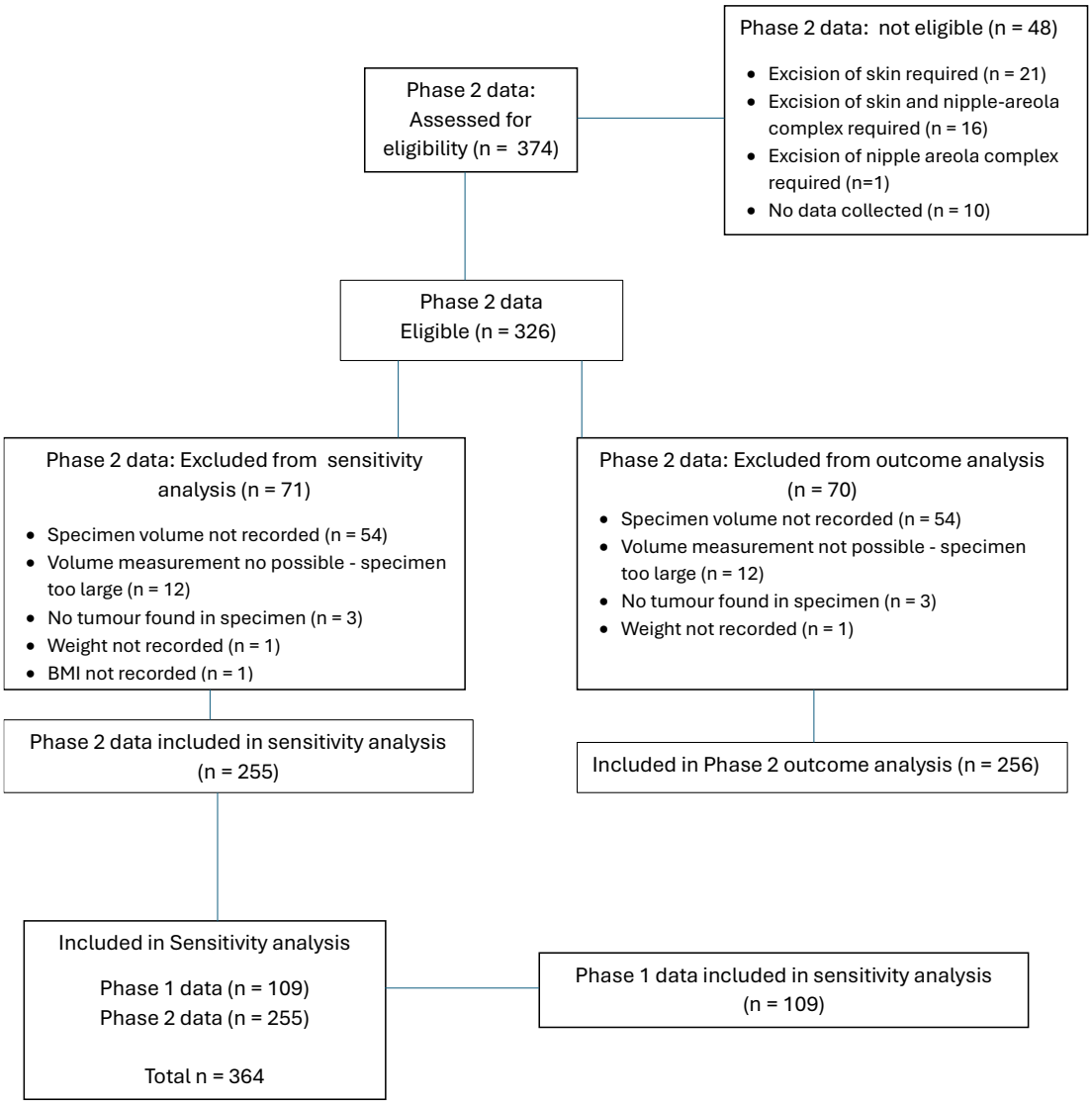
|---|---|
| | samples weighing more than 37g the current method tended to be more accurate. For samples between 18 and 37g it was unclear which estimation method produced the most accurate estimates. Tissue sample volume estimates developed for a planned sensitivity analysis and the estimates from the additional analysis described above did not consistently offer more accurate estimates than either the current or the phase 1 methods.<br><br>**What does this mean?**<br><br>These results suggest that simply changing the calculation method is unlikely to improve how tissue volume is estimated during surgery. However, utilising a combination of estimation methods based on the sample weights may improve the tissue volume estimates, especially for patients with relatively low- or high-weight samples.<br><br>**What happens next?**<br><br>Unfortunately, none of the methods investigate in this study has been found to be significantly more accurate than the currently used method. The findings will be shared through a scientific publication in line with local policy to ensure that other researchers are aware of these results. |
| **Changes to the Trial:** | 28/10/2024 – study extension to 31/01/25 |
| **Participant Flow:** | A total of 519 patients undergoing Wide Local Excision have been screened, of which 454 were eligible (87.5%).<br>89 of the eligible patients had incomplete records and were excluded from the study.<br>Reasons for exclusion:<br>- Volume not measured (65)<br>- Specimen too big for volume measurement (14)<br>- Poor quality specimen x-ray (4)<br>- BMI not recorded (2)<br>- No tumour found in specimen (3)<br>- Weight not recorded (1)<br><br>The main reason for exclusion was the specimen volume was not being recorded during dissection (12.5%). Most instances happened at the beginning of the study and later on when new histopathology staff joined the team of dissectors/preppers. |

