A Technologist Perspective on Conducting Theranostic Clinical Trials – Dosimetry Emphasis

Freddy Gonzalez MBA, ARRT(N), NMTCB(CT), PET

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Walter Durham Lecture

- In memory of Walter Durham, outstanding leader in nuclear medicine and a man of faith. January 28, 1946 – October 6, 2000
- Native of Galveston, Tx started as a patient transporter at UTMB, discovered nuclear medicine, studied and became a certified nuclear medicine technologist.
- Inquisitive and eager to learn, constantly asking radiologists/technologists about various exams and observing in the clinic.
- UTMB Nuclear Medicine Supervisor
- SWC -TS President - Elect 2000 – 2001

Disclosures

- No Financial Disclosures
- SNMMI-TS Molecular Therapy Task Force
- Nuclear Medicine Technologist Certification Board (NMTCB)
  - Board of Directors

Purpose

- To provide a technical general overview of the nuances of collecting good quality data for theranostic clinical trials.
- Overview is based on previous experience with theranostic clinical trials.
- Research specific presentation with applicable daily theranostic practices.

Agenda

Review the following:

- Three phases of clinical trials
- Infusion methods
- Quantitative data acquisitions and biological sample collections
- Post therapy radiation precautions
- Technical protocol document (Local Practice)
- Patient Perspective

Theranostics

- “Theranostics allows us to see what we treat and treat what we see” Dr. Richard Baum
- Theranostic radiopharmaceutical therapy (TRP) paradigm consists of diagnostic and therapeutic radiopharmaceutical matched pairs.
- Fundamental nuclear medicine practices are at the basis of every theranostic clinical trial.
- First CODE: **2811**

Effective Communication

- Theranostic trials involve a complex multi-disciplinary team effort
  - Principal Investigator, Authorized User, Medical Physicist, Pharmacist, Nurses, Technologists, etc.
- Internal or external protocol sponsor, medical monitors, and imaging vendor.
- Crucial to have good communication systems in place for all team members for safe and effective patient management.
- Plan for potential patient reactions and radiation safety.

Protocol Manual Review

- We must allocate sufficient time to review and prepare protocols manuals.

- Manuals may include:
  - Investigators Brochure
  - Primary Manual
  - Pharmacy Manual
  - Lab Manual
  - Technical Operations Manual

For every 1-hour spent with a patient, 2-hours are spent preparing.

Phase 0/I Clinical Trials

- Novel investigational product is administered to a small number of patients.
- Patients enrolled typically have received multiple lines of therapy.

Investigational Products	**Clinical Trials ID**
• AvidinOX + ^{177}Lu-DOTA-Biotin* (Intravenous)	NCT03188328
• ^{227}Th-Her2 (BAY2701439) (Intravenous)	NCT04147819
• ^{14}C-SNDX (Oral Solution)	NCT05406817

- The investigational product needs to demonstrate safety, specificity and identify any side effects.
- Identify any post-treatment toxicities.
- Typically, single or limited sites conduct the clinical trial.

Jeffers et al, JNMT 2022

Phase II Clinical Trials

- Novel investigational product is administered to a few hundred patients.
- Patients enrolled typically have received some lines of therapy.
- **Investigational Products** **Clinical Trials ID**
  - ^{68}Ga + ^{177}Lu-FAP-2286 (LuMIERE) NCT04939610
    - Intravenous

- Identify proof of efficacy.
- Reveal less common side effects.
- Additional safety data is obtained and analyzed.
- Typically, a single to a limited number of sites participate.
- If enough patients benefit from the investigational product, with acceptable side effects then can proceed to phase III.

Jeffers et al, JNMT 2022

Phase III Clinical Trials

- Novel investigational radiopharmaceutical is administered to several hundred patients.
- Patients enrolled may be receiving TRP as a front line.
- **Investigational Product**
  - ^{177}Lu-PSMA-617
    - (PSMAddition)

Clinical Trials ID
NCT04720157

- Compare safety and efficacy of the radiopharmaceutical against standard of care therapy.
- Typically, these are large multi-center clinical trials.

