Clinical Guideline for the measurement of glomerular filtration rate (GFR) using plasma sampling

Report 2018
replaces 2004
guideline

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This guideline must be read in conjunction with the BNMS Generic GFR guidelines (1) that give general advice on service delivery (standards of service, scientific support, staffing etc). It should also be read in conjunction with the existing GFR guidelines (2), as these new guidelines seek mostly to present proposed changes to practice rather than duplicate explanations of basic underlying principles and established practice.

Purpose

The purpose of these guidelines is to assist specialists in nuclear medicine in recommending, performing, interpreting, and reporting the results of glomerular filtration rate (GFR) studies. They will help individual departments in the development of local protocols.

Background

The 2004 BNMS GFR guidelines (2) were written largely in response to the results of a national audit in 2001 (3) which showed significant variability in the methods for calculation of GFR. A re-audit conducted in 2013 (4) concluded that the guidelines had been very successful in their aim of standardising approaches to GFR calculation within the UK.

Quality control (QC) of the data remained an issue; the 2013 audit also concluded that the previous guidelines had not specified QC methods in such a way as to ensure that centres could apply them rigorously as a support to practice. Recent work by McMeekin et al (5) has demonstrated that the previously recommended 'post-calculation' QC methods which can be applied to multiple sample (ie greater than one sample) data but not to single sample data are not sufficiently sensitive, nor do they have sufficient positive predictive value to warrant the extra resources required by multiple sampling. Instead a set of proactive QC checks should be implemented to ensure a robust result (see Table 2).

Work by the same authors (6) concluded that single sample GFR (SS-GFR) can be as accurate and precise as slope-intercept GFR (SI-GFR), adding to the body of literature already in support of this. Indeed the guidelines of both the Radionuclides in Nephrourology Group (7) and also the paediatric committee of the European Association of Nuclear Medicine (8) suggest that a sufficiently accurate GFR may be obtained from a single sample in cases where the GFR is not low. Piepsz reiterated his support of the single sample approach in correspondence (9) following the publication of the 2004 guidelines. The concerns of the authors of the 2004 guidelines with respect to SS-GFR, were that 'one-sample techniques are generally less precise than the slope-intercept technique' and 'there is also no means of quality control for the eventuality of experimental errors'. The single sample review paper by McMeekin et al (6) provides strong and recent evidence that if a single sample approach is performed using best technique and practice then it does not have inferior accuracy or precision to slope intercept techniques. The QC paper by McMeekin et al (5) demonstrates that in such a centre there is little value to any published or suggested QC technique and these guidelines therefore recommend the use of SS-GFR for routine measurement of GFR in conjunction with the proactive QC checks detailed in Table 2 .

Conditions which commonly require GFR assessment by plasma sampling include:

- Calculation of carboplatin dose in chemotherapy (10)
- Assessment of potential live donors for kidney transplantation (11).
- Monitoring of patients receiving drugs that can cause nephrotoxicity.
- Assessment of renal function in chronic kidney disease
    - including the evaluation and follow up of renal function in chronic glomerulonephropathies (such as diabetes mellitus and haemolytic uremic syndrome).
- Detection of renal failure in patients in whom:
    - Serum creatinine results might be misleading, for example due to abnormal diet or musculature;
    - Missing a decline in renal function might be disastrous, for example in those with a single kidney, renovascular disease or a renal transplant;
- The evaluation of single kidney function in conjunction with relative renal function measurements from static or dynamic radionuclide imaging, including patients about to undergo renal surgery.
- Complex urological problems or long term urological conditions such as diversions
- Assessment of kidney function as part of the work up for receiving a liver transplant.

Contraindications

If patients have ascites or oedema then a different sampling and calculation regime is recommended (see 8.10).
ARSAC guidance (12) is available for patients who may be pregnant or breastfeeding.

Radiopharmaceuticals and Activity

^{99m}Tc diethylenetriaminepentaacetic acid (DTPA) or ^{51}Cr ethylenediaminetetraacetic acid (EDTA) . ARSAC DRL for adults: 10 MBq for ^{99m}Tc DTPA and 3 MBq for ^{51}Cr EDTA (12).

Radiation Dose

The effective dose for GFR is 0.05mSv for ^{99m}TcDTPA and 0.006mSv for ^{51}CrEDTA (12).

Preparation for the patient visit and checks prior to administration

An information sheet about the test should be sent to the patient with the appointment details.