**Phase 1 CONSORT diagram:**



**Phase 2 CONSORT diagram:**




**Main Findings:**

**Phase 1**

The tissue samples from 145 patients were screened for inclusion in the study (Figure 1) and 17 samples were not eligible. Sixteen of these samples included skin or skin and at least part of the nipple areola complex. No data were recorded for the other ineligible sample. Their sample ID was only recorded in the screening dataset and no screening data were recorded.

Of the 128 eligible samples, 18 had incomplete data, which meant they could not be included in the analysis. The information that was most likely to be missing was the sample tissue volume (missing for 13 samples). It was not recorded for 11 samples and could not be measured for a further two because the tissue sample was too big to fit into the measuring cylinder.

Data from 110 samples could be included in the regression model. This was the required sample size specified in the protocol

**The regression model for Phase 2 of the Study**

A regression model was fitted (Table 1) and the residuals were checked. The residuals of the models in this study are the difference between the measured specimen volumes and the specimen volumes calculated using the model. The methods used to assess the models require the residuals to be normally distributed but they were not, which seemed to be due to one unusually large residual. The five highest residuals from the first regression model were 64ml, 21ml, 19ml, 11ml and 10ml. The sample with a difference of 64ml between the fitted sample volume and the measured sample volume caused concern. The difference was three times the next highest difference and when this record was compared to the other specimen records no reason for this could be identified. None of the relevant explanatory variables (i.e. age, BMI, specimen weight, specimen volume, healthy tissue density, tumour histology, tumour grade, whether a mass was present) were particularly high or low, and the sample volume was extremely high compared to the sample volumes of records with similar values for the explanatory variables. After confirming that there were no data transcription errors for this sample, it was removed from the data due to concerns that the specimen volume was abnormally high given the other variables collected from the sample.

The model was refitted excluding this record and the residuals from the new model were approximately normal. The model changed considerably from the first time the regression analysis was carried out and the model to be used for phase 2 is:

Specimen Volume = -0.09 + 1.03(Specimen Weight) + 0.05(Density)

**Table 1: Model Fitting - First Regression Model**

| SAP section ref | Variable added | Variable removed | Variables included in model | Akaike Information Criterion* |
|---|---|---|---|---|
| D.3.1 | Not applicable | Not applicable | Specimen Volume | 733.01 |
| | Specimen Weight | Not applicable | Specimen Volume<br>Specimen Weight | 487.74 |
| | Age | Not applicable | Specimen Volume<br>Specimen Weight<br>Age | 482.86 |
| | BMI | Not applicable | Specimen Volume<br>Specimen Weight<br>Age<br>BMI | 481.28 |
| | Best fit regression model | | | |
| | Specimen Volume=22.97+1.03(Specimen Weight)-0.22(Patient age)-0.23(Patient BMI) | | | |

*Models that fit better will have lower values for the Akaike Information Criterion

**Table 2: Model Fitting - Second Regression Model**

| SAP section ref | Variable added | Variable removed | Variables included in model | Akaike Information Criterion* |
|---|---|---|---|---|
| D.3.1 | Not applicable | Not applicable | Specimen Volume | 722.35 |
| | Specimen Weight | Not applicable | Specimen Volume<br>Specimen Weight | 394.49 |
| | Density | Not applicable | Specimen Volume<br>Specimen Weight<br>Density | 394.36 |
| | Best fit regression model | | | |
| | Specimen Volume = -0.09 + 1.03(Specimen Weight) + 0.05(Density) | | | |

*Models that fit better will have lower values for the Akaike Information Criterion

**Phase 2**

In phase 2, data were collected from 374 tissue samples. Of these, 48 samples were ineligible for the study (Figure 1). A further 70 were excluded from the primary and secondary analyses due to missing data, leaving 256 samples included in the analysis.

