Modification Of Diet In Renal Disease Study

The Central GFR Laboratory Manual of Operations

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The Cleveland Clinic Foundation
Desk A101

MODIFICATION OF DIET IN RENAL DISEASE STUDY

The Central GFR Laboratory Manual of Operations

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GFR Functions

Part 1

Part 1 Table of Contents

1.1 Laboratory Responsibilities

a. The Central GFR Laboratory at the Cleveland Clinic Foundation will implement and coordinate the glomerular filtration rate (GFR) functions including GFR sample receipt and counting, GFR calculation, and result reporting.

b. The Clinical Centers will be responsible for performing the GFR test including the shipment of the processed samples and the completion of the GFR data form (Form#16).

1.2 Telephone and Written Communications

a. Telephone inquiries having to do with aspects of GFR test performance, GFR data forms, etc. may be directed to the GFR Central Laboratory at The Cleveland Clinic Foundation: (216) 444-4552 or 444-5040. Calls to this number will generally be answered between 9 a.m. and 5:00 p.m. Eastern Time, weekdays only.

b. Written inquiries should be addressed to the GFR Central Lab at the address listed in the MDRD Address Directory or by electronic mail.

c. The GFR Central Lab will communicate with participating Clinical Centers, if need be, at the addresses/phone number listed in the most recent MDRD Study Address Directory.

1.3 GFR Central Lab Activities

a. GFR Sample Receipt

GFR samples will be sent via next day mail by participating centers,to the Central GFR Laboratory. Upon receipt mailers will be logged-in and the contents will be inspected.

b. GFR Sample Counting

One-half ml aliquots of GFR samples will be pipetted into counting vials using a 500 microliter pipettor which is routinely checked (See GFR Laboratory Quality Control Section page 6) for volume tric accuracy and precision. Samples will be identified by printing specific sample designations on the tube tops with permanent markers. The full set of GFR samples from each patient will be placed incounter racks in the

following order (listed from first to last counted tube): backgound urine, U1, U2, U3, U4, background serum, S0,S1, S2, S3, S4. One ^{125}I standard will precede the first GFR tube counted in any run and a second like standard will follow the last tube counted. These standards will be made at the GFR Central Lab and will consist of actual ^{125}I-sodium iothalamate diluted as follows: 0.10 ml of undiluted ^{125}I-sodium iothalamate (as received from Isotex, Inc.; approximately 1.0 mCi in 4.0 ml) will be dispensed from a 1.0 ml syringe into a Class A 500 ml volume tricflask and will be diluted to the line with water. After mixing by inversion 8-10 times, small aliquots of this standard solution will be retained in the GFR Lab; 500 microliter volumes of the solution will be pipetted using a calibrated pipettor into vials for the gamma counter. The two standards must match to within $\pm$ 5%. The standards will be used to detect gamma counter power supply changes or other problems occurring during counting of a series of tubes. The principal gamma counter for the study samples will be a Packard 5550 Gamma counter. The instrument has three counting channels. The channel A window will be set to count 15 - 80 kEv, channel will count 80 - 470 kEv, and channel C is set to count 15 - 80kEv. Channels A and C should count ^{125}I identically (within dial accuracy and statistical variation), while channel B will detect any ^{131}I, ^{99m}Tc, etc., which should not be present in any case in this study. Counter parameters will be: standard deviation = 1.5%, maximum count time 10 min. and low count reject = 60 counts/15 sec. These parameters will ensure that samples of $\geq$ 450 counts per minute will be counted to 4,500 total counts/1.5% S.D. In the event that the Packard counter should fail, a Beckman Gamma Counter is available as an alternate counter. Both instruments will be calibrated versus a ^{137} Cesium standard to insure accurate window settings.

c. GFR Test Data Forms

The GFR Central Lab will receive the MDRD Form #16, GFR Determination Worksheet Form, with each set of patient GFR samples. The information from this form will be used to fill out MDRD Form #42, the Central Lab GFR Report Form, and to provide test information for the GFRcalculation program accessable through the CCF VAX computer system. The written forms will be filed.

d. GFR Calculations

GFR calculations will be done as described in Appendix 4.1 at the end of this chapter. GFR calculations will be done on the CCF VAX system using an in-house GFR program. This program will calculate the individual GFR periods, the GFR calculated as one period and the coefficient of variation. The coefficient of variation is defined as $\frac{\text{Standard Deviation}}{\text{Average GFR.}} \times 100\%$

This program includes provisions for data/result storage and reporting.

e. Reporting of GFR Results

1. During baseline the GFR reports will include the four individual GFR periods, the GFR calculated as one period, the GFR coefficient of variation, the urine flow rates for each period, and the urine flow coefficient of variation.
2. During follow-up only the coefficient of variation will be reported the urine flow rates and the urine flow CV. Central GFR personnel will review variable GFR's and discuss the tests with the responsible technologists. If the CV of the GFR at BV3 exceeds 35%, this value cannot be used for randomization. The GFR may be repeated once within one month. If the repeat GFR has a CV greater than 35% the patient is excluded from the study. Given that the GFR Worksheet Form #16 has been transmitted to the DCC, the GFR reports will be sent out by electronic mail.

f. GFR Data Storage

The GFR Worksheet (Form #16) and Central GFR Lab Report (Form #42) will be filed by the Data Coordinating Center. The GFR data will also be stored in the study data base and these files will be accessable for result reporting via electronic mail and/or printed mail as needed. The GFR Lab will file its copy of Form #16 with the gamma counter results and a copy of the GFR software output for each GFR processed.

g. GFR Laboratory Radiation Safety

The GFR Central Lab is regularly monitored by the lab technologists themselves as well as by the CCF Radiation Safety Officer. Regular records of these inspections

are filed in the Lab/Radiation Safety Office. In general, the lab countertop surfaces are regularly washed with Radiacwash or a comparable decontaminating detergent, and are covered with plastic-backed absorbent sheets to contain any radioactive sample losses for disposal. Such contaminated material is collected as double-bagged contaminated solid trash and this trash is picked up by CCF housekeeping staff when notified by GFR Lab, and hand delivered to a contaminated trash incinerator for suitable approved disposal. These pick ups are recorded. The GFR Lab does have an approved disposal sink for water disposal of ^{125}I-sodium iothalamate; handling of MDRD study samples will probably not require any such disposal. GFR Lab personnel wear monthly interval gamma radiation film badges and follow all CCF policies concerning the handling of radioactive materials. Standards will be stored appropriately. Counter background activity will be monitored and clean up of in appropriate levels initiated promptly.