1. **Presence of other radionuclides**

   The potential presence of other radionuclides in the blood stream due to previous nuclear medicine examinations should be investigated. Particular care should be taken when the patient has undergone previous radionuclide therapeutic procedures or diagnostic procedures using radionuclides with long half-lives. If the test cannot be postponed it may be possible to calculate the GFR by counting a pre-test plasma sample and using cross talk estimates to subtract the contribution from the post-

test plasma samples but this is a complex procedure requiring an excellent understanding of counter performance.

In cases where the diagnostic radionuclide the patient has previously been administered is ^{99m}Tc, the approach will depend on which radionuclide is to be used for the GFR test. For GFR tests performed with ^{99m}Tc-DTPA, a pre-sample should be taken if it is suspected that the plasma count rate might be higher than background levels in the ^{99m}Tc energy window before the injection. The GFR test should be postponed until the count rate has returned to background levels. If ^{51}Cr-EDTA is being used for GFR measurement the test can be performed simultaneously with ^{99m}Tc based diagnostic procedures and the plasma samples left to decay for 48 hours before counting as the ^{99m}Tc level in the plasma samples would otherwise overload the NaI(Tl) detector giving erroneous counts for the ^{51}Cr arising from pulse pileup of the pulses from ^{99m}Tc photopeak events. Isotope plasma clearance techniques cannot be combined with diuretic renography due to the possible effect of the diuretic on the GFR.

2. **Medication and other treatments**

Certain drugs can reduce renal function, for example: diuretics; aminoglycoside antibiotics; penicillin; sulphonamides; amphotericin B (13). All medications being taken should be recorded prior to injection. It should also be determined whether the patient is receiving hyperhydration therapy with intravenous fluids as this could invalidate the results of the GFR measurement. On rare occasions patients on dialysis may be referred for a GFR; in such cases care needs to be taken to ensure the test is completed before a dialysis session and only if the patient is in a stable state of hydration. Isotope clearance tests are not suitable for patients on peritoneal dialysis.

3. **Intake of food and drink**

The patient should be adequately hydrated prior to and for the duration of the study. High protein meals should be avoided before and during the study as protein load can affect GFR reproducibility (14). Strict bed rest is unnecessary, but heavy exercise should be avoided. Restriction of activity is necessary for good reproducibility of GFR measurements (14).

Excessive intake of drinks containing caffeine should be avoided from 10 pm the night before the test due to their diuretic effect (15).

4. **Recording of height and weight**

The height and weight of the patient should be recorded to allow for determination of the body surface area. If patients are bedbound or in a wheelchair it is acceptable either to make an estimate or ask the patient for an estimate. The fact that an estimate has been made should be included in the report.

5. **Preparation for intravenous administration**

An anaesthetic cream or cold spray can be used to reduce patient discomfort during injection and blood sampling if required.

GFR Procedure

1. **Administering the activity**

Measuring administered activity

An accurate knowledge of the ratio of activities of tracer administered to the patient compared to the standard is essential to the accuracy of the GFR result. Standard and patient syringes must both be drawn from the same stock. Ensuring a precise measurement of injected and standard activity can be achieved in several ways:

a. **Weight – assuming all is administered.** The injection syringe is weighed pre and post drawing up the activity using high precision weighing scales. The syringe must be thoroughly flushed to ensure all the activity is injected.

b. **Weight – not assuming all is administered.** The injection syringe is weighed pre and post injection, no flush is performed. There must be no blood drawn back into the syringe and the syringe must be recapped with the same hub prior to reweighing. A resheathing block must be used to prevent needlestick injuries.

c. **Activity – not assuming all activity is administered.** The activity is diluted to a fixed volume in the injection syringe and assayed in a dose calibrator. A dose calibrator background measurement is recorded and the background subtracted activity and measurement time is noted. A residual activity measurement post injection is made in the same way. This method is insufficiently precise for use with ^{51}Cr-EDTA.

d. **Volume – assuming all activity is administered.** The stock activity arrives diluted into a volume which is large enough to avoid potential errors due to dead space in the syringe. The required volume of tracer is drawn up into a syringe (larger volumes will give greater precision and if insufficient precision can be obtained for the tracer volume then the solution may be transferred to a universal vial and a pipette used). To ensure the correct volume is delivered from a syringe, the syringe is filled right up to the end of the needle or interlink so the dead space is always filled with tracer. As in method 2, there must be no drawing back of the syringe.

The method adopted by each centre will depend on resources available and consideration of the likely errors involved. As this assessment is so fundamental to the accuracy of the result, it is considered good practice to avoid large errors by employing two methods in parallel and using one

as a quality control measure for the other, ideally for each administration, but certainly by periodic audit.