**Sensitivity and exploratory analyses**

The sensitivity and exploratory analyses were carried out on the combined phase 2 and phase 1 data. In total, 255 samples from the phase 2 dataset were included. The excluded samples were the 70 samples that had to be excluded from the phase 2 primary and secondary analyses and an additional sample that had no BMI recorded. This variable was not needed for the primary and secondary analyses but was needed for the sensitivity analysis. The phase 2 data were amalgamated with 109 records that were collected in phase 1. The phase 1 records were from the final analysis set, that is, after one record that was considered to be an outlier had been removed from the data. The sensitivity analysis consisted of 364 records (Figure 1).

**Primary Outcome - Bland Altman analyses**

Bland Altman analyses are a visual method of assessing the agreement of two estimates or measures of the same item. In this study, two Bland Altman analyses are carried out. The first assesses the agreement between the current estimates of tissue sample volume and the measured volumes (Figure B1a) and the second assesses the agreement between the regression estimates and the measured volumes (Figure B1b).

The Bland-Altman analyses are almost identical. In both cases, the majority of the records are clustered around the mean difference (bias) between the respective measures, indicating that the agreement between the respective estimates and the measurement is independent of the tissue sample volume. In both cases, there are only 5 records that lie outside of the limits of agreement. In both cases it was the same 5 samples that lay outside the limits of agreement.

For the current estimate, the mean difference in the estimated and measured volume (i.e. the bias) is 0.58ml (Table B1a), which indicates the current method tends to underestimate the measured volumes by a small amount. It is the opposite for the regression estimate. That has a bias of 0.52ml, indicating the regression estimates tend to overestimate the measured volumes, by a similar amount as that with which the current estimate underestimates them.

The 95% limits of agreement for the two graphs are also very similar. For each graph, these are the two values within which 95% of the data points are expected to lie. It is a clinical decision whether these limits are sufficiently accurate, however this research is investigating an alternative estimation method which suggests the current estimate is not adequate. As the regression estimate displays a very similar level of agreement to the measured volumes as the current estimate it is unlikely that the regression estimates are adequate either.

**Secondary outcomes**

*Intraclass correlation*

The intraclass correlation measures the agreement between different measurements or scores of the same item. In this study it is measuring the agreement between the measured volumes, the current volume estimates and the regression volume estimates of the tissue samples collected in phase 2. It is being used to determine the accuracy of the two estimates compared to the measured volumes.

There are various ways to carry out an intraclass correlation depending on the data that have been collected and the requirements of the analysis. For this analysis, only the volume measurement and the two estimation methods included in the analysis are of interest. This means the volume measurements and the 2 estimates are fixed effects of the analysis. The 256 tissue samples were a selection from the population of women needing WLE surgery for breast cancer and we want to apply our analyses to all women needing WLE surgery for breast cancer, which means the tissue samples are a random effect. As we have a mixture of fixed effects and random effects, a mixed effects intraclass correlation was calculated.

The outcome of interest was how accurate the different measures and estimates of tissue volume were, so we were calculating the absolute accuracy of the measurement and

estimates of volume. Finally, the interclass correlation assessed for each individual patient. The alternative to this was to assess the average intraclass correlations of the different methods to assess the volume, however that statistic is not meaningful for this study.
The intraclass correlation was 0.86 (Table B3). This is the correlation of each measurement/estimate on the same tissue sample. Values of 0.75 indicate good agreement between the three methods of calculating tissue volume. Although the intraclass correlation indicates the accuracy is good overall, the current estimate of tissue volume is not accurate enough for some tissue samples and the intraclass correlation has similar accuracy to the current method, so like the primary analysis, it also suggests the new estimation method is not appreciably more accurate.

