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Title: UK audit of glomerular filtration rate measurement from plasma sampling in 2013

Short Title: UK GFR audit 2013

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Abstract

Introduction:

An audit has been carried out into UK glomerular filtration rate (GFR) calculation. The results were compared to an identical 2001 audit.

Method:

Participants used their routine method to calculate GFR for 20 data sets (4 plasma samples) in millilitres/minute and also the GFR normalised for body surface area (BSA). Some unsound data sets were included in order to analyse the applied quality control (QC) methods. Variability between centres was assessed for each data set, compared with the national median and a reference value calculated using the method recommended in the BNMS guidelines. The influence of the number of samples on variability was studied. Supplementary data were requested on workload and methodology.

Results:

The fifty nine returns showed widespread standardisation. The applied early exponential clearance correction was the main contribution to observed variability. These corrections were applied by 97% of centres (50%-2001) with 80% using the recommended averaged Brochner-Mortenson correction. Approximately 75% apply the recommended Haycock BSA formula for adults (78% paediatric). The effect of the number of samples used was not significant.

There was a wide variability in the applied QC techniques, especially in terms of the use of the volume of distribution.

Conclusion:

The widespread adoption of the guidelines has harmonised national GFR calculation compared with the previous audit. Further standardisation could further reduce variability. This audit has highlighted the need to address the national standardisation of QC methods. Radionuclide techniques are confirmed as the preferred method for GFR measurement when an unequivocal result is required.

Key words: glomerular filtration rate, GFR, audit, radionuclide measurement, UK

Introduction

A previous national audit in 2001 showed significant variability in the methods used for calculating glomerular filtration rate (GFR), with some considerable outliers [1]. This led to the publication of guidelines by the British Nuclear Medicine Society (BNMS) on GFR measurement with plasma sampling in 2004 [2]. The guidelines presented a standardised method of processing and analysing GFR studies in order to avoid variation in national GFR measurement. The International Scientific Committee of Radionuclides in Nephrourology (ISCORN) has recommended guidelines for GFR measurement in adults and children [3]. The European Association of Nuclear Medicine (EANM) has recommended paediatric guidelines [4]. The Nuclear Medicine Software Quality Group (NMSQG) of the Institute for Physics and Engineering in Medicine (IPEM) now present a repeat GFR audit in order to investigate whether the BNMS guidelines have been adopted in the UK.

Radionuclide-based GFR measurement is used clinically as a reliable and accurate measure of kidney function. A technical review of GFR studies can be found elsewhere [5]. This technique is commonly used in the evaluation and monitoring of renal function in cases of chronic kidney disease, throughout courses of nephrotoxic drugs [6,7] and for the evaluation of renal function in potential live donors amongst other applications [2]. Radionuclide-based techniques allow for the measurement of GFR from plasma samples taken after the intravenous administration of a radionuclide-labelled tracer bolus (Cr^{51} -ethylenediaminetetraacetic acid (EDTA) or $\text{Tc}^{99\text{m}}$ diethylene-triamine-

pentaacetic acid (DTPA) are used in the UK). The tracer diffuses between intravascular and extravascular spaces and mixes throughout the extracellular fluid volume (ECFV); both spaces can be considered to be tracer compartments. The tracer is only cleared by glomerular filtration. GFR can be measured and calculated through the quantification of plasma and standard-volume sample(s) activity using a gamma-counter. It is known that patients with a fluid collection or various solid tumours can cause an inaccurate measurement due to the interference in tracer kinetics by this 'third compartment'. This is a contraindication for GFR studies according to the BNMS guidelines [2].

The routine method of GFR measurement with a radionuclide involves measuring the area under the plasma clearance curve (AUC) [2,5]. GFR can be calculated by dividing the administered dose by the AUC. The AUC is characterised by the count rates from plasma samples obtained after administration of the tracer. The clearance curve is composed of two main exponential phases, early and late, but the late exponential dominates after approx 2 hrs [2,5]. Full characterisation of the clearance curve provides the most accurate and direct method of quantifying renal function [2,5,8,9]. However it requires an onerous number of plasma samples (>5 samples [5]), although the technique is described by the BNMS guidelines, full characterisation is not normally performed in routine practice. Instead a method involving two, three or four samples is recommended by the BNMS guidelines [2]. The guidelines do not recommend any single sample GFR methods.

The BNMS recommend obtaining 2 to 4 venous blood samples between 2 and 5 hours after tracer administration [2]. The samples are not started until two hours after administration to allow for complete mixing of the tracer throughout the ECFV. The whole-blood samples are centrifuged to isolate the plasma. The subsequently obtained plasma samples are part of the 'late' exponential phase of clearance. The count rates from these samples can be plotted against time. This allows for the definition of the 'late' exponential phase through the fitting of an exponential. A linear fit can also be performed if the natural logarithm of the samples counts is used. The AUC of the fitted exponential can be calculated by extrapolation. This method of AUC calculation (and hence GFR calculation) is known as the slope-intercept (SI) method [5,2] and was investigated in the last audit [1]. The SI method allows for the calculation of the tracer volume of distribution in the patient, this can be considered to be the ECFV.