h. GFR Laboratory Quality Control

Internal quality control of the Central GFR lab is accomplished as follows:

1. The pipettor used for GFR samples is evaluated for volumetric accuracy and precision at 6 month intervals using the weighing of water on an electronic microbalance as a quality control technique.
2. The gamma counter is calibrated with ^{137}Cesium standards toassure accurate peak locations/window settings.3. The patient counts are bracketted by matched ^{125}I-sodium iothalamate standards to eliminate instrumental malfunctions during sample counting as an error source.
4. The counter efficiency is monitored daily using ^{137}Cesium standards. Counter background activity is monitored on a daily basis as well.
5. A precision study is run weekly by randomly selecting a GFR study and rerunning it.

The External Quality control of the Central GFR Laboratory will be carried out as follows: Whenever a clinical center sends GFR specimens to the Central GFR Laboratory, backup specimens should be saved. Every three months, each clinical center will perform the following procedure for one GFR: After the GFR results come back from the Central Lab, the clinical

center technician will prepare a patient's backup specimens for mailing, using that center's "quality control identification number and name code" on the tubes and on the Mailing form. The Data Coordinating Center will suggest which patient's backup specimens should be used. (The MDRD technician should use the visit number from the original GFR.) The Clinical Center technician will inform the Data Coordinating Center which patients' GFR the quality control GFR should match using the Central Lab QC ID Matching Form 22. Results from the first GFR and the second GFR will be compared for quality control.

i. Certification of Clinical Center GFR Personnel

At the beginning of the MDRD Study, GFR personnel from all Clinical Centers will receive Central Training in the performance of GFR test. This instruction will include theory and practice of GFR testing in some detail, radiation safety, and a GFR employing subcutaneous injection of ^{125}I-sodium iothalamate (Glofil) will be perfomed during the instruction period. This course will be given by the GFR Central Lab Staff at the Cleveland Clinic. Clinical Center GFR Technicians will be certified by this staff upon successful completion of the course. If, after the study start-up, a new untrained technologist assumes the GFR responsibilities from the previously trained technologist, this person will be required to attend an abbreviated Central Training Session at the Central GFR Laboratory.

j. Procedure for Detecting Possible Radioisotope Misadministration

An upper level of radioactivity for serums was determined by the Central GFR Lab to detect possible overdoses. If a serum count exceeds this upper level the GFR Technician involved in that study will be contacted. It will be their responsibility to investigate the incident for a possible overdose. If an overdose did occur the Principal Investigator of that center and the Chairman of the Clinical Management Committee will be notified. It is the responsibility of the Clinical Center's Principal Investigator to fulfill the reporting requirements listed in the Procedure for Reporting Misadministration of Radioisotope during GFR studies (Appendix 4.4).

1.4 Clinical Centers' Activities

a. GFR Test and Protocol

The certified GFR technologist will perform the required GFR tests according to the

test protocol. The training at the Cleveland Clinic Foundation will insure a common understanding of the testing technique. The Central GFR Lab will be available to answer any questions and if the GFR technician needs advice during a test they should call the GFR Lab to obtain instructions on how to proceed. Written explanations of any deviations from the test routine shouldbe included on the GFR worksheet.

The Glomerular Filtration Rate Protocol is as follows:

1. Principle Urinary clearance of Glofil after subcutaneous injection will be used to determine accurately the level of glomerular filtration in subjects with renal in sufficiency by a method independent of changes in lean body mass or changes in protein intake. The patient ingests an oral water load, is given a saturated solution of potassium iodide, and the Glofil is injected subcutaneously. After a 60-90 minute waiting period, timed collections of urine and serum are performed. GFR is equal to the urinary clearance of the marker.
2. Materials and Equipment
   a. To perform GFR
      1. Saturated solution of potassium iodide (SSKI)
      2. Drinking cup and pitcher of water
      3. Accurate timing device (digital clock and/or stop watch)
      4. Urine collection containers (paper cups with lids, specipans or "hats" for females, and urinals for males)
      5. Graduated cylinder to measure urines
      6. Blood drawing supplies (needles, syringes, tubes, alcohol wipe, guaze, tourniquet or blood pressure cuff, 0.9% saline, heparin-1,000 unit/ml, paper tape, band aid, etc.)
      7. Dose of ^{125}I-sodium Iothalamate (Glofil).

   b. To process samples:

   <u>Only use equipment designated for radioactive specimens.</u>

      1. Refrigerator to store samples
      2. Centrifuge

3. Tubes to store duplicate samples at the center
4. Mailing supplies supplied by the Central GFR lab (labels, tubes, zip lock bags, mailers, ice packs, and packaging tape).

3. Procedure

a. Check eligibility. The patient has been fasting for 12 hours. The patient cannot have anything by mouth except water for 8 hours or more prior to the test. The GFR tech should verify this with the patient to uncover the patient who forgot to fast. Non-steroidal anti-inflammatory agents including aspirin, cimetidine, ranitidine, trimethoprim/sulfa, and trimethoprim should not be taken for at least 48 hours prior to each GFR. Other drugs may be taken up to and including the morning of the GFR tests. Women of child bearing potential (post-pubertal, premenopausal, and not surgically sterilized) must have a qualitative serum pregnancy test. You may use either the Abbott HCG Combo on the day of the GFR or the HCG-RIA with 72 hours prior to the GFR. The GFR is to be cancelled if the test was positive or if the patient did not have the test. Written results must be on file. If the patient has had a radio nuclide diagnostic test in the past month, using anisotope other than ^{99} Technetium, the GFR must be rescheduled. The patient should have had a 5 ml/kg water load at home. The GFR tech should verify every test.

b. Record the patients weight.