Other aspects of administration

- The batch number and expiry date and time of the radiopharmaceutical and any saline used should be recorded.
- The activity must be injected into the blood stream without extravasation as this will invalidate the result. The possibility of extravasation can be checked by using a count rate monitor to compare the count rate from the injected arm to that from the contralateral arm. If administration is via a butterfly/cannula and the residual in this is not to be measured separately then the monitoring must take place prior to removal of the butterfly/cannula.
- The use of a winged needle infusion set or cannula is recommended if no central or peripheral line is present as direct injections have a higher risk of extravasation. Expert advice should be sought on appropriate gauges, particularly for paediatrics. If a dual lumen central venous catheter (CVC) is available the injection and blood sampling must be performed though different lumens to minimise the risk of contamination of the blood samples and it is important to flush the line dead space after administration. Injection and sampling cannot both be performed through a single lumen CVC or through the same peripheral butterfly or cannula (16).
- Before injecting the tracer, the line should be flushed with saline to ensure patency. The tracer is then injected and the line flushed. If the line is to remain in-situ, saline/hepsal will be required and this should be administered according to local procedures.
- The time of injection should be noted to the nearest minute– this is recorded as the midpoint of the administration of the tracer. The clock used should be the same as for the syringe measurement above and also for the samples. If it is not use possible to use the same clock (or many clocks synchronized) then frequent cross checks should be made and corrections applied.
- If the method requires the measurement of the residual activity then care must be taken to ensure that needles etc are resheathed appropriately. If butterflies etc are to be assayed for residual activity care needs to be given to ensuring there is no contamination of the area.

2. Preparation of the stand

A volumetric flask (typically 1 L) should be labelled and half-filled with distilled water. A known aliquot of the radiopharmaceutical stock solution (the same solution as for the patient administration) is added to the flask and thoroughly mixed. The activity added to the flask should be measured and carried out using the same method as for the injected activity (methods 1-4), including whether flushing is required. The activity added should be chosen such that the count rate of the standard tubes is in the

linear range of the counter. Once the activity is fully mixed, the flask must be topped up to the mark and mixed again. An accurate pipette should be used to pipette a fixed volume of the standard solution into pre-labelled counting tubes in duplicate.

3. Blood Sampling

To minimise the risk of contamination blood samples should not be taken from the site of injection and ideally should come from the contralateral arm. If this is not possible, feet can be used. The largest needle/butterfly/cannula possible consistent with the clinical requirements and condition of the patient should be used to withdraw the blood sample to minimise haemolysis. The blood should be withdrawn either directly into a vacutainer or via a syringe into a collection tube containing dry heparin. Clotting of the blood sample should be avoided but will not affect the measurements. The volume of each sample should be 10ml (7 ml for children if taking larger samples would represent a significant percentage of blood volume (9)). If an intravenous line is used to withdraw the blood sample the line should be cleared of any heparin/saline by withdrawing 5 ml blood and discarding. The sample should then be withdrawn and the line flushed according to local procedures. The timing of the blood sample should be recorded to the nearest minute. As the procedure may take a minute or two, the time of sampling is taken as the midpoint of the blood collection time. The same clock as that used to note the time of the injection, or one synchronised with it, should be used.

4. Processing the blood samples

- The blood samples should be centrifuged at 1000 g for 10 min to separate the red blood cells from the plasma. This should be done as soon as practicable after the samples are taken. There is no requirement to refrigerate the samples prior to centrifuging (data presented in poster 72 at Spring BNMS meeting 2017).
- A small degree of haemolysis occurs occasionally, giving a slight pink colour to the plasma; this will not significantly affect the accuracy of the GFR result. Marked haemolysis, in which the centrifuged blood sample has a strong red colour and is almost opaque, with the plasma/red cells interface hard to define, will invalidate the measurement.
- A fixed volume of plasma (typically 1 ml) should be accurately pipetted into pre-labelled counting tubes in duplicate. Care should be taken to avoid disturbing the interface between the plasma and the red cells. The volume pipetted must almost always be the same as that used for the standards. However, in the event of insufficient plasma for duplicate plasma samples of the required volume, the maximum available volume should be determined from the smallest sample. In this circumstance, there are two approaches to counting:

a. Pipette smaller volumes for both the samples and the standard tubes.

b. Make the sample tubes up to the required volume using water and scale the count rate from the sample tubes in the ratio of the standard to sample volumes accordingly. The standard and sample tubes must have the same volume to ensure consistent counting efficiency. If different volumes are to be used routinely, for example a 2 ml sample instead of 1 ml for a 24 hour sample to reduce counting time, a pre-determined geometry factor must be applied.