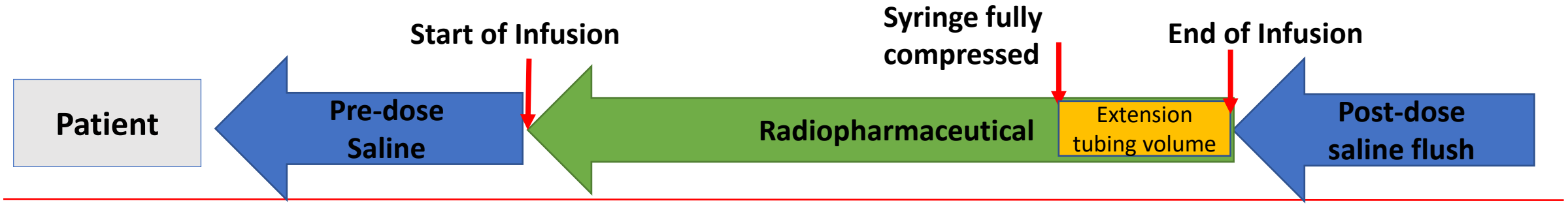
Jeffers et al, JNMT 2022

Radiopharmaceutical Infusion Methods

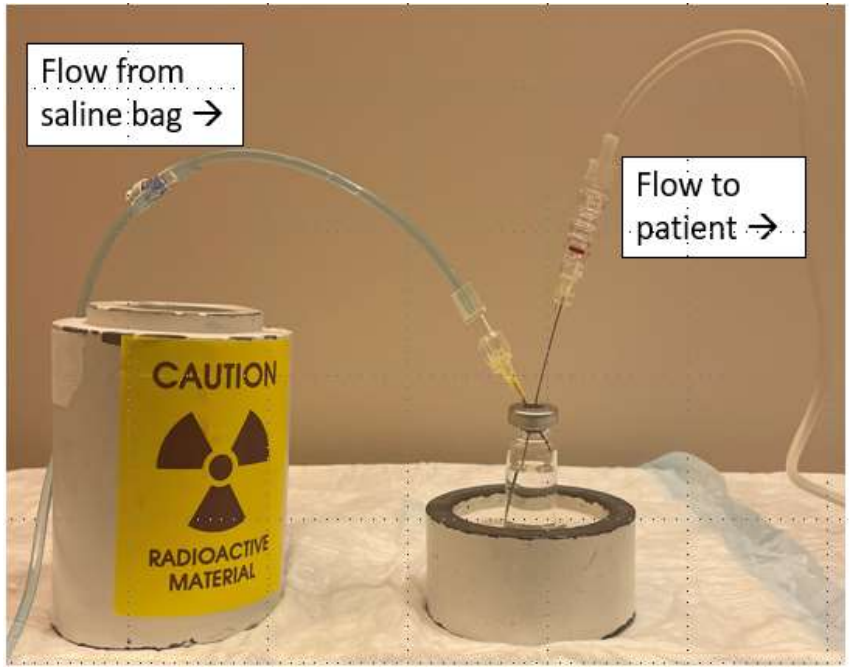
- The clinical trial may indicate which infusion methods to use, or it may be at the discretion of the clinical site.
  - Syringe Pump
  - Gravity Method
  - Peristaltic Pump
- How do these three methods compare for therapeutic radiopharmaceutical (TRP) infusion?

Syringe Pump Infusion

- Mechanical drive accuracy: ± 2%
- Pump shield weighs 91 lbs.



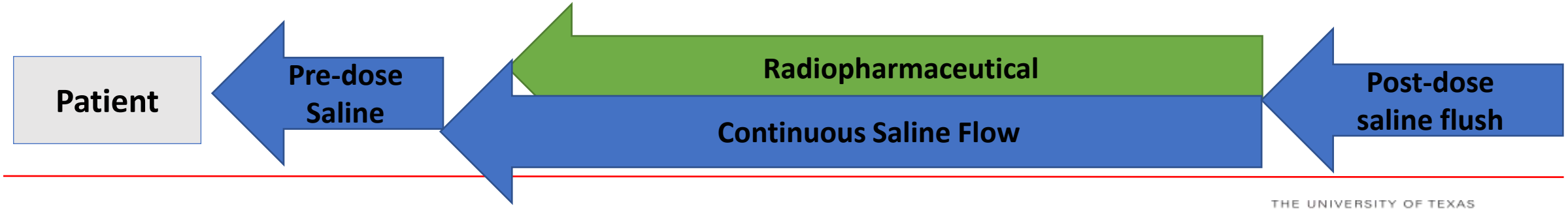
Gravity Method



- Septa integrity is crucial
- Infusion accuracy ___ %

Start of Infusion ?

End of Infusion ?



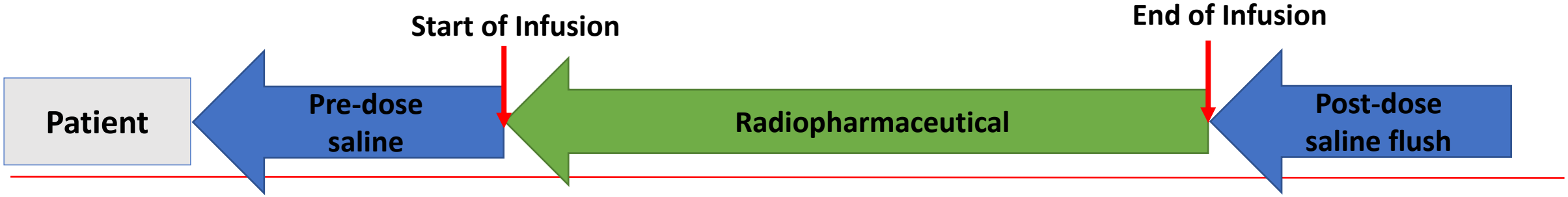
(Davis et al, JNMT 2019), (Ellis et al, JNM 2021)

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Peristaltic Pump

- Safety notifications
- Flow rate accuracy of ± 5%
- Volume-specific administration

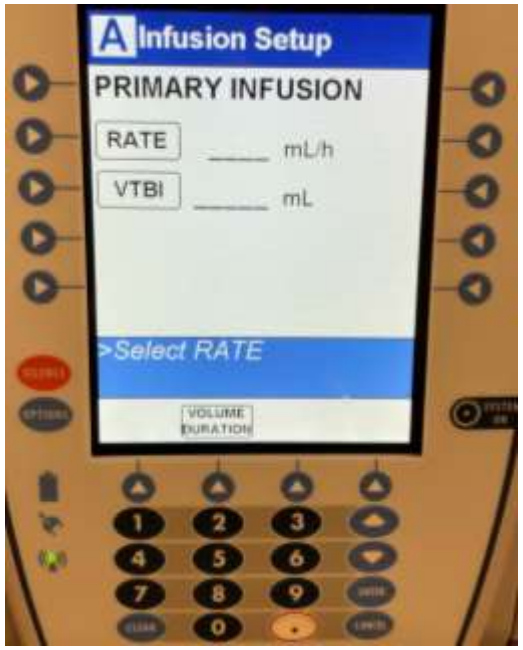
How do we program the pump if each TRP has varying dose volumes?