*Paired t-tests*

The paired t-test was calculated based on the accuracy of the two new estimation methods expressed as a percentage of the measured tissue volume (Table B3). The Chief Investigator indicated that if the volume estimate was more than 5% different to the measured volume that would impact the patient's treatment, regardless of whether the estimate was 5% more than the measured volume or 5% less than it.
The mean percentage difference between the current estimate and the measured volume was 2.70%, whereas the mean percentage difference between the new estimate and thee measured volume was -8.69%. The difference between the two means was over 5% (5.99%) with a confidence interval for the difference of 4.63% to 7.35%.
Similarly to the primary analysis and the other secondary analysis, this also indicates that the estimates developed by regression were not an improvement from the current estimate.

**Sensitivity Analysis**

The sensitivity analysis combined the data from the first and second phases of the trial, excluding one datapoint from Phase 1 that was considered an outlier. The combined dataset was analysed using stepwise regression to check whether the model would change if more datapoints were added. However, the first sensitivity analysis was not a good fit, due to 4 extreme points. These were excluded to establish whether increasing the number of records in the data set would change the model.
The regression model identified in phase 1 was:
Specimen Volume = -0.09 + 1.03(Specimen Weight) + 0.05(Density)
The regression from the revised sensitivity model was:
Specimen Volume = 1.49 + 1.0046(Specimen Weight)

The estimations based on the sensitivity model were not materially better than the current method (Table B4). When the accuracy of the sensitivity estimates and the current estimates were expressed as a percentage of the measured volume and compared, the majority of records were under- or overestimated using both estimation methods (Table B4) i.e. they were at least 5% smaller than the measured volume or at least 5% more than the measure volume, respectively. Of the 359 tissue samples included in the sensitivity analysis 106 were overestimated by at least 5% by both methods and 128 were underestimated by at least 5%. That is a total of 234 out of 359 samples, or nearly two-

thirds (65%) that were estimated inaccurately by both methods. Both methods estimated 83, or around a quarter, of all samples (23%) accurately. Considering the estimation methods separately, the current estimation method estimated 99 samples accurately (28%) and the estimates from the sensitivity regression estimate 106 (30%) accurately.

**Unplanned analyses**

The measured densities were calculated and they ranged from 0.250 g/ml to 2.556 g/ml. The current method provided accurate estimates (estimates within +/- 5% of the measured volume) for densities ranging between 0.912g/ml to 1 g/ml, which is a range of 0.088g/ml. The sensitivity dataset was split into groups of densities 0.088g/ml wide and the median density for each group was used to estimate the tissue sample volume. This was accurate (a maximum of 5% difference between the estimate and the measured volume, based on the measured volume) for 97% of samples. However, as each of these groups include a small range of densities, it is unlikely that this will be of major use to obtain accurate volume estimates.
The potential predictor variables (age, BMI, largest tumour diameter, tumour diameter 90 degrees from the largest (on the X-ray),tumour features (density, size as a percentage of the sample, histology, grade and mass present (yes/no)) were checked to see if they might be used to predict which density-group the sample belonged to but they did not. This was not surprising as if they had predictive value they should have been selected for inclusion in the regression model.

An analysis was undertaken to explore whether including simple tissue measurements already recorded in pathology reports (such as length, width, and height of the tissue sample) could help improve volume estimates. These measurements may have provided a better starting point for calculating tissue volume, which could then be refined using the data collected in this study. The length, width, and height of the tissue sample were used to calculate an estimated sample volume, assuming the tissue samples were ellipsoids. The volume could not be included in a revised regression model as it was highly correlated (i.e. related) to the tissue sample weights. The ellipsoid volume estimate was used to calculate an estimated sample density which could be used in the regression analysis. The stepwise regression analysis including the estimated sample densities produced the following specimen volume estimate:

Specimen volume = 3.07+1.05(specimen weight) - 4.09(estimated sample density)+ 0.05(healthy tissue density)

This was compared to the current method using Bland-Altman, ICC and t-test analyses, but the outcomes were very similar to those from the planned analysis. Using the tissue sample dimensions and calculating an initial volume assuming samples are ellipsoid does not generally produce more accurate volume estimates (Table B6).