5. Choosing the sampling time for the most accurate result

- For patients who are not believed to have ascites, oedema or other expanded body space, a single sample measurement is recommended. Such a judgement may be based on information from the referrer, previous imaging reports or direct observation. The work of McMeekin et al (5) suggests that sensitivity of the QC measures to detect this are inadequate, so the information should be obtained prospectively.

- Jacobsson (17) has shown that the optimum sampling time depends on the GFR and the distribution volume. Recommended sampling times, based on the best available estimate of the Body Surface Area (BSA) normalised GFR are given in Table 1

- Estimates of BSA normalised GFR should be based on any serum creatinine measurements or previous GFR measurements available and on the patient's history and clinical condition. In patients who have pronounced muscle mass or cachexia, the serum creatinine estimate is likely to be inaccurate. In these circumstances a slope intercept is recommended.

Estimate of BSA normalised GFR (mL/min/1.73m^2)	**Recommended sample time (h)**
Above 100	2
70 to 100	3
50 to 70	4
25 to 50	6
Below 25	24

Table 1: Recommended sampling times for single sample GFR measurements

For samples taken at 2, 3, 4, or 6 hours, the single sample formula developed by Fleming et al. (18) is recommended for calculation of the GFR result. The formula was validated with 2, 3, and 4 hour samples by Fleming et al. in their original work; its accuracy at 6 hours for measurement of GFR between 25 and 50 ml/min/1.73m^2 has been

validated by the authors of the guidelines (unpublished). See section 8.9 for details of the calculation.
The method of Gref and Karp (19) is recommended for measurement of GFR < 25 ml/min/1.73 m^2. See section 8.10 for details of the calculation. Single sample measurements are not valid in patients with ascites, oedema or other expanded body space. See section 8.10 for more details on GFR assessment for this patient group.

6. Counting

Duplicate samples of the standard and plasma from each blood sample should be counted.

Counting time for each sample should be sufficient to achieve a precision of better than 2% in the background corrected count rate.

7. Calculating the apparent volume of distribution from the blood sample

The data from the counter will be in the form of counts per minute (cpm) from each tube. For ^{99m} Tc, these will require decay correction. The apparent volume of distribution (V_{app}) at the sample time is a useful quantity to calculate as it appears in the GFR calculation equations described below. It can be understood as the volume into which the tracer must be diluted to achieve the tracer concentration measured in the plasma sample at that time, assuming no other route of tracer extraction. It is not the same as the volume of distribution that can be calculated from the intercept in the slope-intercept approach.

V_{app} for each sample can be calculated using expression 1. Units are included in square brackets for clarity throughout these guidelines. Where cpm is mentioned, the average cpm of both tubes should be used when counting has been in duplicate:

$$v_{app}\,[ml] = \frac{\text{cpm administered } [counts\ per\ min]}{\text{background corrected cpm from sample } [counts\ per\ min/ml]} \quad (1)$$

where cpm administered is calculated using expression 2:

$$\text{cpm administered } [counts\ per\ min] = \text{decay and background corrected cpm from standard } [counts\ pe /ml] \cdot \text{dose to standard ratio} \cdot \text{standard volume } [ml] \quad (2)$$

In general the background and decay correction will be carried out by the counter computer, but there may be circumstances where manual calculations are required.

If you have assayed the contents of the syringes using the activity or volume method these quantities should be substituted for the mass ratio in equation 2.

8. Calculating the body surface area of the patient

Body surface area (BSA) is an important quantity which will be used in calculating the GFR. The patient's height and weight should be accurately measured and entered into the following formula due to Haycock et al. (20) to obtain the BSA:

$$BSA\ [m^2] = 0.024265 \cdot \text{weight [kg]}^{\,0.5378} \cdot \text{height [cm]}^{\,0.3964} \qquad (3)$$

Other formulae are available, such as that of Du Bois and Du Bois (21) and of Sharkey et al. (22) the latter requiring only the measurement of patient weight and not height. The equivalence of these three formulae is demonstrated in the work of Blake et al (23)

9. Technique for GFR measurement in patients with GFR > 25 ml/min/1.73m^2: Fleming et al. (18) single sample GFR

To use this formula, V_{app} at the sample time calculated as described in section 8.7 should be normalized (Vappnorm) to a BSA of 1.73 m^2 and converted to litres/1.73 m^2 using the relation:

$$v_{appnorm}[l/1.73\ m^2] = v_{app}[ml] \cdot \frac{1.73\ [m^2]}{1000.BSA\ [m^2]} \qquad (4)$$

where the patient BSA is calculated as described in section 8.8.