Peristaltic Pump – Volume Specific Infusion

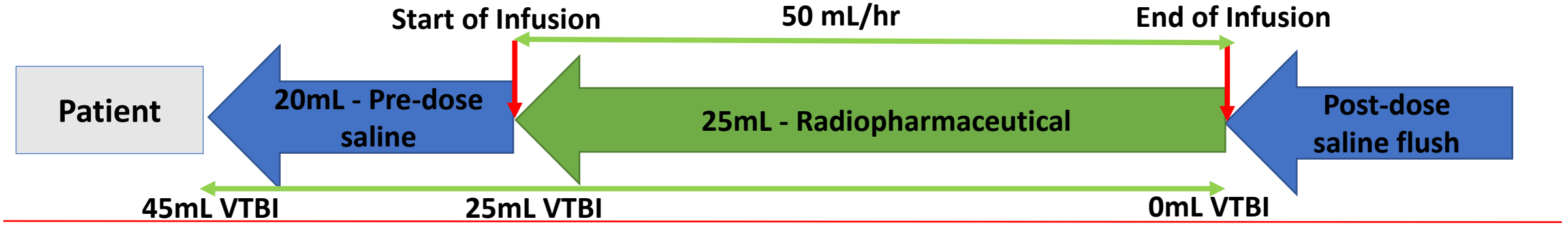
Radiopharmaceutical Volume and Duration	
Radiopharmaceutical Volume (milliliter) mL	25.0
Total volume of extension tubing (milliliter) mL	20.0
Duration of Radiopharmaceutical Infusion (minute) min	30

Rate and VTBI to be entered in the Alaris pump	
Infusion Rate (mL/h)	50
Volume to be Administered VTBI (mL)	45



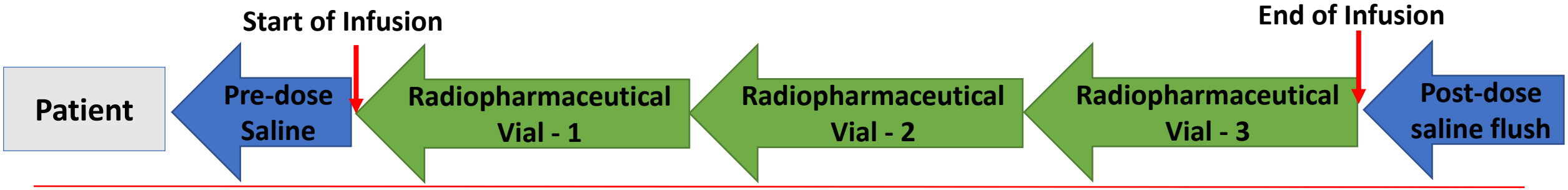
Radiopharmaceutical infusion monitoring by volume	
Peristaltic pump volume indicating start of infusion (mL)	25
Peristaltic pump volume indicating end of infusion (mL)	0

- Method allows for accurate and precise biological sample collections and imaging acquisitions.
- High volume multi-vial infusion?



Peristaltic Pump – Multi-Vial Infusion

- Ideal method for high-volume multi-vial infusion per cycle*
- **Method allows for accurate and precise biological sample and imaging time point collections for multi-vial infusions.**



Biological Sample Collections

- Typically requested in Phase I and Phase II trials.
- Blood and urine samples help identify the blood clearance and rate of excretion of the investigational RPT.
- Bone marrow dosimetry (blood) and bladder dosimetry (urine).
- Bone marrow is radiosensitive and can be dose-limiting for RPT, 2Gy.