c. Mix 5 drops of SSKI in 20 ml of water and give to the patient orally. Note time given. The SSKI prevents thyroid uptake of any free ^{125}I; this protects the patient and eliminates error in the GFR determation due to the additional elimination route for the isotope. (Any patient with a true iodine allergy is excluded from the MDRD Study).

d. Start hydrating the patient. A water load of 10 ml/kg should be given during the next 90 minutes. See Section 6, items a and b, procedure notes.

e. Collect a background urine; record the time. Measure the volume.

f. Draw the background blood sample and the appropriate Biochemistry

samples after inserting the heparin lock, but before the Glofil injection. The recommended procedure for drawing GFR samples is as follows:

1. The subject should be seated during venipuncture.
2. It is recommended that the blood be drawn from an arm vein using a butterfly infusion set with a heparin lock. A recommended set is a 21 guage 3/4 inch infusion butterfly needle with a 12-inch tubing (Abbott #4492 or Argyle Division of Sherwood Medical #8888-111724) and Vacutainer tube holder with a screw-on luerlock adapter (Becton-Dickinson #7290). Use of an infusion set needle eliminates the common occurrence of a hand held vacutainer needle being pulled out of or pushed through a vein during multiple tube changes. The 12-inch line allows free motion for tube changes with no needle shifts. An armboard should be used whenever the butterfly position will be jeopardized by a patient's arm motion.
3. Insert the butterfly needle into the vein. Draw all the Biochemistry samples and the GFR baseline sample. Immediately after obtaining the samples, heparinize the site with at least one ml of 100 u/ml heparin. See Section 6, item e.
4. After heparinization, the line may be re-capped. The needle should be taped down securely with paper tape or some other easily removed hypoallergenic tape. Avoid taping the needle down to an extreme degree; this may pinch off the flow of the blood.

g. At least 30 minutes following the administration of the SSKI, the Glofil is injected subcutaneously in the upper arm. See Section 6, Procedure notes, item f. Record the time.

h. Continue to hydrate the patient at the rate of 200-400 ml/hour as tolerated throughout the study.

i. At least 60 min. after the time of the Glofil injection, the patient should void. Record the time (time #0). Measure the urine volume. See Section 6, item c, Procedure Notes. Determine the difference in time between the collection

of the background urine sample and time #0. Divide the volume of the urine by this difference in times. If the urine flow rate is at least 3 ml/min., then continue with the test. If it is less than 3 ml/min., wait a full 90 min. from the time of the Glofil injection. Have the patient void again. Record the time. Pool both urines to determine the volume of the discard urine. Using the latest time and the time of the background urine calculate the flow rate. If the flow rate is at least 1 ml/min. continue with the test. (See Form 16W).

j. Draw a blood sample (S-#0) using the heparin lock. To draw GFR samples, first clear the heparin from the line plus one ml. of blood to avoid diluting the GFR sample. Discard this initial diluted sample; then draw the GFR sample. Always re-heparinize promptly. The heparinized solution may be used repeatedly for the same patient, but be sure to keep the syringe capped between draws.

k. In 30 min. or more depending on the ability of the patient to void, collect the next urine sample (U-#1). Record the time. Measure the volume.

l. Draw the next blood sample (S-#1). Reheparinize the line.

m. Repeat steps k and l until four timed urines have been collected and appropriate blood samples drawn.

n. When all the blood samples have been obtained, remove the needle. Have the patient apply moderate pressure at the site for five minutes to avoid bleeding. Then apply a bandage.

o. When the blood samples have clotted, prepare the samples for mailing to the Central GFR Lab as follows:

1. Label the mailing tubes with the GFR labels. Be sure to include the patient's name code and number on each tube.
2. Centrifuge the blood samples.
3. Place an aliquot of serum in an appropriately labeled tube; save a duplicate sample in the refrigerator. (Discard the duplicate when GFR results are received.)

4. Place an aliquot of urine in the appropriately labeled tube; save a duplicate sample in the refrigerator. (Discard the duplicate when GFR results are received.)
5. Tighten all the caps of the mailing tubes.
6. Prepare the mailers for shipping with frozen ice packs.
7. Place all GFR tubes in a zip lock bag; place all biochemistry samples in a separate ziplock bag.
8. Check appropriate GFR and Biochemistry forms to make sure that they are filled in completely.
9. Mail the GFR samples to the Central GFR Lab. Mail the biochemistry samples to the CBL.

4. GFR DATA CHART:

PATIENT NAME CODE: _____ PATIENT ID NUMBER: _____

DATE: _____ VISIT NUMBER: _____ PATIENT'S WEIGHT: _____

	TIME	WATER LOAD (ML)	URINE*	URINE VOLUME	FLOW RATE	BLOOD SAMPLE*
IODINE 5 drops in water						
BACKGROUND SAMPLES			U-Bkgrd			S-Bkgrd
INJECTION Glofil						
DISCARD SAMPLE U-#0						S-#0
PERIOD #1			U-#1			S-#1
PERIOD #2			U-#2			S-#2
PERIOD #3			U-#3			S-#3
PERIOD #4			U-#4			S-#4

*Indicate with a check mark when collected or drawn.

5. **GFR Checklist:**

   a. Make sure that your patient is fasting, has not had any radio nuclide diagnostic test recently, and has a negativepregnacy test if necessary.

   b. Record patient's weight.

   c. Give patient iodine; note time.

   d. Start hydration; 10 ml/kg over next 90 minutes.

   e. Collect background urine; measure volume. (U-B)

   f. Obtain background blood sample and appropriate Biochemistry samples, (S-B)

   g. At least 30 min. after the iodine give Glofil injection; notetime.

   h. 60-90 minutes later have patient void; note time (Time #0); measure volume.

   i. Draw blood sample (S-0).

   j. Continue hydrating patient at a rate of 200-400 ml/hr.

   k. In 30 min or more collect next urine sample (U-1); note time; measure volume.

   l. Draw blood (S-1).

   m. Repeat steps j-l until four urine collections have been collected and the appropriate blood samples have been obtained.

   n. When blood samples have clotted prepare samples for mailing.