The SI method overestimates GFR by ignoring the AUC contribution from the early exponential phase [5,2]. This overestimated GFR is known as the uncorrected GFR (ml/min). It has been shown that this overestimation is systematic and increases with increasing GFR [1]. The BNMS recommend a quadratic correction for the early phase contribution called the averaged Brochner-Mortensen (ABM) correction to overcome this overestimation [2]. The volume of dilution can also be corrected in this way and it can be used for quality control (QC) purposes [2]. The ABM correction is applied to the body surface area (BSA) normalised uncorrected GFR measurement

(ml/min/1.73m²). The ECFV has also been suggested as a means of normalising GFR [10]. The BNMS recommend the Haycock BSA formula [11] for adults and paediatrics. The magnitude of the applied ABM correction is dependent on the GFR and the BSA of the patient [1]. The BNMS recommend that this normalisation is reversed, after AUC correction, to calculate the absolute (corrected) GFR [2]. The absolute GFR cannot be directly calculated using the SI method.

The overall aim of the audit was to perform a repeat national investigation into the consistency of both the method and results of SI GFR measurement using plasma sampling. The first objective was to determine the variability between the participating centres for GFR measurement. The second objective was to investigate the adoption of current BNMS GFR guidelines and the third objective was to investigate the variability of QC techniques.

Method

Audit Methodology

Twenty data sets were distributed nationally via regional coordinators and a UK medical physics electronic mail base. The first 10 data sets were the same as those used in the previous audit and these were included to allow for a direct comparison with the previous results. Each data set comprised count rate measurements from four plasma samples taken at specified times after the injection of Cr⁵¹-EDTA. The administered activities were in line with national guidance [12] (max administered activity of 3 MBq). A standard sample count

rate measurement and the details of the patient demographics (age/sex/height and weight) were also included (See Table 1). All data sets had standard dilution volumes of 250 ml but instructions were provided to explain how to alter the counts per minute for the standard sample in cases of software with hard coded standard volumes other than 250 ml.

Participating centres were asked to apply their routine method to calculate the GFR for each data set, expressing the results as BSA normalised and non-normalised GFR. Participants were asked to use the sample data closest to their routine blood sample timing schedule. Supplementary data were requested on workload, normal practice and the applied methodologies.

A total of 64 returns were received from 59 centres (2001: 79 returns from 72 centres). One centre submitted two returns (single-sample and 3-sample method) and one centre submitted three returns (2, 3 and 4-sample method). One centre submitted a return for their current method and also a proposed new method. Only the returns following their routine SI method (59 in total) were analysed. The results were processed and returned, via email, within a period of 7 months. Results for the additional returns were also returned to the respective centres. Graphs were provided (in ml/min and ml/min/1.73m²) presenting the plots of the submitted results against the national median results and the results of a reference method. The reference result for each data set was calculated by the NMSQG following the BNMS guidelines. Participants with outlying results were offered support and guidance. Centres were asked to resubmit

recalculations for any data set returns that were suspected to contain errors. These returns were identified by deviation from the observed systematic trends. Participants also received a report summarising workload, normal practice and applied methodologies on a national level.

Statistical analysis

Descriptive statistics were calculated for the GFR values returned for each data set (in ml/min and ml/min/1.73m²). The quartile values and interquartile ranges were studied for the returns of each data set as they were not normally distributed. Pearson correlations were computed to assess the relationship between the national median results for each data set and the reference results using SPSS version 19 (SPSS IBM, New York, U.S.A).

The absolute and BSA normalised GFR returns were divided into three groups according to whether two, three or four samples were used. The median values for each data set in each group were calculated. These median values were considered to be less affected by outliers than the average value. These values, for both the absolute and BSA normalised GFR returns, were used to assess the significance of the influence of the number of samples on the audit returns using the Kruskal–Wallis test (alpha = 0.05) using SPSS. The last audit only applied the Kruskal–Wallis test to the BSA normalised GFR returns.

Error analysis

The error analysis from the previous audit [1] was repeated. The results from the previous audit were compared with the results for the first ten data sets in

this audit because these were identical. The results in the previous audit were tabulated in the form of v_{ijk} where 'i' is the centre number using an analysis technique, 'j' is the applied analysis technique and the data set number is denoted by 'k'.

The variation (standard deviation) of the results was expressed in two ways in both ml/min and ml/min/1.73m². Firstly the variation is presented relative to the overall mean of results for a particular data set. It provides a measure of the broad variation between all participants ignoring the applied analysis techniques. The variation is due to both the application of different analysis techniques and the differences in the execution of each technique.