The accuracy of the estimates were compared for different weight ranges for the samples collected in Phase 2. The weight ranges were split into 5 roughly equal numbers of records (i.e. quintiles) and the accuracy of the estimate as a percentage of the sample weight was

compared (Tables B7a to B7e). In the group with the lightest weights (2 to 17g) the current method estimated 10% of the sample within +/- 5% of the actual volume, whereas the method identified in Phase 1 (phase 1 method) predicted 25% within +/- 5% of the actual volume. For samples with weights over 38g, the current method tended to be more accurate with 36% of samples within +/- 5% of actual volume in weights between 38 to 53g (Table B7d) and 42% within +/- 5% of actual volume for weights between 54 to 107g (Table B7e). The equivalent statistics for the phase 1 method are 38% +/- 5% of actual volume for weights between 38 and 53g and 38% +/- 5% of actual volume for weights between 54 and 107g. For weights between 18 and 37g it was unclear which was better. The methods identified in the sensitivity and unplanned analyses did not meaningfully outperform either the current method or the phase 1 method for any of the weight groups.

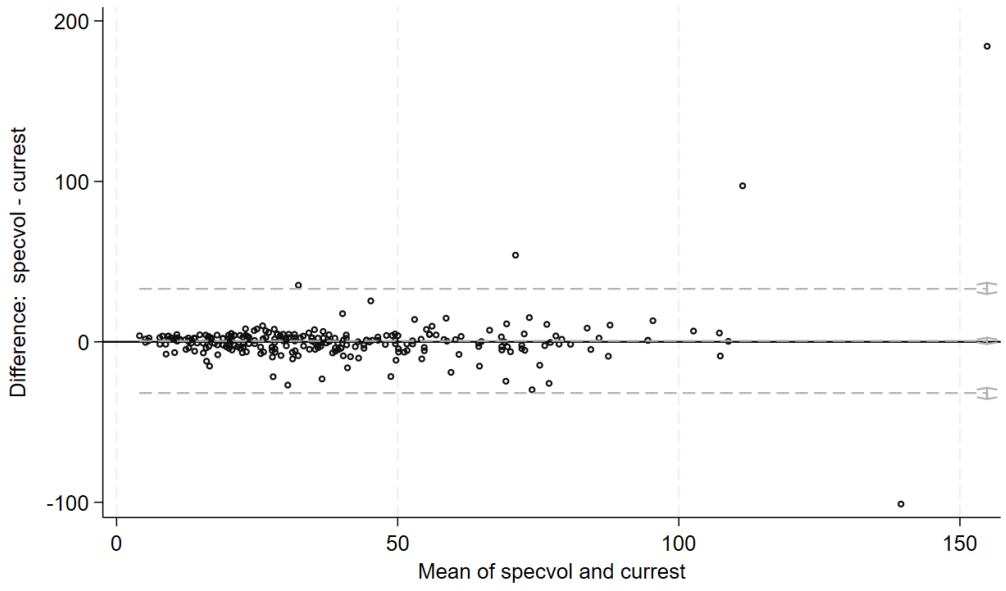
**Patient demographics**

The patients who supplied samples for the phase 1 of the study had a mean age of 63 years (SD=11.71 years) and a mean BMI of 31kg/m$^2$ (SD = 7.78 kg/m$^2$). The patient in phase 2 had a mean age of 60 years (SD=10.72 years) and a mean BMI of 29kg/m$^2$ (SD = 6.55kg/m$^2$).

**Adverse Events**

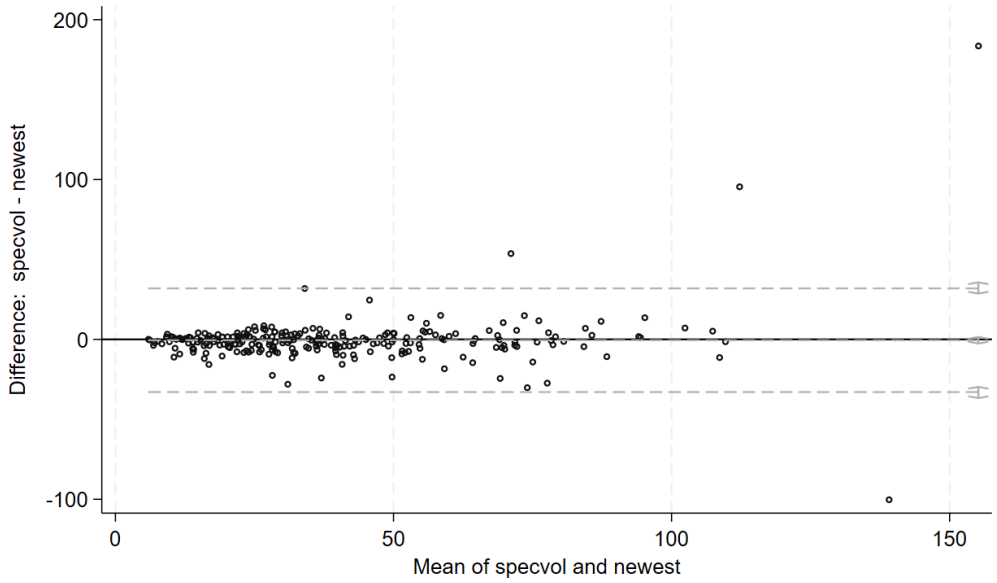
No adverse events were reported for this study. This was expected as the patients who supplied the samples all received usual care and the samples were collected routinely, as part of their usual care. Variables to report adverse events were included in the study due to the importance of recording and reporting them in the very unlikely event that any occurred.