Normalised apparent volume is combined with the BSA and the sample time, t, into this formula:

$$GFR\ [ml/min/1.73m^2] = (t\ [min])^{-1} \cdot \left(-11297 - (4883 \cdot BSA\ [m^2]) - (41.9 \cdot t\ [min]) + \left(5862 + (1282 \cdot BSA[m^2]) + (15.5 \cdot t\ [min])\right) \cdot \ln\left(v_{appnorm}\left[{}^{l}/_{1.73m^2}\right]\right)\right) \qquad (5)$$

[see separate comment]

Note that the GFR calculated using equation 5 is already BSA normalised; there is no need to apply a further normalisation.

If a non BSA normalised result is required the BSA normalisation should be reversed:

$$GFR\ [ml/min] = GFR\ [ml/min/1.73m^2] \cdot \frac{BSA\ [m^2]}{1.73} \qquad (6)$$

10. Technique for GFR measurement in patients with GFR < 25 ml/min/1.73m^2

The 24 hour SS_GFR method of Gref and Karp [13] is recommended in this situation. To use this formula V_{app} should be calculated at 24 hours post injection and the extracellular volume, ECV, should be calculated according to:

$$ECV\ [ml] = (8116.6 \cdot BSA\ [m^2]) - 28.2 \qquad (7)$$

GFR can then be calculated as:

$$GFR\ [ml/min/1.73m^2] = -\ln\left(\frac{ECV\ [ml]}{v_{app}\ [ml]}\right) \cdot \frac{\mathrm{ECV}\ [ml]}{t\ [min]} \cdot \frac{1.73}{BSA\ [m^2]} \qquad (8)$$

Technique for GFR measurement in patients with a third space such as ascites or oedema: The 4 sample technique of Wickham et al. (24,25) should be used.

Thorough checking of clinical history and any previous radiology is crucial for identifying these patients. Engagement with referring clinicians is also important: patients being referred for particular indications, for example, as part of the work up for a liver transplant, or treatment for ovarian cancer are more likely to be at risk of ascites.

Single sample measurements are not accurate for these patients Wickham et al. recommend a 4 sample regime, with samples at 2, 4, 8, and 24 hours. The reciprocal of V_{app} for each sample should be plotted against sample time on a log–linear graph and the area under the plasma clearance curve (AUC) calculated using the trapezoidal rule with extrapolation to zero and infinity. The GFR is then calculated as:

$$GFR\ [ml/min] = \frac{1}{AUC\ [min/ml]} \qquad (9)$$

Next the BSA normalisation is applied. It is important that this is applied before, not after, the Brochner-Mortensen correction.

$$GFR\ [ml/min/1.73m^2] = GFR\ [ml/min] \cdot \frac{1.73}{BSA\ [m^2]} \qquad (10)$$

With this sampling regime the early, fast exponential decrease in plasma tracer concentration is ignored, causing the AUC to be underestimated and the GFR to

be overestimated. The formula derived by Brochner-Mortensen (BM) [20] corrects for this:

$$GFR_{BM-corrected}\ [ml/min/1.73m^2] = 1.0004 \cdot\ GFR\ [ml/min/1.73m^2] - 0.00146 \cdot (GFR\ [ml/min/1.73m^2])^2 \quad (11)$$

This is the BSA normalised GFR result to be reported. If a non BSA normalised result is required the BSA normalisation should be reversed after the BM correction using equation 6.

Patient after Care

There are no specific requirements in terms of patient after care

Image Interpretation

N/A

Reporting

The clinical indication should be identified in the report. The BSA normalised and non-BSA normalised GFRs should be clearly reported with units specified, along with any technical factors that may have affected the accuracy of the result. Normalised and non-BSA normalized GFRs are used for different clinical purposes, so it is important that the distinction between them is clear.

Before the report is made final it should be checked that all of the QC measures detailed in Table 2 have passed.