The second method of expressing variation was calculated only for centres following the BNMS guidelines (ABM correction and Haycock BSA formula in the correct order). This variation removes systematic differences between the analysis techniques and allows the random errors due to each participant's implementation of the BNMS guidelines to be assessed independently.

Errors related to overall means

Errors were calculated in the same way as the last audit [1]. The overall mean result for all centres for a particular data set, k, is given by:

$$\text{Overall_mean}_k = \frac{\sum_{j=1}^m \sum_{i=1}^{n_j} v_{ijk}}{\sum_{j=1}^m n_j}$$

where m is the number of applied analysis techniques and n_j is the number of participants using the analysis technique j .

The standard deviation for all centres for a particular data set, k , compared with the overall mean for that data set is given by:

$$Std_Dev_k = \left[\frac{\sum_{j=1}^m \sum_{i=1}^{n_j} (v_{ijk} - Overall_mean_k)^2}{\sum_{j=1}^m n_j} \right]^{(1/2)}$$

The overall standard deviation or variation across all data sets is given by:

$$Overall_Std_Dev = \left[\sum_{k=1}^l \frac{Std_Dev_k^2}{l} \right]^{1/2}$$

where l is the number of data sets.

Errors related to the inter-centre application of BNMS guidelines

The standard deviation between all the centres applying the BNMS guidelines was calculated by following the same method as above but with the summation across the multiple techniques removed.

Calculation of the RMedS and comparison to previous audit

The previous audit [1] also calculated the variation in terms of the root median square (RMedS). The RMedS variation relative to the overall data set mean can be calculated in a manner analogous to the presented standard deviation above except that after calculating all the squared deviations from the mean the

median value of these squared deviations is used instead of the mean. RMedS has also been used in another previous audit [13]. For the purposes of allowing a direct comparison with the last audit the calculation of the RMedS was repeated. An advantage of the RMedS is that it is purposed to be more robust to outlying results and may therefore be a fairer representation of typical errors. The RMedS variation relative to the overall data set mean was recalculated and compared with the respective results from the previous audit.

Quality control analysis

Participants were asked to comment on the quality of sample count fits for each data set and note any actions undertaken during processing, as part of normal clinical practice. These responses were analysed.

Eight of the data sets were technically unsound. Details can be found elsewhere (see pdf, Supplemental Digital Content 1, which contains further details). Some contained erroneous sample counts or timings and some had a volume of dilution above the expected range for adults defined in the guidelines which could be an indication of extravasation of the administered tracer or failure to inject all the calibrated activity. These issues were expected to be detected during processing and dealt with appropriately as per the BNMS guidelines. As the participants applied their routine processing method, these responses were used to study the national variation in QC. Data sets 1, 5, 7 and 9 were included in the first audit (before the guidelines were adopted) and they have been retrospectively considered unsound based on the current BNMS guidelines.

Data sets 12, 16, 17 and 18 were deliberately constructed as unsound for the purposes of this audit.

Results

The results are presented in two parts. The analysis of the submitted supplementary audit data (workload, normal practice and applied methodologies) is presented first. The results from the last audit, where available, are presented in brackets. The analysis of the returned measured GFR values from the audit data sets are presented second. All GFR results were rounded to nearest whole number.

Supplementary audit data

A total of 59 centres (2001: 72 centres) replied to the audit. Thirty five centres said they participated in the last audit, 10 said they did not, 3 centres provided no response and 11 did not know (mostly due to staff changes). When asked if they had changed their calculation method since the last audit, 38 centres said yes, 6 said no, 5 did not know, 8 provided no response and 2 stated that their GFR service started after the last audit.

The median annual number of studies per centre is 200 with a maximum of 2000 and a minimum of 2 studies. (2001: median 150, max 2300). Figure 1 is a histogram of the annual number of studies per centre. There were a total of

approximately 16,800 GFR studies performed each year in the UK by the participating centres. According to the returns, there has been a reduction in the number of centres currently offering GFR studies, but on average these individual centres appear to be performing more studies per year compared to the last audit. The reasons for renal function assessment referrals were as follows: 70% - oncology patients, 16% - Renal function assessment in living donors, 10% renal patients, 1% - dermatology and 3% - others (2001: 75% oncology, 19% renal, and 6% others).

Fifty seven centres provided information on the type of radionuclide tracer being used. Forty five (79%) centres use Cr⁵¹-EDTA and twelve (21%) centres use ^{99m}Tc-DTPA. This is identical to the last audit.

The percentages of participants using each number of plasma samples was as follows: 2 samples – 49% (2001: 44%), 3 samples – 31% (2001: 32%) and 4 samples – 20% (2001: 18%). One centre (1.7%, 2001: 6%) routinely use a single sample method (Watson [14] modified Christensen and Groth [15] method) for GFR assessment.