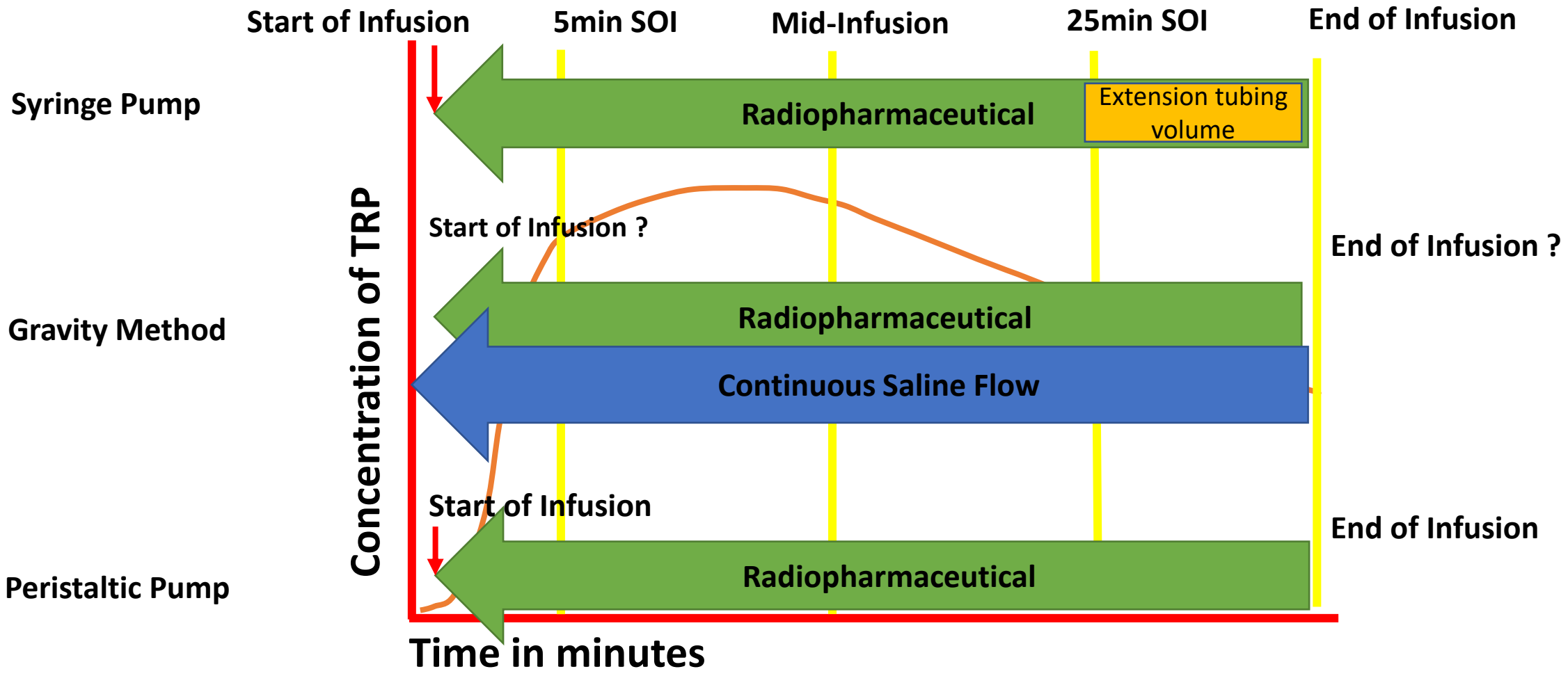
Biological Sample Collections – Blood

- Blood samples **MUST** be collected from the opposite extremity of the RPT infusion.
- Typically draw whole blood samples using collection tubes with and anti-coagulant such as Na-Heparin or EDTA.
- Trying to identify the activity per mL of aliquot (activity concentration) during counting.
- ~5 Liters of blood in adults (approximately) varies per person.
  - Example: 1uCi in 1mL of blood ~ 5 mCi in 5 Liters

Post Infusion - Biological Sample Collections

- Trying to identify the blood concentration of TRP post Infusion.
- At the end of infusion, blood collections may be required at: 0.5hr ± 5min, 1hr ± 10min, 2hr ± 15min, 4hr ± 15min,24hrs ± 2hrs, etc.
- Staff must know the end of TRP infusion to collect blood within the specified variance.
- How do we collect accurate intra-infusion blood collections from start of infusion(SOI) to the end of infusion(EOI)?
- What effect does the infusion method have on intra-infusion sample collections?

Intra-Infusion – Biological Sample Collections

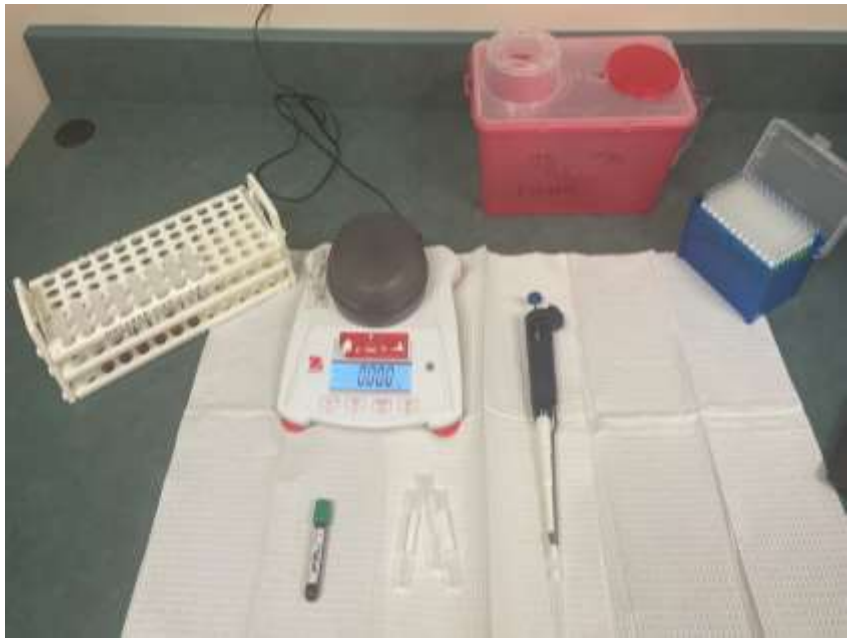


Biological Sample Collections – Urine

- In general, unabsorbed RPT's are renally excreted.
- May have single or multiple collections hours or days post RPT admin.
- It is ideal to use fixed urine containers with marked volume increments.
- Plastic foley bags may need to weighed pre and post urine collections for accurate urine volume estimation.
- Assumption for urine volume
  - 1 milliliter of distilled water has 1 gram of mass. (1 mL = 1 gram)

Processing Biological Samples – Blood

- Use a scale and micropipette to weigh aliquoted samples.
- Assumption: the sample weight is equivocal to volume.
  - 1 mL = 1 gram
- Important: QC equipment
  - scale and micro pipette
- Using the weight of sample is a good method for verifying volume.