6. **Procedure notes**

   a. A well-hydrated patient is crucial to a valid GFR study. While 200-400 ml/hour is the recommended water-load, the technicians should use their own good judgement based on the patient's kidney function to determine the appropriate amount of hydration. A desirable flow rate is 4-6 ml/min, but this may not be achievable in some patients. A flow rate of 2-3ml/minute is adequate. The GFR may not be performed at flow rates less than 1 ml/minute.

   b. Water loading serves to increase urine volume and the frequency of spontaneous voiding. The use of spontaneously voided urine should decrease the likelihood of incomplete bladder emptying, a source of possible error. Bladder emptying should be assessed using ultrasound in the screening control period in patients with symptoms suggestive of lower urinary tract obstruction (frequency, hesitancy,

diminished urinary stream). In these patients a pre and post void echo of the bladder will beobtained after an oral water load of 500 ml. If the patient develops these symptoms during Baseline, see Protocol Section 4.4.6, Exclusion Criteria.

c. Accurate timing of urine collections and careful measurement of urine samples are essential. The timing of the urine samples is critical. All times are recorded based on the time of completion of the urine collection and recorded to the nearest minute using an accurate timing device such as a digital clock. The voiding intervals will vary since they are based on spontaneous voidings. Subjects with lower GFR function may excrete the water load more slowly.

d. All Biochemistry samples must be drawn prior to the Glofil injection.

e. The heparin saline solution used in drawing the GFR blood samples is made by drawing 1000 unit/ml sodium heparin into a 5ml. syringe down to the 0.5 ml. line and then diluting with 0.9% saline to a total of 5 ml. The solution must be well mixed by rolling the syringe vigorously between the palms of your hands. Never use 10,000 unit/ml. heparin. Always check the bottle prior to use.

f. A locally approved individual will inject Glofil subcutaneously in the upper arm region. This will be provided in ½cc. Insulin syringes as a sterile, pyrogen free solution containing approximately 35 microcuries per dose. The entire volume (approximately 0.2 cc) will be injected subcutaneously at one site. A skin fold in the back of the upper arm will be grasped and the needle inserted at a 90 degree angle up to the needle hub. Refer to Appendix 4.2 at the end of this chapter for more information on ^{125}I-Sodium-Iothalamate and radiation safety.

g. After the study the patient should be encouraged to maintain a high urine output and to void frequently to minimize radiation exposure to the bladder.

h. The following conditions make the GFR sample inaccurate.

   1. An incomplete urine collection makes the GFR period unacceptable. Collect another period.
   2. When another isotope contaminates the patient samples and its interference cannot be substracted or allowed to decay to background, the GFR cannot be calculated.

3. If fecal contamination occurs, collect an additional period 4. If the flow rate is less than 1 cc/min, the test is not accurate.

The GFR technician should call the Central GFR Lab if they have any questions.

i. Refer to Appendix 4.5 at the end of this chapter for references.

b. GFR Test Worksheet Completion (see MDRD Form #16)

The GFR Technicians will fill out completely and include with each GFR sample mailing the GFR Worksheet Form. The form incorporates questions which will help the GFR Central Lab ascertain GFR test problems. All items must be answered or, if not, explanations must be included for deviations from the test protocol.

c. GFR Test Troubleshooting

In cases with unusally discrepant results for the four periods, the GFR Central Lab will 'troubleshoot' to determine what factors might have caused the imprecise test.

d. Actions Based Upon GFR Test Results

GFR stop points are as follows (from the MDRD protocol Section 10.3.3):

1. For Study A patients, a decline in GFR from Baseline Visit 3 (B3) to the level indicted below:

B3 GFR	Follow-Up GFR
$\geq$ 40 ml/min/1.73m^2	$\leq$ 20 ml/min/1.73m^2
25-40 ml/min/1.73m^2	<50% of B3 value

Because the Clinical Center's staff members are blind to GFR results, during follow-up, the Data Coordinating Center will notify the involved Clinical Center when a GFR Action Item occurs. The GFR must be repeated within one month. The Data Coordinating Center will notify the Clinical Center if a stop point was reached. If the repeat GFR is above the level indicated above, then the patient continues in Follow-up and the GFR is measured at the next routine visit.

2. Study B and C patients. No GFR stop point exists; initiation of dialysis or transplantation is a stop point.

Lab Sample Handling Functions

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Central GFR Lab Sample Handling Function

2.1 Laboratory Responsiblilities

a. The Central GFR Laboratory at the Cleveland Clinic Foundation will receive specimens for GFR only.

b. The Central Amino Acid Laboratory will process Amino Acid samples and report results.

c. The Central Biochemistry Laboratory at the Cleveland Clinic Foundation will receive and perform all Biochemistry testing and reporting of results.

d. The Clinical Center GFR Technician will be responsible for collecting all samples, processing them, and mailing them to the appropriate Central Lab.

2.2 Telephone/Written Communications

a. Telephone inquiries having to do with aspects of sample collection/processing/mailing may be directed to the Central GFR Laboratory or the Central Biochemistry Laboratory. Calls to these numbers will be answered between 9 a.m. and 5:00 p.m., Eastern Time, weekdays only.

b. Written inquiries can be sent to the Central GFR Laboratory or the Central Biochemistry Laboratory at the addresses in the MDRD Address Directory or by electronic mail.

c. The Central GFR Lab and the Central Biochemistry Lab will communicate with participating Clinical Centers, if need be, at the addresses/phone numbers listed in the most recent revision of the MDRD Study Address Directory.