**Figure B1a: Bland-Altman plot of current estimate compared to measured volume (ml)**




**currest = current estimate (= weight/0.958)** **specvol = measured volume**

**Figure B1b: Bland-Altman plot of new estimate compared to measured volume (ml)**




**newest = new (regression) estimate** **specvol = measured volume**

**Table B1a: Summary of Bland-Altman analyses**

| SAP section ref | PRIMARY ANALYSIS<br><br>Bland Altman analyses | Mean difference / Bias (SD) | 95% Limits of agreement (LOAs) (g) | Number (percentage) of observation outside LOAs |
|---|---|---|---|---|
| | Current estimate vs measured volume mean (g) | 0.58 (16.57) | -31.89 to 33.05 | 5 (1.95) |
| | Regression (New) estimate vs measured volume (g) | -0.52 (16.55) | -32.96 to 31.91 | 5 (1.95) |

**Table B2b: Patients with observations outside of the Limits of agreements**

| SAP section ref | **Subject ID** | **Measured specimen volume (ml)** | **Current estimate of volume (ml)** | **New estimate of volume (ml)** |
|---|---|---|---|---|
| | 168 | 89 | 189.98 | 189.17 |

| | | | | |
|---|---|---|---|---|
| | **176** | 247 | 62.63 | 63.31 |
| | **371** | 160 | 62.63 | 64.41 |
| | **373** | 50 | 14.61 | 18.03 |
| | **384** | 98 | 43.84 | 44.17 |

**Table B3: Secondary analysis - Intraclass correlation and paired t-test of accuracy of new and current estimates as a percentage of the specimen volume**

| SAP section ref | **SECONDARY ANALYSES** | **icc or mean (n = 256)** | **95% Confidence interval** | **p-value** |
|---|---|---|---|---|
| | **Intraclass correlation (icc)** | 0.86 | 0.83 to 0.89 | P< 0.0005 |
| E.1.1 | **Paired t test** (mean, ml) | | | |
| | **Current estimate** | -2.70 | -6.46 to 1.07 | - |
| | **New estimate** | -8.69 | -12.72 to -4.65 | - |
| | **Paired difference between estimates** | 5.99 | 4.63 to 7.35 | P< 0.00005 |

**Table B4: Comparison of sensitivity model estimates and current estimates measured as a percentage of the measured volume**

| SAP section ref | **Sensitivity model estimates** | **Current estimates** | | |
|---|---|---|---|---|
| | | **At least 5% higher** | **Within 5%** | **At least 5% lower** |
| | **More than 5% higher** | 106 | 9 | 1 |
| | **Within 5%** | 5 | 83 | 18 |
| | **More than 5% lower** | 0 | 7 | 128 |

**Table B5: Comparison of ellipsoid model estimates and current estimates measured as a percentage of the measured volume (Phase 1 sample)**

| Ellipsoid model estimates | Current estimates | | Total |
|---|---|---|---|
| | Different by more than +/-5% | Within +/-5% | |
| Different by more than +/-5% | 61 | 29 | 90 |
| Within +/-5% | 10 | 10 | 20 |
| Total | 71 | 39 | 110 |

**Table B6: Summary of Bland-Altman analyses after unplanned (ellipsoid) analysis**

| PRIMARY ANALYSIS Bland Altman analyses | Mean difference / Bias (SD) | 95% Limits of agreement (LOAs)) | Number (percentage) of observation outside LOAs |
|---|---|---|---|
| Current estimate vs measured volume mean (ml) | 0.58 (16.57) | -31.89 to 33.05 | 5 (1.95) |
| **Planned** regression estimate vs measured volume (ml) | -0.52 (16.55) | -32.96 to 31.91 | 5 (1.95) |
| **Unplanned** regression estimate vs measured volume (ml) | -0.53 (16.49) | -32.84 to 31.78 | 4 (1.57) |