Biological Sample - Radioactive Counting

- Recommended to use a multi-channel well counter for multiple samples vs a single channel.
- Ideal for counting microCuries to nanoCuries of activity.
- Can program specific counting protocols by nuclide, window width, counting duration, etc.

Biological Sample - Radioactive Counting

- Need to ensure samples are ~2 uCi or less.
- Provides counts per minute (CPM) per sample.
- Recommended to have a two-person verification of sample counting.

Dosimetry Imaging

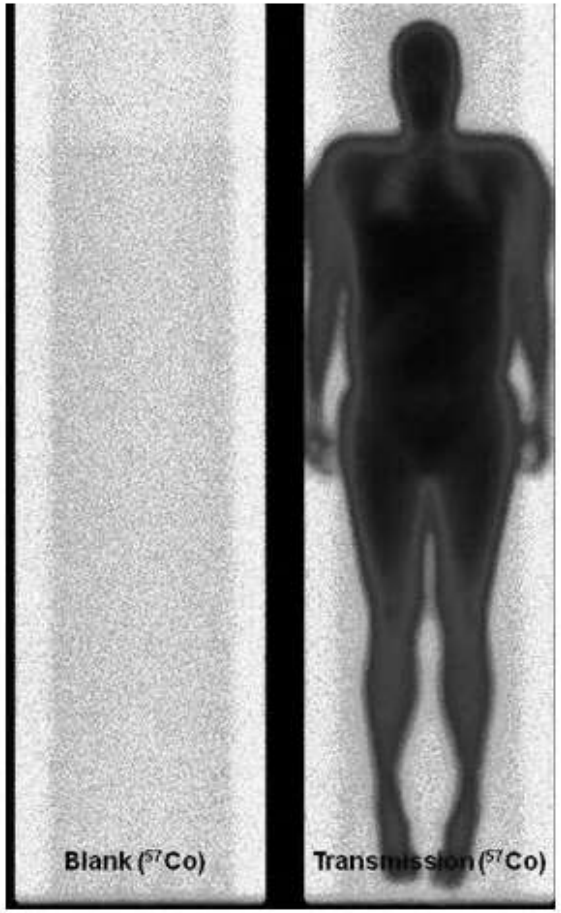
- Multi-time point quantitative imaging helps identify organ and whole-body biodistribution of the RPT.

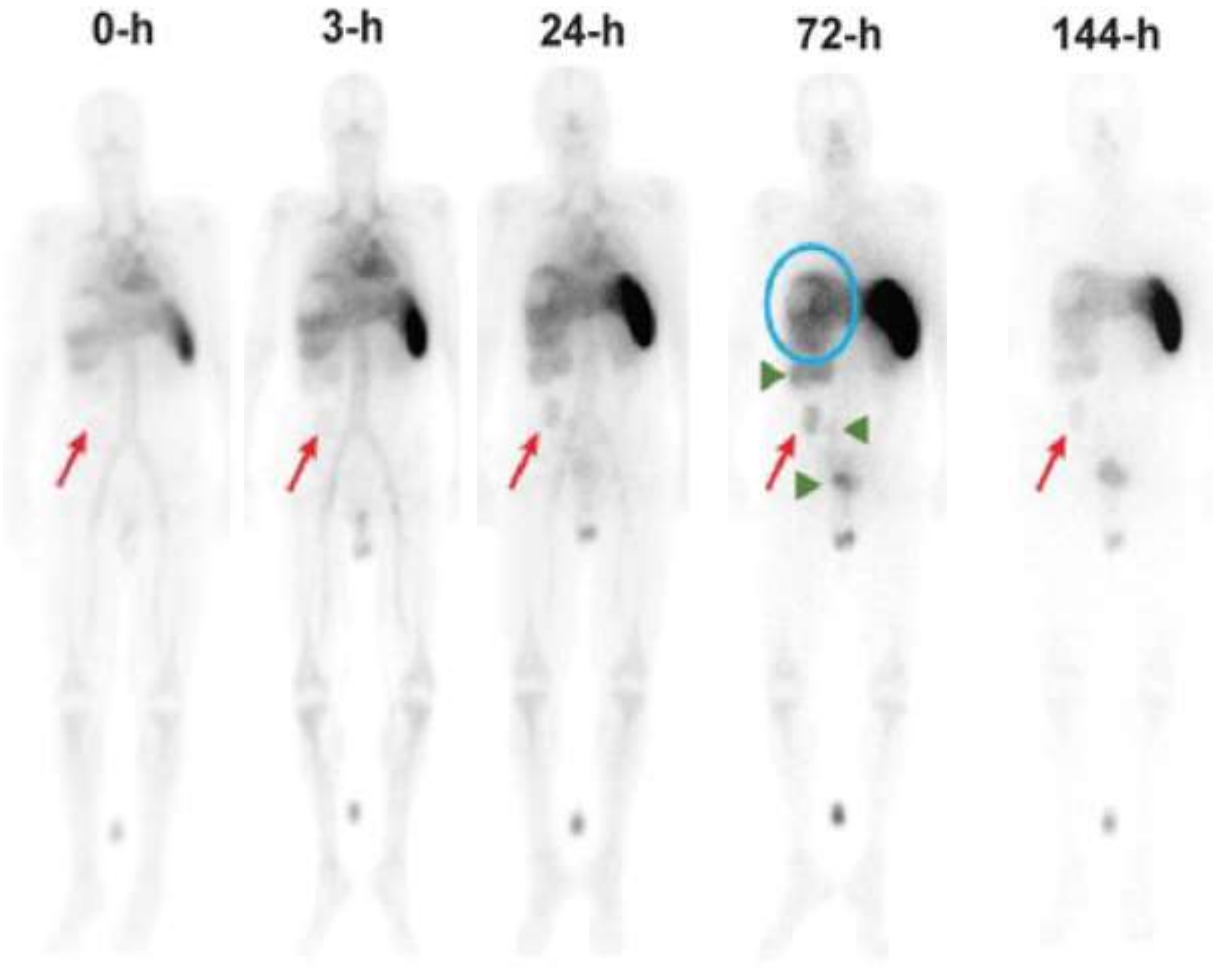
- Dosimetry imaging aids in identifying optimal RPT dosage to achieve a specified absorbed dose either to the dose-limiting normal tissue or to the tumor.