Participants were asked what AUC correction, if any, was used. Fifty eight centres (98%) (2001: 50%) were using a correction of some sort. This compared to approximately 40-45% of participants in the last audit who were not using an AUC correction with the SI method. Two centres used both the adult [16] and child [17] Brochner-Mortensen correction in clinical practise

where appropriate. For those participants applying a correction, the most popular were the ABM [2] (80%) and the Brochner-Mortenson correction for adults [16] (11%). Two centres were using the Chantler correction [2] which involves AUC correction though multiplication with a constant factor. Further details are provided in Table 2. Ten centres were found to be performing the AUC correction and body size normalisation in the wrong order. There were nineteen centres (32%) in total that were applying specifically the ABM correction and Haycock BSA formula in the right order as per the BNMS guidelines.

Fifty nine centres replied to the question about body size normalization. All participants normalised to BSA. Two centres had previously normalised to ECFV in the last audit. Seventy-five percent and seventy-eight percent of responding centres were using the BNMS recommended Haycock BSA formula for adults and paediatrics studies respectively. This is compared to seventy-five percent of centres using the Du Bois formula [18] in the last audit which did not differentiate between the usage on adults and paediatrics. A series of BSA formulae are being used in very small numbers [19-23]. Figure 2 provides a breakdown of the use of BSA formulae for adults and paediatrics.

Participants were asked what actions would be undertaken for a GFR measurement study request in a patient with known fluid collection. This is a contraindication for a GFR study in the BNMS guidelines, as a fluid collection can affect the kinetics of plasma clearance from the intravascular volume,

invalidating the study. The breakdown of these responses by the percentage of participants for various actions is presented in table 3. Some centres provided more than one action.

The replies of the participants were analysed in terms of the applied GFR normal ranges (if any). The ranges for both adults and paediatrics were both analysed. The breakdown of the percentage responses by centre number applying normal ranges in adults were as follows: Granerus and Aurell [24] – 29 (49%); no response – 14 (24%); do not provide – 6 (10%); Grewal and Blake [25] – 5 (8%); use locally derived range – 3 (5%); values on EDTA manufacturers kit data sheet 1 (2%) and HJ Testa and MC Prescott [26] - 1 (2%). The majority follow the normal range quoted by Granerus and Aurell [24] which is also suggested by the BNMS guidelines. The breakdown of the responses by centre number (%) applying normal ranges in paediatrics were as follows: no response – 15 (25%); do not perform paediatric studies – 14 (24%); do not provide – 13 (22%); Brochner-Mortensen corrected Piepsz-1994 method [27] – 6 (10%); Piepsz-1994 [28] – 5 (8%); use locally derived range – 3 (5%); Blake-2005 [29] – 2 (3%) and Piepsz-2006 [30] – 1 (2%).

Statistical Analysis

The results for the non-normalised and BSA normalised results are summarised in table 4 and 5 respectively. The returns for each data set were found to be not normally distributed or symmetrical in nature. The minimum, maximum, median, first and third quartile values were calculated to characterise the variability in

each data set. The standard deviation and RMedS were also calculated for each data set in order to allow for a direct comparison with the last audit. One centre provided no returns for data set 6 (data set with the smallest BSA) as they did not perform paediatric studies. Several participants provided non-normalised returns only for other data sets for the same reason.

The observed minimum and maximum interquartile ranges, in the non-normalised results, were 0 and 16 ml/min respectively across all data sets. The maximum value was for patient 15. It had the third and fourth samples were swapped which led to the largest observed variation for all data sets. The average interquartile range was 2 ml/min across all data sets. This compared to an averaged full range of 25 ml/min across all data sets. The averaged full range for data sets 1 to 10 was 28 ml/min (2001: 42 ml/min). The drop in this averaged full range reflects an increase in precision.

The first and third interquartile values were compared against the guidelines based results. The absolute average percent differences, for all data sets, were found to be less than 1.8% in both cases. The minimum and maximum full range values were also compared against the guidelines based result. The averaged minimum and maximum percent differences, for all data sets, were found to be -11 and 19% respectively. This suggests a greater tendency for the non-normalised GFR results to be overestimated (under AUC corrected) relative to the guidelines based result.

The variability of the BSA normalized results was very similar to that of non-normalised results. This is to be expected as inconsistencies in the various applied BSA formulae would only contribute a relatively small amount of the observed variation. There was a respective minimum and maximum interquartile range of 0 and 12 ml/min/1.73m² across the body-size normalised data sets. The maximum value was again observed for patient 15. There was an average interquartile range of 2 ml/min/1.73m² in contrast to an averaged full range of 28 ml/min/1.73m² across all data sets. The averaged full range across data set 1-10 in was 33 ml/min/1.73m² (2001: 41 ml/min/1.73m²). The drop in the averaged full range since the last audit indicates an improvement in precision.