1. **Reference ranges**

   At the present time there are no published reference ranges for GFR results calculated using the single-sample equation of Fleming et al (18). The authors have therefore re analysed previously published ^{51}Cr-EDTA data (26) with 2, 3 and 4 h blood samples that were used to construct a reference range for Brochner-Mortensen corrected GFRs calculated following the methods described in the 2004 BNMS guidelines . The subjects were 904 healthy individuals (468 women, 436 men; age range 18-84 y) who underwent assessment as prospective, living kidney donors. Single-sample GFRs were calculated using the equation of Fleming et al (18), and a new SS-GFR reference range constructed. Figure 1 shows the scatter plot of the SS-GFR measurements plotted against age for both sexes, and the central curve shows the degree-1 fractional polynomial equation fitted to the pooled data:

   SS-GFR = 101.5 – 0.0058 x Age^2 mL/min/1.73 m^2 (12)

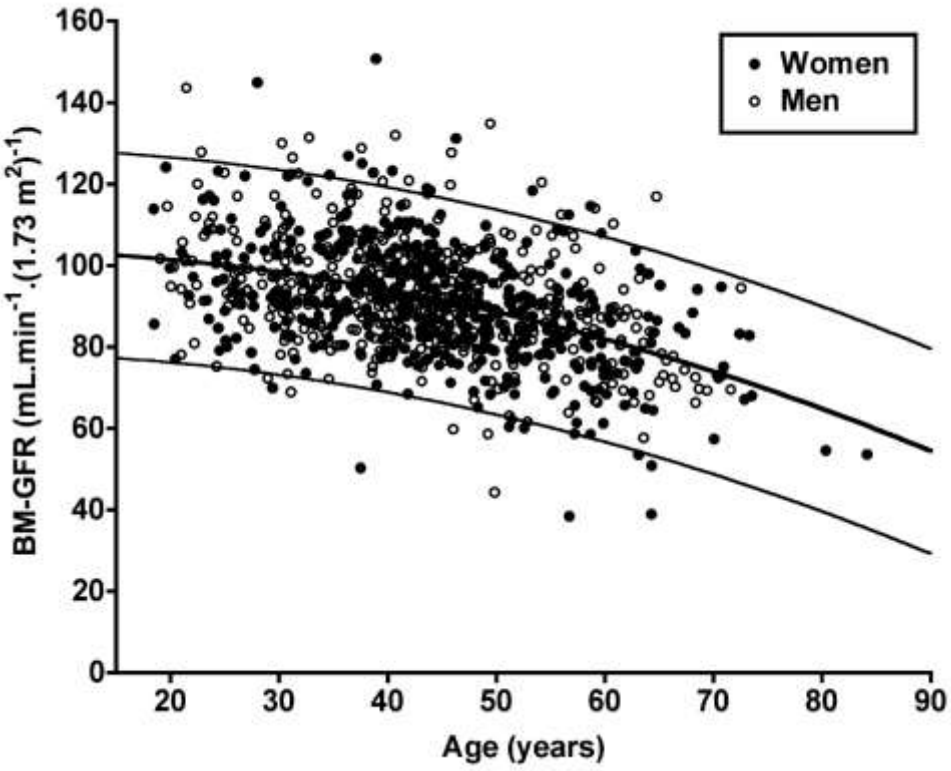

Figure 1 Graph showing dependence of GFR with age for men and women

The upper and lower curves are ± 2 SD (± 24.3 mL/min/1.73 m^2) from the mean. After the individual GFR results were adjusted for age using Equation 11, a Student t-test showed no statistically significant difference in mean GFR between men and women (P = 0.849).

2. Repeat measurements

Measurement of GFR is subject to errors from a variety of sources. Monte Carlo modelling of a 5% error in activity measurement combined with a 2 minute error in sample time gives an average error of about 4% in the calculated clearance (27). Estimates of the repeatability of GFR measurement on the same patient over time suggest a variation of approximately 10% (28), and a study by Wilkinson et al. (14) found a coefficient of variation of 12% in duplicate measurements of the same subject when permitted free exercise, and 8% when at rest.

3. Assessment of biological half clearance and volume of distribution

Some authors such as Peters have long advocated the assessment of kidney function using half clearance team, or GFR normalized to extracellular volume. Blake et al (28) have demonstrated in a study of serial follow up of patients with chronic renal disease that the coefficient of variation of GFR is larger than that of clearance time, suggesting that

this might be a better measure. However there have been no studies that have demonstrated the clinical benefit of this in approach and it is the normalised body surface area GFR that is currently the widely accepted measure of kidney function.

The single sample approach does not, of course provide a means for assessment of half clearance time. IF this is required then a slope intercept approach should be used, but these guidelines do not support routine use of this approach until studies have demonstrated clinical benefit.