**Table B7a: Comparison of estimates by sample weights: weights between 2 to 17g (n=51)**

| Cumulative percentages | | | | |
|---|---|---|---|---|
| Accuracy of sample estimate compared to measured volume | Current method | Phase1 method | Sensitivity method | Ellipsoid method |
| Within +/- 5% | 9.80 | 25.49 | 21.57 | 17.65 |
| Within +/- 10% | 15.69 | 47.06 | 39.22 | 35.29 |
| Within +/- 20% | 56.86 | 72.55 | 68.63 | 49.02 |
| Within +/- 30% | 74.51 | 80.39 | 80.39 | 64.71 |
| Within +/- 40% | 90.20 | 86.27 | 88.24 | 74.51 |
| Within +/- 50% | 92.16 | 86.27 | 92.16 | 84.31 |
| Within +/- 60% | 94.12 | 90.20 | 96.08 | 88.24 |
| Within +/- 70% | 96.08 | 92.16 | 96.08 | 90.20 |
| Within +/- 80% | 96.08 | 96.08 | 96.08 | 94.12 |
| Within +/- 90% | 96.08 | 96.08 | 96.08 | 96.08 |
| Within +/- 100% | 98.04 | 96.08 | 96.08 | 98.04 |
| more than +/-100% | 100.00 | 100.00 | 100.00 | 100.00 |

**Table B7b: Comparison of estimates by sample weights: weights between 18 to 27g (n=51)**

| Cumulative percentages | | | | |
|---|---|---|---|---|
| Accuracy of sample estimate compared to measured volume | Current method | Phase1 method | Sensitivity method | Ellipsoid method |
| Within +/- 5% | 11.76 | 5.88 | 11.76 | 13.73 |
| Within +/- 10% | 25.49 | 33.33 | 29.41 | 29.41 |
| Within +/- 20% | 70.59 | 62.75 | 70.59 | 56.86 |
| Within +/- 30% | 84.31 | 82.35 | 84.31 | 70.59 |
| Within +/- 40% | 92.16 | 88.24 | 92.16 | 78.43 |
| Within +/- 50% | 92.16 | 92.16 | 92.16 | 84.31 |
| Within +/- 60% | 96.08 | 92.16 | 92.16 | 88.24 |
| Within +/- 70% | 96.08 | 92.16 | 96.08 | 90.20 |
| Within +/- 80% | 96.08 | 96.08 | 96.08 | 90.20 |
| Within +/- 90% | 96.08 | 96.08 | 96.08 | 94.12 |
| Within +/- 100% | 96.08 | 96.08 | 96.08 | 96.08 |
| more than +/-100% | 100.00 | 100.00 | 100.00 | 100.00 |

**Table B7c: Comparison of estimates by sample weights: weights between 28 to 37g (n=48)**

| Cumulative percentages | | | | |
|---|---|---|---|---|
| Accuracy of sample estimate compared to measured volume | Current method | Phase1 method | Sensitivity method | Ellipsoid method |
| Within +/- 5% | 18.75 | 25.00 | 20.83 | 16.67 |
| Within +/- 10% | 45.83 | 43.75 | 47.92 | 25.00 |
| Within +/- 20% | 75.00 | 75.00 | 75.00 | 52.08 |
| Within +/- 30% | 83.33 | 85.42 | 83.33 | 70.83 |
| Within +/- 40% | 91.67 | 93.75 | 91.67 | 77.08 |
| Within +/- 50% | 97.92 | 97.92 | 97.92 | 87.50 |
| Within +/- 60% | 97.92 | 97.92 | 97.92 | 91.67 |
| Within +/- 70% | 97.92 | 97.92 | 97.92 | 100.00 |
| Within +/- 80% | 97.92 | 97.92 | 97.92 | 100.00 |
| Within +/- 90% | 97.92 | 97.92 | 97.92 | 100.00 |
| Within +/- 100% | 97.92 | 97.92 | 97.92 | 100.00 |
| more than +/-100% | 100.00 | 100.00 | 100.00 | 100.00 |