2.3. Sample Handling Activities in Detail

a. Procurement of Mailing Supplies for GFR Samples

The Central GFR Lab will provide all necessary mailing supplies including styrofoam insulated mailing containers with cardboard outer mailing boxes, polypropylene and serum and urine mailing tubes, zip-lock type plastic bags, freezer packs, packing tape, suitable labels, etc. Participating Clinical Centers will be expected to provide sample processing supplies (e.g. tubes, needles) themselves.

b. Distribution of Mailing Supplies to Participating Clinical Centers Mailing supplies, will be shipped to each participating Clinical Center as needed. These supplies will

be returned to the participating Clinical Centers by the Central GFR Lab shortly after each set of patient samples is received. Styrofoam mailing containers and freezer packs will be re-used whenever possible and replaced by the Central GFR Lab as needed. Plastic sample mailing tubes and zip-lock bags will be discarded by the Central GFR Lab after each mailing and replaced. Supply Order Forms will be sent back to Clinical Centers with each re-mailing of shipping boxes. Clinical Center technologists may check off needed supplies on these forms and return them to the GFR Central Lab with the next sample mailing to indicate their need for additional supplies. The Supply Order Form is illustrated in Appendix 4.3.

c. Postal Inquiries

Participating Clinical Centers should keep a log of sample mailing dates for reference. The Central GFR Lab will log-in samples received. In the event that mailing difficulties occur, the Central GFR Lab will follow up as needed when notified of a problem.

d. Sample Package Receipt at CCF

Samples should arrive as next-day-mail at CCF. Packages are delivered directly to the GFR Lab.

e. Initial Sample Inspection and Log-in

Mailers will be logged in with the date of receipt. Boxes will be opened and the patient number, name code, center and type of samples will be recorded.

f. Communication with Participating Clinical Centers Concerning Sample Receipt Problems, Protocol Changes, etc.

The Central GFR Lab will communicate sample receipt problems, protocol changes, etc. to the participating Clinical Center as needed.

The Central GFR Lab Manual of Operations

Part 3

GFR Central Laboratory Software User's Guide

DATE OF GUIDE

The following guide incorporates information available through November 1, 1986.

PURPOSE OF GUIDE

This guide describes user information for the GFR calculation software written at the Data Coordinating Center at the Cleveland Clinic Foundation, for use in the MDRD Study. This software is available in-house only on the CCF VAX system and this guide is directed to MDRD GFR Central Lab and Data Coordinating Center personnel at CCF.

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3.1 Connection to VAX

To use the GFR program, one must connect to the CCF VAX through one of the CCF local area network terminals (e.g. Digital VT 100, Digital VT 240) or via modem from other micro computer inputs which have the capacity to emulate these terminals. The GFR lab accountname and password are part of the computer file located at the Data Coordinating Center.

3.2 Access to GFR Program

Once the VAX connection is made, access the GFR program by typing F42. The following prompt will appear: GFR ? Type the letter Y and hit the carriage return. At this time a GFR screen with no data will appear. If this does not occur, contact Kathy Fatica at Biostatistics and Epidemiology (x42980).

3.3 GFR Calculation

1. Access the available data on the patient by Keyentering the ID number in the first field. Hit a carriage return. Type a 2 for a baseline GFR or a 3 for a follow-up GFR. Hit CR and the rest of that patients data appears on the screen.
2. Review the identifying information to confirm that you are looking at the correct set of data (specifically, review the visit type and number--also, not the sequence number).
3. Hit the CR once. Keyenter the date the sample was received and CR. Do the same for the data of the assay, the serum counts and the urine counts.
4. Go the the 2nd page of data (the next screen) by typing ">".
5. Type in general comments about the condition of the samples, etc.
6. Type in your certification number.
7. Type in a "1" at the "enter 1 to calculate GFR" prompt.
8. Go to the first page of data by typing "<".
9. Review the GFR data.
10. To finish the session, type "#" - this also saves the data.
11. To revise and recalculate the data, go to the recalculating GFR's section (III)

3.4 Recalculating the GFR's

1. Get to the "GFR ?" prompt and type "Y."
2. A blank GFR screen will appear on your terminal.
3. Call the data up to the screen:
   a. Type in the ID number you wish to recalculate the GFR for.
   b. Hit return so the most recent set of data for that ID appears.
   c. Review the identifying information to confirm that you are looking at the correct set of data (specifically, review the visit type and number).
   d. Go to the 2nd page of data (the next screen) by typing ">".
   e. Type in A "1" at the "recalculate GFR 1=Y, 2=N" prompt.
   f. Go to the first page by typing '<".
4. Revise the data.
   a. Move to the field you wish to reverse.

      You can move around the screen several ways:

      - hit the return key or the up arrow key to advance to the next field.
      - hit the down arrow key to go back to the previous field.
      - hit the "/" key to move to the next grouping or cluster of fields.

   b. Change the data by typing the correct value over the original value.
5. Recalculate the GFR.
   a. Once all the revisions have been made, to the second screen by typing ">."
   b. Enter text to describe the revision made at the revision comments fields.
   c. Hit the down arrow key until you reach the "enter 1 to calculate GFR." Type A "1".
   d. You will notice that the "enter 1 to calculate GFR" and "recalculate GFR 1=Y, 2=N" fields are automatically reset to "0."
   e. Review the data. You will not be able to revise the data again unless you set the field "recalculate GFR 1=Y, 2=N" to "1" and go back to step 4.
6. To finish the session, type "#". This also saves the data.
7. To exit the forms session, type "." at the "GFR ?" prompt.

3.5 GFR Report

Once a calculation has been made, a GFR Report will be electronically mailed to the Clinical Center and GFR Lab the following day.

APPENDICES
Part 4

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APPENDIX 4.1
GFR CALCULATIONS