The first and third interquartile values, for the BSA normalized results, were also compared with the reference results calculated following the BNMS guidelines. The absolute average percent differences, for all data sets, in both situations were less than 2.2%. The minimum and maximum full range values were compared with the reference result. The averaged minimum and maximum percent differences, for all data sets, were found to be -13% and 23% respectively. This again indicates a tendency to overestimate the GFR result.

Interquartile ranges were not available for the 2001 audit but the averaged full range for data sets 1 to 10 was seen to decrease (in both ml/min and ml/min/1.73m²) indicating better accuracy, most likely due to standardisation.

Significant correlations (Pearson $r = 1.0$, 2-tailed, $p < .001$) were found between the median results for each data set (in both ml/min and ml/min/1.73m²) and the reference results calculated following the BNMS guidelines.

The Kruskal–Wallis test found that the difference between the median values, for each data set, of the grouped returns (2, 3 or 4 plasma samples) was not significant at the 0.05 level. The last audit found that this result was 'just significant' for the BSA normalised GFR data. This change in significance is mostly likely due to the standardisation of the GFR study processing since the last audit.

Error analysis compared to overall mean

The overall standard deviation in the non-normalized results for the first ten data sets was 4.8 (2001: 10.1) ml/min, whereas the corresponding RMedS variation was 1.3 (2001: 5.8) ml/min. There is a noticeable reduction in these values since the last audit. It is probably because there were fewer outliers in this audit and this may explain the similarity of both the standard deviation and RMedS results. This may be attributable to the considerable national adoption of the BNMS guidelines since the last audit. The overall standard deviation and RMedS variation for all twenty data sets were 4.8 and 2.6 ml/min respectively.

Similar values were calculated for the BSA normalised returns. The overall standard deviation for the first ten data sets in this audit was 5.9 (2001: 10.3) ml/min/1.73 m², whereas the corresponding RMedS variation was 1.84 (2001:

5.8) ml/min/1.73 m². The overall standard deviation and RMedS variation for all twenty data sets were 5.2 and 2.4 ml/min/1.73m² respectively.

Errors related to the inter-centre application of BNMS guidelines

The variability of the results was analysed for the 19 centres fully adopting the ABM correction and Haycock BSA formula. There was little variability for both ml/min and ml/min/1.73m². For the non-normalised results, the averaged standard deviation and RMedS variation were less than 2.4 ml/min for all twenty data sets (< 0.6 ml/min for data sets 1 to 10). While for the BSA normalised results the standard deviation and RMedS variation were less than 2.1 ml/min/1.73m² for all twenty data sets (< 0.7 ml/min/1.73m² for data sets 1 to 10). The difference in the results for all data sets and just the first ten may be largely due to inclusion of data set 15 (large variation in the returns).

These results confirm that the adoption of the ABM correction has led to a more precise technique for the non-normalised measurement of GFR. The remaining variability may be due to rounding errors and other minor contributions such as the varying least square fitting methods employed by each centre.

Quality control analysis

The analysis of the QC responses, for all data sets, submitted by participants is shown in Figure 3. The percentages of responses for various QC issues were

aggregated to simplify presentation. The responses relating to the unsound data sets show a poor detection rate.

The results for data sets with high calculated volume of dilution (data sets 1, 7, 9 and 18) show that this issue was detected, in the worst case (data set 7), by a minimum of 42% of participants. It would appear that the majority of centres do not study the volume of dilution as a QC technique or at least in a consistent way. Upon analysis of the returns, it was found that 78% of centres were not correcting the volume of dilution, 12% provided no volume of dilution data, 7% are correcting the volume of dilution and 3% appear to be incorrectly correcting the volume of dilution (although their returns contained GFR results in line with the BNMS guidelines based results). It should be noted that one centre was not applying an AUC correction so they could not correct the volume of dilution.

Unfortunately the correction of the volume of dilution is not directly mentioned in the guidelines. The effect of not applying the correction produces an artificially high volume of dilution. In this case, normal ranges defined in the BNMS guidelines may lead to some studies being incorrectly reported as 'potentially inaccurate' due to the incorrectly high volume of dilution. This may be leading to unnecessary repeated studies. This may also help to explain the relatively small yet consistent number of 'high volume of dilution ' QC responses for the sound data sets in figure 3.

The results for the data sets with sample count or timing anomalies (data sets 5, 12, 15 and 17) show that these issues were detected, in the worst case by a minimum of 22% of participants. This was in the case of data set 12 that had an early first sample (only 62 minutes post administration). Only seven centres (12%) questioned if the samples for data set 15 were swapped as they had been. The distribution of the absolute GFR results for data set 15 is presented in figure 4. This shows that there may not be a consistent method of analysing the goodness of fit to the count data in GFR studies. There is a troublingly large spread (46-74 ml/min) in the returned absolute GFR results for data set 15. The guidelines suggest that if 3 or 4 samples are used then the goodness of fit to a single exponential should be checked by a visual method or by the value of the correlation coefficient. The correlation coefficient r-value should be greater than 0.985 for patients with a normal GFR. This should certainly have led to rejection of the fit for data set 15, where the r-value was only 0.628, and also doubts about data sets 5 and 17. Anomalies may have been missed by some centres using only 2 or 3 samples if certain samples were ignored because they did not match a specific local sampling schedule. However, it was hoped that in the spirit of the audit these anomalies would have been detected and at least commented upon by participants.