- Dosimetry imaging can be acquired retrospectively or prospectively to the TRP.

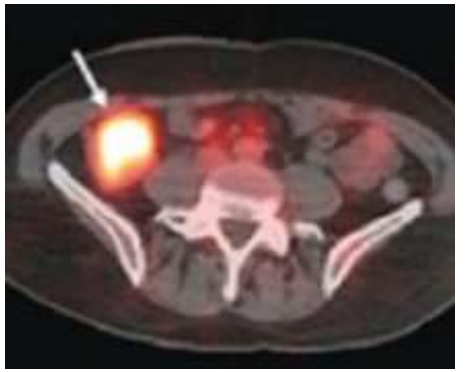
Prospective Dosimetry Imaging – WB Planar

Transmission Scan Example:





- ^{111}In-FF-21101
- 5 mCi ± 10%
- Localizes to P-Cadherin
- Cell Surface Glycoproteins

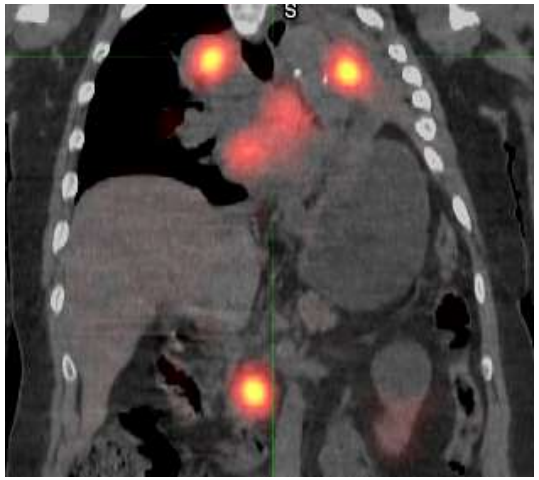


Bailey,D.L, Et Al., EJNM Phys 2015 ; Subbiah Et Al., Clinical Cancer Research 2020

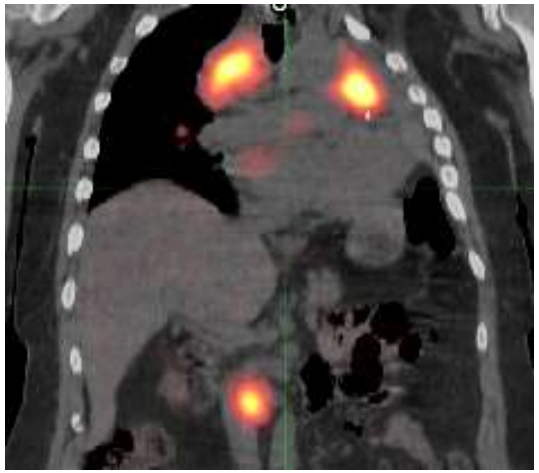
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History®