GFR is equal to UV/P

U = activity in urine, corrected for background

P = activity in serum, corrected for background

V = urine volume/time of collection period

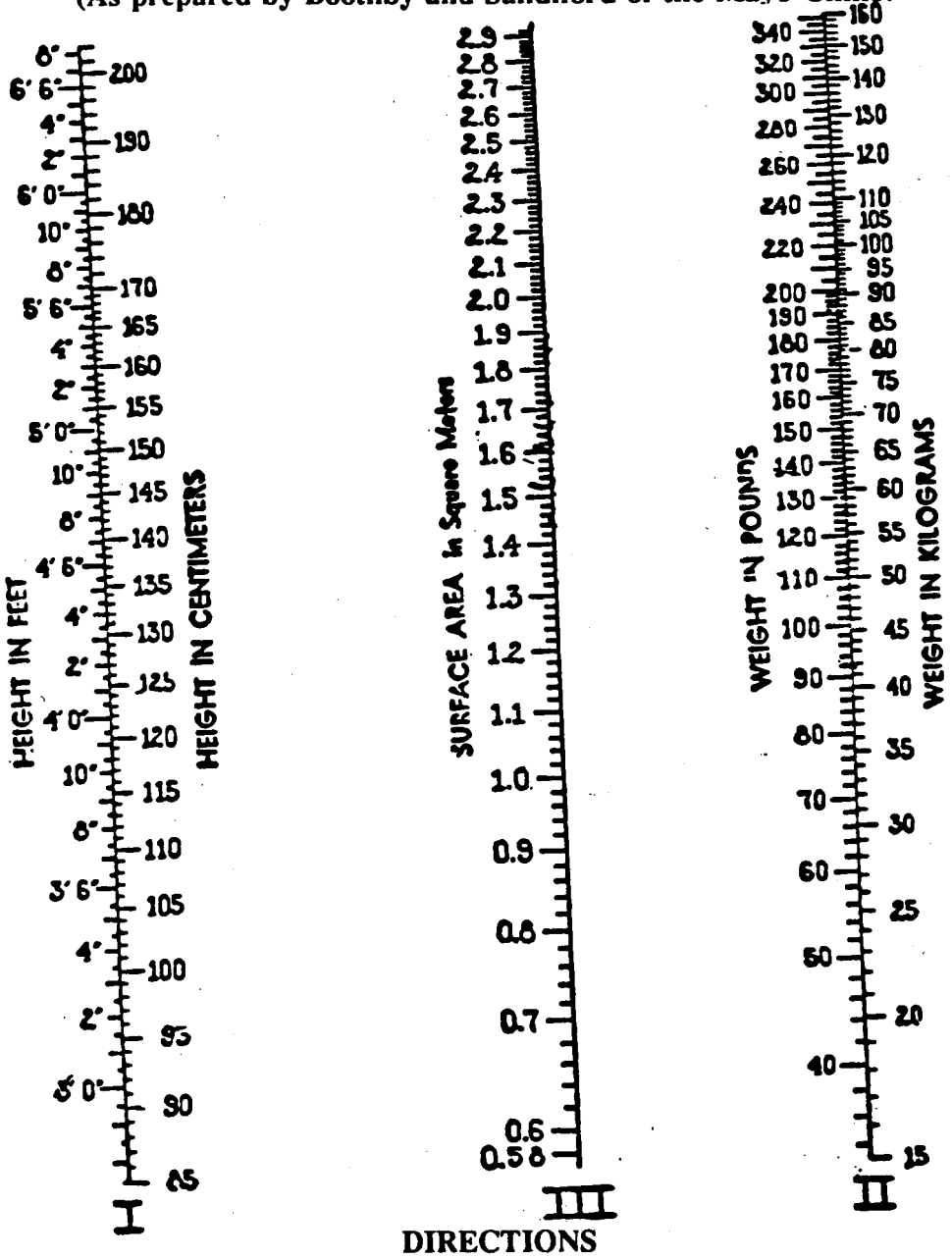
The serum activity for any given period will be the log mean of the serum samples at the beginning and end of that period. For example, the serum activity corresponding to URINE #1 is derived from BLOOD #0 and BLOOD #1.

$$GFR = \frac{U_1 \times V}{10\,(\text{Log } B_0 + \text{Log } B_1)/2}$$

All GFR measurements will be corrected to 1.73 m^2 using the most recent height measurement and the weight determined on the day of study. The BSA is obtained from the nomogram of Booth by and Sandiford. (See Appendix 4.1 Figure 1).

The GFR for a given study will be calculated two ways, first as the average of the clearance periods (shown in Figure 2). In addition, the GFR will also be calculated as if there were only one long collection period (Figure 3).

Figure 1
DUBOIS BODY SURFACT CHART
(As prepared by Boothby and Sandiford of the Mayo Clinic)



DIRECTIONS

To find body surface of a patient, locate the height in inches (or centimeters) on scale I and the weight in pounds (or kilograms) on Scale II and place a straight edge (ruler) between these two points which will intersect Scale III at the patient's surface area.

Alternatively, one may use the formula:

$$BSA \text{ (in } M^2) = [W^{0.425} \times H^{0.725} \times 71.84]/10{,}000$$

where W = weight in kilos
H = height in centimeters

APPENDIX 4.1

Figure 2

Sex (0=M, 1=F): 1 Height (cm): 155

Weight (kg) 55.1

Avg. Creatinine Clearance: Average Urea Clearance:

Time Period	Actual Time Hrs:Min	Elapsed Time (min)	Urine Volume	Serum Count	Urine Count	GFR
B	09:20		$B_{Back} = 20$	$U_{Back} = 25$		
0	10:21	61	$B_0 = 2319$			
1	11:04	43 94.0	$B_1 = 2121$	$U_1 = 14443$	16	
2	11:47	43 86.0	$B_2 = 1801$	$U_2 = 11967$	14	
3	12:31	44 96.0	$B_3 = 1695$	$U_3 = 10830$	15	
4	13:12	41 86.0	$B_4 = 1516$	$U_4 = 9847$	15	

Average GFR: 15.1 GFR as 1 period: 15 CV: 6

Body Surface Area (BSA) = 1.53 m^2

Urine Flow Rates (V) **Log Mean Serum Counts (P)**

Period 1: 94.0/43 = 2.19 ml/min $P_1 = 10^{\frac{\text{Log (2299)} + \text{Log (2101)}}{2}} = 2198$

Period 2: 86.0/43 = 2.00 ml/min $P_2 = 10^{\frac{\text{Log (2101)} + \text{Log (1781)}}{2}} = 1934$

Period 3: 96.0/44 = 2.18 ml/min $P_3 = 10^{\frac{\text{Log (1781)} + \text{Log (1695)}}{2}} = 1727$

Period 4: 86.0/41 = 2.10 ml/min $P_4 = 10^{\frac{\text{Log (1675)} + \text{Log (1496)}}{2}} = 1583$

GFR Corrected for BSA (UV/P)

P_1: $\frac{14418 \times 2.19}{2198} \times \frac{1.73}{1.53} = 16.25$ ml/min/1.73m^2

P2: $\frac{11942 \times 2.00}{1934} \times \frac{1.73}{1.53} = 13.96$ ml/min/1.73m^2

P3: $\frac{10805 \times 2.18}{1727} \times \frac{1.73}{1.53} = 15.42$ ml/min/1.73m^2

P4: $\frac{9822 \times 2.10}{1583} \times \frac{1.73}{1.53} = 14.73$ ml/min/1.73m^2

Avg. GFR = 15.09

SD = 0.98

CV = $\frac{0.98}{15.09} \times 100\% = 6.47\%$

APPENDIX 4.1

Figure 2. Average GFR Calculation For a Four-Period GFR

See data columns listed on the previous page. Serum and urine counts are labeled with sample designations currently used. First, we calculate the body surface area from patient's height and weight values using the nomogram/formula given on page 30; BSA = 1.53 m^2 to two decimal places.

