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Overview of ACMUI Activities

Hossein Jadvar, M.D., Ph.D.
ACMUI Chair/Nuclear Medicine Physician
April 9, 2024

Today's Agenda

- Hossein Jadvar, M.D., Ph.D., ACMUI Chair
  - Overview of ACMUI activities

- Richard Harvey, DrPH, ACMUI Radiation Safety Officer Representative
  - ACMUI's Review and Analysis of Reported Medical Events from Fiscal Years 2021-2023

Today's Agenda (cont'd)

- Megan Shober, ACMUI Agreement State Representative
  - ACMUI Comments on Revisions to Regulatory Guide 8.39, Release of Patients Administered Radioactive Material

- Josh Mailman, ACMUI Patients' Rights Advocate
  - Patients' Rights Advocate's Perspectives on
    - Regulatory Guide 8.39, Release of Patients Administered Radioactive Material
    - Reporting of Nuclear Medicine Injection Extravasations

Overview of the ACMUI

- ACMUI Role
- Membership
- 2022-2024 Topics
- Current Subcommittees
- Future

Role of the ACMUI

- Advise the U.S. Nuclear Regulatory Commission (NRC) staff on policy & technical issues that arise in the regulation of the medical use of radioactive material in diagnosis & therapy.
- Comment on changes to NRC regulations & guidance.
- Evaluate certain non-routine uses of radioactive material.
- Provide technical assistance in licensing, inspection & enforcement cases.
- Bring key issues to the attention of the Commission for appropriate action.

ACMUI Membership (13 members)

- Nuclear Medicine Physician, Chair (Dr. Hossein Jadvar)
- Nuclear Pharmacist, Vice Chair (Mr. Richard Green)
- Nuclear Cardiologist (Dr. Andrew Einstein)
- 2 Radiation Oncologists (Drs. Michael Folkert & Harvey Wolkov)
- Diagnostic Radiologist (Vacant)
- FDA Representative (Dr. Michael O'Hara)

ACMUI Membership (13 members)

- 2 Medical Physicists: Nuclear Medicine (Ms. Melissa Martin) & Radiation Therapy (Mr. Zoubir Ouhib)
- Patients' Rights Advocate (Mr. Josh Mailman)
- Agreement State Representative (Ms. Megan Shober)
- Healthcare Administrator (Ms. Rebecca Allen)
- Radiation Safety Officer (Dr. Richard Harvey)

ACMUI Consultant

- Interventional Radiologist (Dr. John Angle)

ACMUI Topics December 2022 - April 2024

- Decommissioning financial assurance for sealed and unsealed radioactive materials
- Impact of ABR's termination request and review of NRC's process for recognition of specialty boards
- Medical events
- A review of prescription error reduction methods

ACMUI Topics December 2022 - April 2024 (cont'd)

- Akesis Galaxy RTi Unit licensing guidance
- Eye90 Microsphere Device licensing guidance
- Liberty Vision Y-90 episcleral brachytherapy source licensing guidance

ACMUI Topics in 2023 by Non-NRC Entities

- Overview of ICRP Publication 153, Radiological Protection in Veterinary Practice

Staff Presentations to the ACMUI (2022-2024)

- Medical events
- Limited revisions to the NRC's abnormal occurrence criteria
- Reporting of nuclear medicine injection extravasations
- Overview of NRC requirements and guidance for release of animals administered radioactive material
- Financial Assurance for Disposition of Category 1 and 2 Byproduct Material Radioactive Sealed Sources

Staff Presentations to the ACMUI (2022-2024) (cont'd)

- Recent medical events related to radiopharmaceutical administrations
- ACMUI Reporting Structure
- Medical Team Updates
- INFOSEC, Ethics, and Allegations Training

Current ACMUI Subcommittees

- Eye90 Microspheres
- Akesis Galaxy RTi unit
- Liberty Vision Y-90 brachytherapy source
- Training and Experience for All Modalities Subcommittee
- Extravasations and Medical Event Reporting