In general more centres detected issues in the sample count or timing anomalies than with the volume of dilution, but a worryingly large percentage of centres failed to query the quality of the unsound data sets. The results show that the QC of GFR measurement studies is not standardised. The QC

responses of seven centres (12%) mentioned the use of single sample GFR calculation as a means of QC for the slope-intercept studies. Although this useful QC method is not obligatory it could be implemented more frequently.

Discussion

The last audit demonstrated that there was significant national variation in GFR measurements. The results of this audit show that there has been an improvement in terms of accuracy and precision since the last audit through the widespread adoption of the BNMS guidelines. The consideration of the BNMS guidelines as a reference method allowed for the assessment of the accuracy of audit returns while the spread of the results for centres adopting the guidelines enabled precision to be investigated. The results of this audit reaffirm that radionuclide techniques are the preferred method for GFR measurement when an unequivocal result is required [31].

The vast majority of the participants (80%) are using the ABM correction during GFR measurements. This is in contrast to the last audit where only 51% of centres were performing a type of AUC correction. These results reflect the successful adoption of this aspect of the BNMS guidelines, although there is still scope for improvement. Non-standardised AUC correction is one of the greatest sources of variability especially as GFR increases. This audit showed that only 2% of centres were not performing an AUC correction and 17% of participants were applying a non-recommended AUC correction. This audit presents an

opportunity for these centres to re-evaluate their practise in the context of national trends. This in itself represents one of the advantages of performing national audits; they allow outlying centres to confidentially improve their practice and avoid undue errors. It is appreciated that the adoption of a new AUC corrections in clinical practice is a challenging process and requires a lot of planning and a multi-disciplinary approach.

There has been marked adoption of the recommended Haycock BSA formula. This standardisation is welcomed even though it is know that variability between the returns due to different BSA normalisation is relatively small compared to the variation from in the type of applied AUC correction. Although these minor systematic differences should be considered when interpreting results. The Haycock BSA formula is applied by 75% of participants for adult studies and 78% of participants are applying it for paediatric studies. It may be advantageous to use a single BSA formula for both adult and paediatric studies. Relatively minor but undesirable systematic errors may occur over the transition between adult and paediatric formulae in a series of studies, in patients followed throughout adolescence to adulthood.

The audit results found that ten centres were performing the AUC correction and body size normalisation in the wrong order. All of these centres were informed and given an explanation of why this was incorrect. This effect may lead to significant errors in paediatric studies. The theoretical results provided in the last audit found that the effect is small, in patients with GFR up to

approximately 80 ml/min/1.73m². The result showed that the effect increases in significance as GFR increases above this level, particularly for participants with a BSA below 1m². This poses obvious concerns for paediatric studies. In adults the effect is less of a concern and should not lead to a general systematic error, as on average the patients will have a BSA close to the standard of 1.73m². It should be noted that this will have a detrimental effect on the precision of adult GFR studies. GFR is overestimated in adults with a relatively small BSA and vice versa. Fortunately this issue with the respective centres can now be remedied.

The poor detection rate for the unsound data sets stresses the importance of the need for QC standardisation. The BNMS guidelines suggest that the results of each GFR calculation should be judiciously inspected to confirm the study results and count data is self-consistent before the clinical report is issued.

The audit found that the majority of participants do not study the volume of dilution as a QC technique or at least not in a consistent way. The BNMS guidelines state that for adults the expected volume of dilution is around 8 times the BSA with a two standard deviation range of +/- 25% (that is it should be between 6 and 10 times BSA). This is translated in the guidelines to 11-17 litres in women and 13-20 litres in men. There can be a mixed interpretation of this with some centres taking these fixed figures as the expected range while some may calculate it for each patient based on the patient BSA. The expected range is also only defined for adults but some centres may apply it to paediatric

studies also by establishing the expected range on the BSA calculation. Hopefully the expected range can be described in a more specific way in the next version of the guidelines. Also it is hoped that an expected range for paediatrics will be described.