To determine GFR calculations, first subtract the background serum count from each of the following serum counts; subtract the background urine count from each of the following urine counts similarly. Next, calculate the urine flow rates for the four urine collection periods; for example, the flow rate for Period 1 is 94.0 ml. divided by 43 minutes, which gives 2.19 ml/min. Next, calculate the log mean serum counts for each collection period. For period one, the B_0 blood sample was drawn when the discard urine was collected and the blood sample B_1 was drawn when the urine U_1 was collected. Therefore, the samples B_0 and B_1 bracket the U1 collection period and their log mean value is defined as:

$$10^{[(\text{Log}\,(B_0 - B_{\text{Background}}) + \text{Log}\,(B_1 - B_{\text{Background}}))/2]}$$

Filling in the counts, this value becomes ten raised to the (Log 2299 + Log 2101)/2 power, which is $10^{3.341982512} = 2197.77 = 2198$. The log mean values for the remaining periods use their respective bracketing blood samples.

Finally, the $^{U}V/P$ calculation is done, where U represents the urine counts for a period minus urine background, V represents the urine flow rate for that period, and P is the log mean serum count for the same period. For period one, U is U_1 counts minus $U_{\text{Background}}$ counts = 14418, and GFR = (14418 x 2.19)/2198 = 14.37 ml/min. This is then corrected for Body surface area by multiplying by 1.73/BSA; GFR = (14.37)(1.73/1.53) = 16.25 ml/min/1.73m^2. This GFR result is rounded to the nearest whole number and used in the GFR value column for period one. Other period GFR values are calculated in like fashion. The average of these individual period GFR values is then reported as average GFR. The calculation program also calculates the standard deviation (SD) for the four GFR values and reports the coefficient of variation (CV) for this data, where CV is defined as CV = (SD/average GFR) x 100%.

APPENDIX 4.1

Figure 3

Time Period	Actual Time Hrs:Min	Elapsed Time (min)	Urine Volume	Serum Count	Urine Count	GFR
B	09:20			$B_{Back} = 20$	$U_{Back} = 25$	
0	10:21	61		$B_0 = 2319$		
1	11:04	43	94.0	$B_1 = 2121$	$U_1 = 14443$	16
2	11:47	43	86.0	$B_2 = 1801$	$U_2 = 11967$	14
3	12:31	44	96.0	$B_3 = 1695$	$U_3 = 10830$	15
4	13:12	41	86.0	$B_4 = 1516$	$U_4 = 9847$	15

Average GFR: 15.1 GFR as 1 period: 15 CV: 6

Body Surface Area (BSA) = 1.53 m^2

Total Urine Volume = 362 ml
Total Test Time = 171 min
(Periods 1-4)

Log Mean Serum Counts (P)

Period 1: 2198
Period 2: 1934
Period 3: 1727
Period 4: 1583

Urine Counts Minus Background (U)

Period 1: 14418
Period 2: 11942
Period 3: 10805
Period 4: 9822

Urine Counts Weighted by Volume

$$U = \frac{14418(94)}{362} + \frac{11942(86)}{362} + \frac{10805(96)}{362} + \frac{9822(86)}{362} = 11780$$

Log Mean Serum Counts Weighted by Time

$$P = \frac{2198(43)}{171} = \frac{1934(43)}{171} \; \frac{1727(44)}{171} + \frac{1583(41)}{171} = 1863$$

GFR As One Period

$$\frac{11780 \times (362/171)}{1863} \times \frac{1.73}{153} = 15.1 \text{ ml/min/1.73m2}$$

APPENDIX 4.1

Figure 3. GFR Calculation

As One Long Collection--For a Four-Period GFR

Calculations are identical with those shown in Figure 2 for the average GFR calculation through the log mean P values. Then the four P values are weighted by their respective period time/total time ratios and combined. Likewise, the urine counts U for each period are weighted by their respective period volume/total volume ratios and combined. The GFR value is then determined by a single calculation employing these combined U and P values and the total urine volume divided by the total test time. BSA correction is as usual.

APPENDIX 4.2
Radiation Information

a. ^{125}I-sodium iothalamate (Glofil)

The sole supplier of Glofil in the United States at the present time is Isotex Inc, Box 909, Friendswood, Texas 77546, phone (713) 482-1231. The material is synthesized on a monthly schedule and is available in 4 ml aliquots (1.0 mCi). It is stored at 4°C in its lead container in a suitable nuclear medicine area and is stable for 45 days according to the manufacturer, although the half-life of ^{125} iodine is 60 days. The limit to Glofil's usable life is a function of the chemical instability of the isotopic label, which is slowly released as free ^{125} iodine from the iothalamate molecule. As this free ^{125} iodine accumulates, the clearance of Glofil deviates from the true GFR. The material should not be used past the manufacturer's expiration date.

The iothalamate is drawn up in a ½ ml plastic syringe with a 28 gauge x ½ inch needle. The total activity in the dose for an adult patient should be 35 micro curies. The syringe weight/activity before and after the shot is not measured, and no standard solution of the iothalamate is required. The iodine-allergic patient should not be given the iothalamate.