Another instance in which the use of half clearance time is recommended is in carboplatin dosing in children (29). This recommendation arose because the authors were alarmed that several children in the study had unfeasibly high GFRs measured from a slope intercept approach, but half clearance values within the normal range and abnormal volumes of distributions. They took the view that half clearance time would be a better measure in these children, but this was assumed rather than demonstrated. It is quite possible that in these children their disease had altered the kinetics of the tracer, in much the way described by Wickam (ref), and in this case neither SI GFR nor half clearance would be an adequate measure of clearance, a different model needs to be employed.

Auditable aspects and QC

We recommend that all the quality control checks described in Table 2 are implemented in order to ensure a reliable result.

Potential error	Check to be implemented
Presence of a third space in the patient, for example due to oedema, ascites, or effusion, which invalidates the single compartment model assumed by the standard technique.	Thorough checking of clinical history, previous radiology etc. and engagement with referring clinicians.
Inaccuracy in the measurement or composition of the standard activity.	The counts expected from the standard can be calculated from knowledge of the activity concentration of the radiopharmaceutical and the sensitivity of the counter. A check could be implemented to ensure the measured counts are within 10% of this value.
Incorrect measurement of the administered activity.	• The activity in the syringe prior to administration should be double checked against that expected from kit activity concentration

	• Checks should be implemented to ensure that either a) minimal activity remains in the syringe/cannula or b) all activity remaining has a quick check using a second technique to complement the primary means Can this apply to Cr51 (I am uncertain)?
Not all activity administered intravenously	• Checks should be made to ensure that there has been minimal extravasation (this can be achieved by using a mini monitor to compare the count rate from the injected arm to that from the contralateral arm). This can be achieved for both ^{99m}Tc and ^{51}Cr, but with much reduced sensitivity for the latter. Departments should check they can assess extravasations of ~5% of injected dose. • Checks should be carried out with butterfly in place, unless this is counted separately • If measuring a CVC, it should be monitored at various points along its length
Inaccuracy in the timing of the injection or blood sample.	All clocks where injections are administered or bloods are taken should be synchronised. If the time of the blood sample is >15 min from the planned time then a note should be made on the worksheet. Times must only be written on tubes after the blood has been taken, not before.
Variation in the pipetted volume of the plasma samples, causing the count rate from the tubes to be inaccurate.	Plasma samples should be counted in duplicate and a check implemented to ensure the difference does not exceed expected levels (pipetting accuracy <2%, with counting errors <2%).
Presence of counts from other sources of radioactivity, such as contamination from other sources of radioactivity in the counting tubes, or on their surface, or inadequately shielded sources nearby.	• Daily background checks should be carried out on the gamma counter. • Background checks may also be made after each sample

	rack, but such checks are no substitution for constant vigilance. • Careful working practices should be observed to minimise the possibility of contamination. Gloves must ALWAYS be changed before handling plasma samples • The time required for an accurate background measurement is long and therefore the background rack of the counter may not need to be used every day, but a shorter check of blank tubes will catch gross errors.
Transposition of blood samples from different patients.	Departments should have robust IRMER procedures for identification of patients. Identification of blood tubes should be completed directly after blood has been taken and before the patient leaves the room. When pipetting, samples from different patients should be clearly separated.
Count data from one patient may be ascribed to a different patient either by incorrect loading order on the sample counter or by transposing counts to the incorrect analysis sheet..	A system of double checking with counter signatures should be implemented to ensure that this does not happen.
Incorrect transcription of the count data from the counter to the calculation spreadsheet.	Where possible count data should be transferred from the counter electronically and all other data should be double checked.
Compromised blood count data due to the patient having had another nuclear medicine test or radionuclide therapy recently.	Prior to booking, it should be ensured that the remaining count rate in the blood from any recent nuclear medicine administrations will be at background levels for the GFR test. It should be verified on arrival that the patient has not received any recent radioactive administrations.
Patient sample volume and standard sample volume are not the same	Document the volume of plasma pipetted and volume of standard pipetted at the time that these are done. If they are different verify that they were made up to the same volume before counting and that the calculation sheet has allowed for this.

	Otherwise document what correction factor was applied.
Other methodological errors not captured by the above checks.	Other available measures of GFR such as serum creatinine or creatinine clearance may be available. Significant differences in the absence of abnormal musculature may indicate a problem with the isotope clearance. Further work is required on this subject to give firm guidelines as to how eGFR might be used as a QC technique.