Retrospective Dosimetry Imaging – SPECT/CT

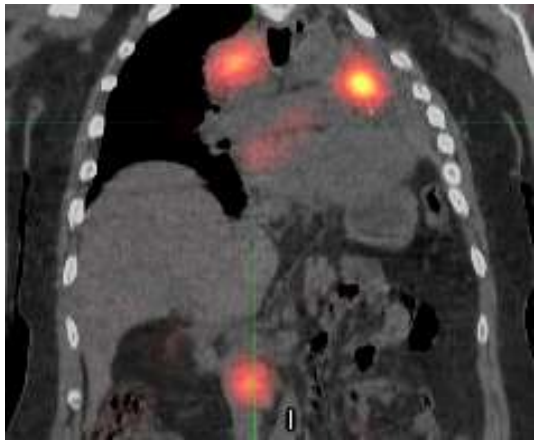
4hrs



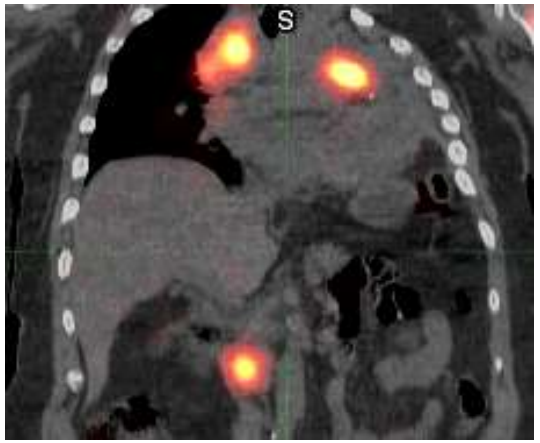
4hr Chest/ABD SPECT/CT



24hr Chest/ABD SPECT/CT



48hr Chest/ABD SPECT/CT



96hr Chest/ABD SPECT/CT

- Complex case off label ^{177}Lu-Dotatate Therapy
- Estimate absorbed organ dose
- Multi-time point SPECT/CTs at: 1hr, 4hrs, 24hrs, 48hrs, and 96hrs
- Optimal SPECT/CT positioning
- Consider using body immobilization devices for consistent positioning

Post Treatment Radiation Safety Precautions

- ADIOS – Internally developed radiation release software based on the NRC guidelines developed by medical physicist Dr. Richard Wendt.
- ADIOS - Instructions are based on specific patient lifestyle release criteria and the radiopharmaceutical treatment administered.
- Technologists enter in all the data, ADIOS calculates and provides specific dates and times when patients can travel, return to work, be around children and pregnant women etc.
- The NMT, Physicist, and Authorized User verify the final ADIOS document.

ADIOS

- Second CODE: **2824**

Department of Nuclear Medicine
The University of Texas M. D. Anderson Cancer Center

Tentative Specific Instructions for Lutathera Test

Patient: Lutathera Test **ID:** 123456
Radionuclide: Lu-177 **Half-life:** 6.6 days **Dosage:** 200 mCi
Date and Time of Administration: Tue, Jul 5, 2022 at 12:00 PM
Measured Exposure Rate: 2.0 mR/hr at 1.0 m on Tue, Jul 5, 2022 at 2:30 PM
Date and Time of Planned Release from Radiation Safety Restrictions: Tue, Jul 5, 2022 at 4:00 PM

These are your personal instructions. They are different from those given to other patients. They use the information that you have given us. Please follow them to protect the safety of others.

- Do not start your travel before Tue, Jul 5, 2022 at 4:00 PM.
- Sleep alone (farther than six feet from anyone else) until Sun, Jul 10, 2022 at 11:56 PM.
- Completely stay away from children and pregnant women until Wed, Jul 6, 2022 at 4:00 PM.
- Then limit time closer than six feet to children and pregnant women until Sat, Jul 9, 2022 at 11:01 PM.
- Stay farther than six feet from others until Thu, Jul 7, 2022 at 5:30 AM.
- Do not go back to work or school before Tue, Jul 5, 2022 at 4:00 PM.

Upon Discharge: After you have been discharged, please leave the premises immediately and return to your accommodations. Please do not stop into the clinics, pick up prescriptions, eat at a restaurant or go shopping after your discharge.

For the next week, please

- Rinse the bathroom sink well after use.
- Flush the toilet three times after each use.
- Sit to urinate (both ladies and gentlemen). This will minimize splashing.

You should carry with you a copy of your specific release instructions for the next few days. The information about your therapy might be helpful in an emergency situation.

Contact Information: If, in the next day or two, you have questions about your instructions, please contact the Nuclear Medicine Department at (832)-817-4898 (telephone, 6 am-6 pm) or (713)404-3704 (pager, 6 pm-6 am) or your home clinic.

Technical Protocol Document

Patient: _____ MRN#_____ PT Study ID#_____

Treatment #: Date: _____-_____-_____

Theranostic protocol title and IRB Number

Patients are scheduled to receive six ^{177}Lu – RPT therapeutic cycles every six weeks (window of -1 to +7 days). Dose amount will depend on cohort patient was enrolled in.

Dose Levels, **Circle dose level patient is consented to:**

- Dose Level (1) 100 mCi ± 10% of ^{177}Lu RPT
- Dose Level (2) 150 mCi ± 10% of ^{177}Lu RPT
- Dose Level (3) 200 mCi ± 10% of ^{177}Lu RPT
- Dose Level (4) 250 mCi ± 10% of ^{177}Lu RPT

Dose Measurement

^{177}Lu - RPT Initial assay: _____ mCi _____(GBq) at ___: ___ Protocol Approved Dose Calibrator S/N 123456

Total volume to be infused: _____mL D.C. Cal factor: 455 x 10

^{177}Lu - RPT residual: _____ mCi _____(GBq) at ___: ___

Approximate residual volume: _____ mL

^{177}Lu - RPT NET admin: _____ mCi _____(GBq) at ___: ___

Administration site: _____ **Lot/Batch Number:** _____

Expiration Date and Time: _____

*Use Investigational injectable radiopharm (IV) for ordering and documenting ^{177}Lu - RPT

^{177}Lu - RPT Start of Infusion: _____

- Sponsor suggested duration of administration of ^{177}Lu - RPT over 30min.
- Dose will be in a volume of 18mL ± 2mL
- Suggested infusion rate: 36mL/hr → VBTI 20mL + (Dose volume) = total volume to be infused
- May need to adjust mL/hr rate based on dose volume.