Unfortunately the guidelines do not explicitly state that the expected range does not apply to the uncorrected volume of dilution (calculated from the intercept of the late phase exponential) but to the corrected volume of dilution. Since the uncorrected GFR is equal to the uncorrected volume of dilution multiplied by the exponential rate constant, by analogy the absolute GFR should be equal to the corrected volume of dilution multiplied by the same rate constant. The corrected GFR is derived by applying the ABM correction to the uncorrected GFR and so the corrected volume of dilution can be derived by applying the same ABM correction to the uncorrected volume of dilution. Since the ABM correction factor is always less than 1.0, it follows that the corrected volume of dilution will always be less than the uncorrected volume of dilution. This was mentioned during a presentation [32] about the last audit results at a BNMS meeting but it was not directly mentioned in the published guidelines. The audit results demonstrate that the vast majority of centres (78%) in the UK are not correcting the volume of dilution calculated during GFR studies. A large percentage of centres may be applying the expected ranges from the guidelines to the uncorrected volume of dilution. Practically this may be leading to repeated studies in cases where an uncorrected volume of dilution is being used for QC. This oversight in the guidelines will hopefully be clarified in the next version of

the guidelines. Also a greater emphasis should be given to the study of the correlation value for fits to the plasma sample counts ($r^2 > 0.985$) during QC.

The audit found that the vast majority of participants were performing GFR studies in patients with known third compartments even though this is a contraindication in the BNMS guidelines. GFR studies within this sub-group are known to have a higher probability of causing inaccurate measurement due to the effect of the third compartments on tracer kinetics. This is of most concern in studies where the GFR measurement is used in chemotherapy dosing. This audit found that the main national use of GFR studies is for oncology purposes. The tumours being treated may be invalidating the very GFR study being used for chemotherapy dosing, leading to potential suboptimal chemotherapy treatments. The application of GFR studies on this sub-group and the related recommended contraindication should be readdressed in future guidelines.

GFR measurement calculation is unique as there is no CE marked proprietary software available. Before the guidelines most centres used software that was developed in-house without guidance. This contributed to the significant variability in national GFR measurement as detected by the last audit. This led to the creation of the BNMS guidelines which recommended that a standard method of analysis to avoid undue variability. The repeat audit shows the wide spread adoption of these national guidelines on GFR. This repeat audit successfully completes the GFR measurement software audit loop and demonstrates core clinical governance values. This is a prime example of a

good audit process involving the commencement of an initial audit, analysing the results, identify issues, developing improvements / standards (in this case via national guidelines) and a follow-up audit. Feedback to the participants is paramount at each stage. While there is, as ever, the need for improvement this audit shows that the major issues with variability have been addressed on a national scale by the nuclear medicine community in the UK. This reduction in variability is advantageous considering the necessity of unequivocal nationally standardised GFR measurement.

Another advantage of this audit is that it will allow for the benchmarking of GFR software against the current BNMS guidelines. The audit data sets, instructions and calculated results following the correct implementation the BNMS guidelines can be found on the NMSQG website (www.nmsqg.org). The lattermost of which can be found elsewhere (see pdf, Supplemental Digital Content 2, which contains the GFR calculation for each data set, following the current BNMS guidelines).

Conclusion

This audit has shown a significant reduction in the national variability of GFR measurement compared to the 2001 audit. The main source of the previous variability was due to different method of analysis chiefly varying AUC corrections. Ignoring outliers, the widespread adoption of the BNMS guidelines has relatively standardised national GFR measurement. More standardisation can further reduce the observed differences. This audit has highlighted the need

to address the standardisation of QC methods for GFR studies, particularly the use of a correction to the volume of dilution when applying it as QC measure.

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Figure 1 Histogram of the number of annual studies per UK centre

Figure 2 Analysis of the national usage of BSA formulas.

Figure 3 Analysis of the aggregated percentages of different types of QC responses, by participants for each data set. The data sets known to be technically unsound are highlighted with arrows. (VoD – Volume of dilution)

Figure 4 Histogram of the responses (based on local protocol) for data set 15 which had the 3rd and 4th samples swapped. The following are various calculated absolute GFR results for defined sample selections (following the BNMS guidelines) with the respective linear r^2 values: (61 ml/min, all samples with 3rd and 4th samples swapped back, $r^2 = 0.995$), (56 ml/min, all samples with 3rd and 4th samples not swapped, $r^2 = 0.628$), (71 ml/min, (sample 1, 2 and 3), $r^2 = 0.953$), (46 ml/min, (sample 1, 2 and 4), $r^2 = 0.981$).

Table 1 Data set for patient number 1

Patient demographics	
Age (yrs)	54
Sex	M
Height (m)	1.78
Weight (kg)	70
Data standard and doses	
Weight of syringe and patient dose (g)	6.573
Weight of empty syringe (g)	4.535
Weight of syringe and standard dose (g)	4.962
Weight of empty syringe (g)	4.456
Standard counts per minute	56450
Plasma sample details	
Counts per minute	Time post admin (min)
918	120
770	150
658	180
476	240

Table 2 Details of the AUC correction applied by the 59 participants. Two centres contributed both the adult and child correction. This produced a total of 61 applied corrections. BM - Brochner-Mortenson, ABM - Averaged Brochner-Mortenson, AUC- area under clearance curve

Correction type	Number (%)
ABM	49 (80%)
BM adult	7 (11%)
BM child	2 (3%)
Chantler	2 (3%)
No correction	1 (2%)