**Table B7d: Comparison of estimates by sample weights: weights between 38 to 53g (n=50)**

| Cumulative percentages | | | | |
|---|---|---|---|---|
| Accuracy of sample estimate compared to measured volume | Current method | Phase1 method | Sensitivity method | Ellipsoid method |
| Within +/- 5% | 36.00 | 28.00 | 36.00 | 18.00 |
| Within +/- 10% | 64.00 | 58.00 | 66.00 | 40.00 |
| Within +/- 20% | 82.00 | 80.00 | 82.00 | 62.00 |
| Within +/- 30% | 94.00 | 92.00 | 94.00 | 76.00 |
| Within +/- 40% | 94.00 | 94.00 | 94.00 | 90.00 |
| Within +/- 50% | 96.00 | 96.00 | 96.00 | 94.00 |

| | | | | |
|---|---|---|---|---|
| Within +/- 60% | 96.00 | 96.00 | 96.00 | 98.00 |
| Within +/- 70% | 96.00 | 96.00 | 96.00 | 98.00 |
| Within +/- 80% | 96.00 | 96.00 | 96.00 | 98.00 |
| Within +/- 90% | 96.00 | 96.00 | 96.00 | 98.00 |
| Within +/- 100% | 98.00 | 98.00 | 98.00 | 98.00 |
| more than +/-100% | 100.00 | 100.00 | 100.00 | 100.00 |

**Table B7e: Comparison of estimates by sample weights: weights between 54 to 107g (n=50)**

| Cumulative percentages | | | | |
|---|---|---|---|---|
| Accuracy of sample estimate compared to measured volume | Current method | Phase1 method | Sensitivity method | Ellipsoid method |
| Within +/- 5% | 42.00 | 38.00 | 42.00 | 14.00 |
| Within +/- 10% | 66.00 | 66.00 | 68.00 | 32.00 |
| Within +/- 20% | 84.00 | 84.00 | 86.00 | 66.00 |
| Within +/- 30% | 90.00 | 90.00 | 90.00 | 84.00 |
| Within +/- 40% | 92.00 | 92.00 | 94.00 | 94.00 |
| Within +/- 50% | 96.00 | 96.00 | 98.00 | 96.00 |
| Within +/- 60% | 100.00 | 98.00 | 100.00 | 98.00 |
| Within +/- 70% | 100.00 | 100.00 | 100.00 | 98.00 |
| Within +/- 80% | 100.00 | 100.00 | 100.00 | 100.00 |
| Within +/- 90% | 100.00 | 100.00 | 100.00 | 100.00 |
| Within +/- 100% | 100.00 | 100.00 | 100.00 | 100.00 |
| more than +/-100% | 100.00 | 100.00 | 100.00 | 100.00 |

**Trial Limitations:**

The main limitations of the study were due to potential inter-operator variability for both the specimen x-ray assessment and volume measurement. In order to mitigate this, clear standard operating procedures were devised for both these tasks and training was provided to both radiologist and pathology dissectors.

**Discussion & Conclusion:**

- The estimates calculated using regression model identified in Phase 1 of the trial had very similar levels of accuracy to the currently used estimation method.
- The regression model calculated using the combined phase 1 and phase 2 samples was slightly different from the model identified in phase 1 but it did not provide improved estimates of the tissue volumes compared to the current method.
- The measured tissue sample densities from the combined Phase 1 and Phase 2 samples ranged from 0.250g/ml to 2.56g/ml and the current estimate estimates provide good estimates of the sample densities (i.e. within +/- 5% of the measured volume) for just over one quarter of the patients (28%), with tissue sample densities ranging from 0.91g/ml to1.00g/ml (inclusive).

Unfortunately, the new estimate method did not result in any significant improvement in accuracy. However, during discussion with the statistician it was suggested that it may be possible to obtain more accurate estimates if an initial indication of the size of the tissue sample could be provided. This would be possible by using the specimen measurements routinely performed (height, width and length), which are recorded in the pathology report. . These data were used to make initial estimates of the tissue sample volume and density. The estimated density was included in the regression analysis but did not produce improved estimates of the actual tissue volumes. The accuracy of the models appear to be related to

| | |
|---|---|
| | the weight of the sample. For samples under 18g in weight, the method developed in phase 1 tends to produce more accurate estimates of tissue volume. For the heaviest samples (weighing at least 38g), the current method teds to be the closest to the actual values. It is unclear which method is most accurate for weights between 18 and 37g. |
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