Table 2: Recommended methodological checks in order to ensure a robust GFR measurement

References

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Review

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Appendix – Details for equipment requirements

Radiopharmaceutical/sample preparation area

Newly built or refurbished areas for the preparation of patient injections must include a Class A cabinet in which the injections are prepared. In existing facilities patient injections must be prepared according to locally validated procedures for ensuring the safety of the product. Further details are given in the guidance on safe drawing up of radiopharmaceuticals in nuclear medicine departments published by the UK Radiopharmacy Group on behalf of BNMS (30) .This guidance must be followed in order to minimise the risks that arise from drawing up patient doses of radiopharmaceuticals in areas other than controlled radiopharmaceutical environments. Plasma samples may have activities of less than 100 Bq. Staff must change gloves before starting work in this area.

Ideally sample preparation will take place in a different room from drawing up and preparing patient doses. IF resources require that this is the same room then some demarcation of areas must be employed and procedures should be audited to test for cross contamination.

Refrigerator

A pharmacy standard refrigerator may be required for the storage of tracer prior to administration. There are no stability issues that require Tc-99m DTPA or Cr-51 EDTA to be kept in a refrigerator, but refrigeration may be required to ensure safety against microbial contamination, and tracer should be stored according to the label instructions. If the tracer is supplied as a multi-dose kit from which individual doses are withdrawn aseptically for each patient over the course of a working day, then the kit should be stored in a refrigerator between withdrawals. A risk assessment should be carried out to ensure safety against microbial contamination if withdrawals will be made from a multi-dose vial of Cr-51 EDTA over a period of more than one day.

It is not necessary to refrigerate blood samples between before processing and counting (see .8.4)

Radionuclide calibrator

A radionuclide calibrator is used to check the activity administered to the patient for the purpose of monitoring patient dose and compliance with ARSAC guidance. For this purpose a quality assurance programme based on guidance from the National Physical Laboratory [5] must be implemented to ensure that measured activities are accurate to within 5%.

If an activity based method is used for comparing the injected activity with the activity used to make up the standard, then the precision of these measurements should be better than 2%.

Pipette
An Eppendorf or equivalent pipette is used to draw up fixed volumes of the standard and plasma samples for counting.

A programme such as that described by Schofield et al. [6] must be implemented to ensure that operators preparing counting samples are able to draw up the required volume with an accuracy of better than 2%. Pipetting consistency can be continuously monitored by checking consistency of standards and consistency of counts from duplicate counting samples (see section 7).

Balance for sample measurement
If a weight based method is used for measuring the injected activity and the activity used to make up the standard (section 6.4) , then the precision of the difference between the syringe weights before and after drawing up, or before and after injection should be better than 2%.

Counter
A gamma counter is used to compare the activity of plasma samples taken from the patient with the activity of the standard used as a measure of the injected activity. The counter must be linear to within 2% over the range of activities to be counted, from the most active standard to the least active plasma sample. Modern counters are likely to include some correction for the effects of dead time and pulse pile up, but you must check that these corrections are satisfactory up to the count rate encountered for the most active standard. If not, consider adapting the procedure, by diluting the standard to a larger volume or using a smaller volume of the tracer to make up the standard, or apply a further correction to the count rate.

In general, all count samples should be made up to the same volume. If larger volume samples are used for some samples, for example 24 hour blood samples, a correction factor must be established for comparing counts from the different volumes used. If all samples related to a patient are not counted simultaneously then counts must be corrected for differences between count times. If all the samples related to a patient are counted in the same run, then a check must be made that the counter is applying decay correction for differences in counting time between samples. If more than one run is used for a patient, for example 24 hour samples are counted separately, then additional decay correction will be required to correct for the difference between the start times of the runs. Background correction must be applied. Background measurements must be made at least daily. Ensure that there is adequate shielding from other samples, particularly in multi-well counters, and from other radiation sources.

Summary of equipment requirements
See table 1 for a summary of equipment requirements.

Item	Usage	Requirements/accuracy/precision
Refrigerator	Storage of tracer prior to injection	Temperature requirements
Scales and a drop down tape measure	Patient height and weight measurement	1 kg, 2 cm? bed/wheelchair bound patients?
Radionuclide calibrator	Measurement of injected and standard activities	5% 2%
Balance (optional)	Measurement of patient administrations and standards	2% precision is required for the difference between the syringe weights before and after drawing up, or before and after injection
Clock	For timing injections and blood samples	1 minute – use same clock if possible for all timings
Radiation monitor	Checking the injection site for extravasation	
Volumetric flask	Preparation of standard	1%
Pipette	Preparation of counting samples	Precision better than 2%
Centrifuge	Spinning blood samples	1000g for 10 minutes
Gamma counter	Counting plasma samples and standards	Precision better than 2%

Table 3: Summary of equipment requirements