Table 3 Actions for patients referred for GFR studies with known fluid collection. The percent of centres suggesting each individual action is presented. Some centres suggested multiple actions. (MPE- medical physics expert)

%	Action
37	Continue study with no more samples/ discard 1st sample
31	Discuss with referrer/MPE/more experienced centre
24	Make comment on report
22	Continue study with more/ later samples
14	Abandon study
10	Delay study until fluid is drained
10	Study volume of dilution and exponential fit
2	Full characterisation with 7+ samples
2	Request patient to stop oedema medication

Table 4 Summary of non-normalised GFR results (millilitre/ minute) for the audit data sets

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Returns	59	59	59	59	59	58	59	59	59	59	59	59	59	59	59	59	59	59	59	59
Min	131 (81)	74 (76)	34 (47)	81 (78)	99 (95)	66 (73)	27 (29)	22 (19)	115 (108)	121 (138)	133	74	104	22	45	47	62	73	106	85
1 st Qrt	134	79	51	84	111	71	34	26	116	140	145	77	109	25	55	47	80	74	111	93
Median	134 (164)	79 (85)	51 (52)	84 (92)	111 (123)	71 (90)	34 (36)	26 (26)	117 (142)	141 (168)	146	80	110	25	58	48	80	75	112	94
3rd Qrt	135	80	51	84	112	75	35	26	119	141	147	82	110	26	71	48	81	75	112	94
Max	176 (180)	90 (92)	55 (58)	99 (109)	132 (151)	96 (104)	39 (69)	29 (34)	151 (155)	179 (211)	180	101	128	29	74	52	92	84	131	107
BNMS	134	80	51	84	112	71	34	26	117	141	147	80	110	25	61	47	79	75	112	93
SD	8 (18)	2 (5)	2 (3)	2 (6)	4 (11)	6 (7)	2 (5)	1 (2)	6 (13)	8 (17)	7	5	4	1	10	1	3	1	4	3
RMedS	2 (16)	1 (5)	0 (2)	1 (6)	1 (9)	3 (7)	0 (1)	0 (1)	2 (11)	1 (12)	1	2	1	0	10	0	1	1	1	1

Returns—number of returns, Min—minimum, Max—maximum, Qrt – quartile, SD –Standard deviation, RMedS - Root median square, The eight highlighted data set numbers represent the unsound data sets. The row marked 'BNMS' represents the reference value calculated following the BNMS guidelines. Values in brackets are the respective rounded values from the 2001 audit (dataset 1-10).

Table 5 Summary of BSA normalised GFR results (millilitre/ minute/1.73 m²) for the audit data sets

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Returns	59	59	59	59	59	57	58	59	59	59	59	58	59	59	59	59	59	59	59	59
BSA	1.86	1.93	2.00	1.71	2.09	0.93	1.29	2.13	1.64	2.10	2.37	1.21	2.38	2.05	2.33	1.53	1.90	1.75	2.34	2.09
Min	122 (75)	69 (69)	30 (41)	82 (86)	83 (88)	122 (134)	36 (38)	18 (14)	120 (114)	100 (114)	97	91	75	19	33	52	59	73	78	70
1 st Qrt	124	71	44	85	92	132	45	21	122	115	106	109	80	21	41	54	72	74	83	77
Median	125 (147)	72 (79)	44 (46)	86 (93)	92 (101)	132 162.5	46 (46)	21 (21.5)	123 (147)	116 (138)	108	114	80	22	44	54	73	74	83	77
3rd Qrt	125	73	44	86	93	134	46	21	125	116	109	115	83	22	53	54	76	75	85	79
Max	163 (182)	85 (88)	51 (54)	100 (108)	111 (108)	178 (192)	61 (69)	23 (25)	183 (164)	147 (174)	135	139	98	24	58	58	88	86	101	91
BNMS	125	72	44	85	93	132	46	21	123	116	108	114	80	21	45	54	72	74	83	77
SD	7 (18)	3 (5)	2 (3)	2 (6)	4 (9)	11 (14)	3 (5)	2 (2)	9 (14)	7 (15)	6	7	4	1	8	1	4	2	4	3
RMedS	2 (16)	1 (5)	0 (2)	1 (6)	1 (7)	4 (14)	1 (2)	0 (1)	3 (13)	1 (10)	1	5	1	1	7	0	2	1	1	1

Returns—number of returns, Min—minimum, Max—maximum, Qrt – quartile, SD –Standard deviation, RMedS - Root median square, BSA – Body surface area (m²) calculated from the patients height and weight with the Haycock formula. The eight highlighted data set numbers represent the unsound data sets. The row marked 'BNMS' represents the reference value calculated following the BNMS guidelines. Values in brackets are the respective rounded values from the 2001 audit (dataset 1-10).

Supplemental Digital Content 1.pdf

Supplemental Digital Content 2.pdf