Technologists handling the iothalamate should take all safety precautions to protect both the patient and themselves from unnecessary radiation exposure. Technologists should wear appropriate gamma ray-sensitive film badges and follow their exposure levels; the iothalamate should be stored and delivered in shielded containers. ^{125} iodine emits low energy gamma radiation with a maximum energy of 36 KeV and lead will shield the user very effectively (1 mm of lead will stop 99.96% of the radiation from an ^{125}I source). The syringes may be handled briefly, while the shot is given to the patient, without shielding. Gloves should be worn in case of dose leakage or if other unsafe conditions arise. All syringes, needles, empty isotope bottles and any other radioactive trash should be disposed of via established contaminated refuse protocols (consult radiation safety and/or disposal regulations); as a rule of thumb, any isotope decays to less than 1% of its original activity in seven half-lives. This is 420 days for 125 iodine. Small amounts of 125 iodine may be disposed by flushing with large amounts ofwater down the drain in approved disposal sinks.

b. Dose Estimates for the Skin

The dose estimates to the skin from subcutaneous injection of Glofil are shown in the table below. These estimates are based on the following assumptions: injection of 35 uCi in a volume of 0.2 ml, 3 minute effective half time at the injection site, site modeled as a disk of radium 1 cm and thickness 0.064 cm, disk directly beneath the skin surface and in contact with skin. The distances, then, are the distances from the face of the disk into the overlying skin.

	Dose (rad/35uCi)		
Distance (cm)	Photon	Beta	Total
0.0015	0.05	0.0035	0.0535
0.002	0.0475	0.000425	0.048
0.003	0.045	---	0.045
0.008	0.0375	---	0.0375
0.018	0.030	---	0.030
0.028	0.0275	---	0.0275
0.038	0.0248	---	0.0248

Dose Estimates for Major Body Organs

The dose estimates for major body organs for intravenous administration of Glofil are shown in the table below. These estimates may be used interchangably as estimates for subcutaneous injection due to the long physical half life of ^{125}I. These estimates are based on essentially the same distribution data as the estimates in the Abbott package insert (done in 1972), but using improved calculational techniques and including the dose to the urinary bladder, which turns out to be very important. No thyroid dose has been calculated.

APPENDIX 4.2

Radiation Dose Estimates* for I^{125} Iothalamate

* Assumed distribution and retention:

Organ	Estimated Radiation Dose 2.0 hours** MGy MBq	rad mCi	4.8 hour** MGy MBy	rad mCi
Bladder	0.058	0.21	0.16	0.58
Kidneys	0.16	0.059	0.016	0.059
Liver	0.0040	0.015	0.0040	0.015
Ovaries	0.0015	0.0055	0.0026	0.0095
Red Marrow	0.0015	0.0057	0.0017	0.0063
Tests	0.0051	0.019	0.0057	0.021
Total Body	0.0014	0.0053	0.0021	0.0077

* Assumed distribution and retention:

Liver	11.52%	t_b = 1.72 hr
Kidneys	10.26%	t_b = 1.72 hr
Testes	0.41%	t_b = 1.72 hr
Remainder	77.81%	t_b = 1.72 hr

** Bladder voiding interval

Acknowledgement

The data regarding dose estimates for the skin were provided by Michael Stabin, Radio pharmaceutical Internal Dose information Center, Oak Ridge Associated Universities (ORAU) in April, 1985.

The address for ORAU is P.O. Box 117, Oak Ridge, Tennessee 37831-0117.

APPENDIX 4.3
Central GFR Order
"Supply Form"

REQUEST FOR MDRD SUPPLIES

Center Number_____ Date of Request_____

Please check supplies needed and return this form to the GFR Central Lab in your next sampl emailing. We will send the supplies when we return your mailer. Please notify us before you run out completely. Thanks.

- ☐ Packing Tape
- ☐ Polar Packs
- ☐ Sample Tubes
- ☐ GFR tube lables
- ☐ Ziplock bags
- ☐ Mailing boxes
- ☐ 'Radioactive' Tape
- ☐ Mailing Labels

Comments: _____

_____

_____

_____

_____

Date Supplies Mailed _____ GFR Lab Person _____

APPENDIX 4.4

PROCEDURE FOR REPORTING MISADMINISTRATION OF RADIOISOTOPE DURING GFR STUDIES

It is the responsibility of the Clinical Center Principal Investigator to fulfill the reporting requirements listed below in the event of a radioisotope misadministration during MDRD GFR procedure:

1. An error in isotope administration may be identified by clinical center personnel or by staff of the Central GFR Laboratory. Errors should be reported to the Quality Control Committee. Errors which result in misadministration of more than the prescribed dose must be reported immediately to the Clinical Management Committee Chairman. In the event that the error is detected by the staff of the GFRCentral Lab, it will be reported directly to the Clinical Center Principal Investigator and GFR Technician and to the Clinical Management Committee Chairman by the GFR Lab Director.
2. The local institution radiation safety officer must be consulted to determine if the error is classified a "misadministration" according to the Nuclear Regulatory Commission, or for "agreement states", according to the state regulations. The Clinical Management Committee must be notified, in writing, of the determination. If a misadministration has occurred, it must be investigated and reported in compliance with federal or state law, and copies of all subsequent correspondence and reports should be forwarded to the Clinical Management for review. If a misadministration has not occurred, no further investigation or reports are necessary, unless requested specifically by the radiation safety officer, the Clinical Management, or NIH.
3. In the event of a misadministration, an investigation by Clinical Center staff and the institution's radiation safety officer will be requested to provide the following information to the Clinical Management Committee within three months of the occurence or notification of the misadminstration (unless stipulated otherwise by federal or state regulations):
   a. The date of each misadministration and the study subject involved.

APPENDIX 4.4

Procedures for Reporting Misadministration of Radioisotope During GFR Studies (continued)

b. The amount of radioisotope administered and an estimation of the radiation absorbed dose for each misadministration.

c. A statement from the radiation safety officer whether the patients' safety was compromised; i.e., whether the radiationdose administered or absorbed exceeds the acceptable limits forstudy subjects and whether performance of subsequent GFR measurement is permissible.

d. A statement from the investigational review board whether the patient's consent was compromised; i.e., whether the dose administered or absorbed exceeds the amount stated on the consent form and whether performance of subsequent GFR measurements is permissable under the original consent.

e. A statement from the radiation safety officer whether it is necessary to notify the patient and the referring physician.

f. A statement from the radiation safety officer how the misadministration occurred and what steps have been taken to correct the circumstances which led to the misadministration.

4. The Clinical Management Committee will review the above reports and will provide NIH with interim and final reports regarding the manner in which the misadministration is addressed and resolved.

APPENDIX 4.5

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APPENDIX 4.5

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