^{177}Lu - RPT End of Infusion: _____

Post infusion Multi-Bed SPECT/CT Imaging

- Per Protocol Amendment 5, only acquire multi-bed SPECT/CTs.
  - Image Vertex to Mid-thigh with arms down.
- B5 is the primary SPECT/CT camera for this protocol.
- Use Medium Energy Collimators.
- SPECT/CT workflow is stored in the category labeled: ^{177}Lu - RPT.

Multi-Bed Patient SPECT/CTs

- A three bed SPECT/CT takes approx. 74min
  - One bed takes approx. 24min

Gamma Camera Bed Parameter

- Bed height: _____ cm
- Use the same bed height for all patient SPECT/CT(s)

Day (1) post ^{177}Lu - RPT admin: 4hrs ± 2hrs post injection.

- 4hr acquisition Date: _____
  - Image Vertex to mid-thigh with arms down.

4hr ± 2hrs post injection multi-bed SPECT/CT

- SPECT/CT 1: Start: _____ End: _____
- SPECT/CT 2: Start: _____ End: _____
- SPECT/CT 3: Start: _____ End: _____

Were all three SPECT/CT's acquired consecutively? Yes / No

- If No: specify which acquisitions were acquired non-consecutively.
  - _____

Patient Perspective

- It is a privilege to care for patients
- Need adequate time to prepare for patient care
- Collect good-quality data

It is a privilege to care for patients

Take Away Points

- Clinical sites must allocate sufficient time, resources, and staff to conduct theranostic clinical trials.
- For every 1-hour spent with a patient, 2-hours are spent preparing.
- A well-informed Technologist is a crucial member of the clinical trial team and can help bridge knowledge gaps.

Conclusion

- It takes a well-coordinated medical army to conduct theranostic clinical trials.
- Fundamental nuclear medicine practices are at the basis of every theranostic clinical trial.
- Meticulous planning is required for clinical trials to provide quality care for research patients and collect good quality data.

Questions

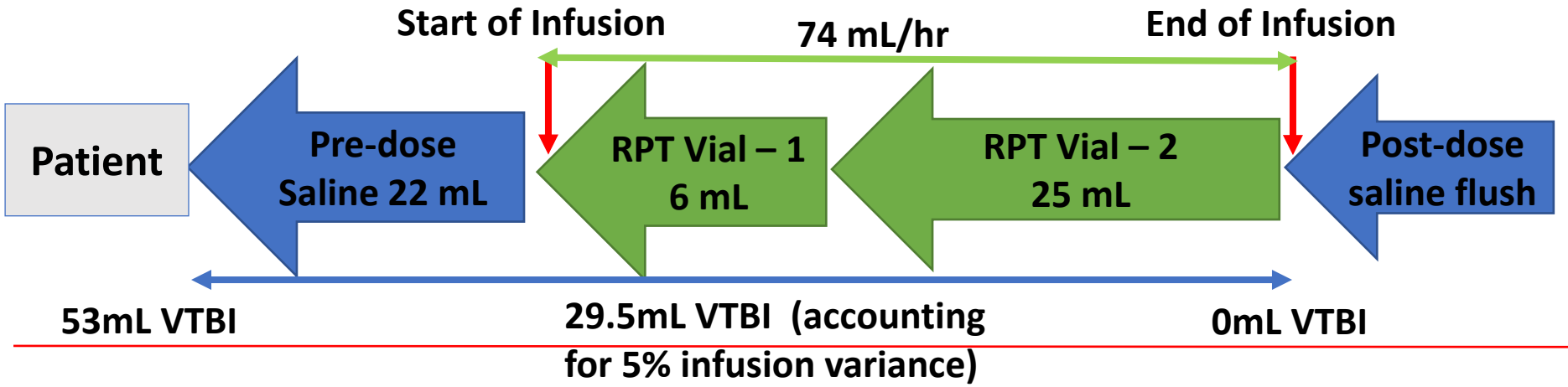
- Jagonzalez1@mdanderson.org

Peristaltic Pump – Two-Vial Volume Specific Infusion

Radiopharmaceutical total volume and total infusion duration		
Vial 1 Volume (milliliter) mL	6	Preference is to infuse smaller volume first
Vial 2 Volume (milliliter) mL	25.0	Larger volume to infuse
Total Radiopharmaceutical Volume (milliliter) mL	31.0	Enter the radiopharm volume to be infused (mL)
Total volume of extension tubing (milliliter) mL	22.0	Enter the volume of the extension tubing (mL)
Duration of Radiopharmaceutical Infusion (minute) min	25	Enter the duration of radiopharm infusion in minutes

Rate and VTBI to be entered in the Alaris pump		
Infusion rate milliliters per hour (mL/hr)	74	Calculated infusion rate to be entered in the Alaris pump (mL/hr)
Volume to be Administered VTBI (milliliters) mL	53	Calculated volume to be entered in the Alaris pump (mL) includes the pre-saline and TRP

Peristaltic pump volume indicating start of infusion (mL)	29.5	Indicates approximate start of infusion based on TRP volume (mL) with a 5% variance
Peristaltic pump volume indicating end of infusion	0	Indicates approximate end of infusion based on TRP volume (mL)



Flow rate accuracy of ± 5% !!!!!!

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History®