Future

- ACMUI will continue to
  - Provide advice and technical assistance
  - Comment on NRC regulations and guidance
  - Evaluate uses of radioactive material
  - Bring key issues to the attention of the Commission

Acronyms

- ABR – American Board of Radiology
- ACMUI - Advisory Committee on Medical Uses of Isotopes
- EMT – Emerging Medical Technologies
- FDA – U.S. Food & Drug Administration
- ICRP – International Commission on Radiological Protection
- INFOSEC – Information Security
- ME – Medical Event
- NRC – U.S. Nuclear Regulatory Commission
- T&E – Training and Experience
- Y-90 – yttrium-90

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ACMUI's Review and Analysis of Reported Medical Events from Fiscal Years 2021-2023

Richard P. Harvey, DrPH

Advisory Committee on the Medical Uses of Isotopes

April 9, 2024

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Subcommittee Members

- Richard Harvey, DrPH (Chair)
- Michael Folkert, M.D.
- Richard Green, B.S.
- Darlene Metter, M.D.
- Zoubir Ouhib, M.S.
- Harvey Wolkov, M.D.

- Consultant: John Angle, M.D.
- NRC Staff Resource: Daniel DiMarco, M.S.

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Subcommittee Charge

- Review Medical Events (MEs) to advise the Advisory Committee on the Medical Use of Isotopes (ACMUI) and United States Nuclear Regulatory Commission (NRC) about emerging trends that may need regulatory attention.

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Background

- The NRC and ACMUI review MEs that occur throughout the country.
- MEs occur when radioactive material use in healthcare results in unexpected radiation dose to patients. (Please refer to 10 CFR 35 Subpart M – Reports and more specifically 10 CFR 35.3045 – Report and Notification of a Medical Event for more information.)
- The Medical Events Subcommittee of the ACMUI reviews the data to analyze the nature of medical events, identify emerging trends and provide recommendations to the ACMUI and NRC.

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Medical Event Review

- FY21 – October 1, 2020 to September 30, 2021
- FY22 – October 1, 2021 to September 30, 2022
- FY23 – October 1, 2022 to September 30, 2023

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Summary

- Two overarching themes remain
  - Human Error
    - Communication/feedback
    - Failure to work in teams
  - Inexperience
    - Rapidly evolving use of radiopharmaceuticals
    - Dissemination of use to smaller institutions with lower frequency of procedures performed

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Specific Issues

- Increasing MEs: new and increasing use of current therapeutic radiopharmaceuticals
- ^{90}Y microsphere procedures remain the most common MEs.
    - ACMUI Action: Added 2 specialty-specific subcommittee members
    - ACMUI recommendation: AU adhere to manufacturer recommendations (i.e. avoid aggregation: use recommended catheter size and needle gauge)

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35.200 Use of Unsealed Byproduct Material for Imaging and Localization

Medical Events Summary

	2017	2018	2019	2020	2021	2022	2023	Total
Cause								
Wrong Drug	0	0	0	0	1	0	1	2
Wrong Dosage	2	0	0	0	1	0	0	3
Wrong Patient	1	0	0	0	2	0	0	3
Extravasation*	1	0	0	0	0	0	0	1
Human Error	0	0	1 (8 patients)	0	0	0	0	1 (8 patients)
Total	4	0	1	0	4	0	1	10

5/5 (100%) possibly preventable by time out in 2021 & 2023 (Wrong Drug, Wrong Dosage & Wrong Patient)

*NRC does not have reporting requirement for extravasations

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35.300 Use of Unsealed Byproduct Material, Written Directive Required

Medical Event Summary

	2017	2018	2019	2020	2021	2022	2023	Total
WD not done or incorrectly	2	1	2	0	0	1	1	7
Error in delivery (# capsules)	1	0	1	0	0	1	0	3
Wrong Dose	0	0	0	0	4	3	8	15
Equipment	0	1	4	0	2	1	0	8
Human Error	0	0	1	2	3	4	0	10
Wrong Patient	1	0	1	0	0	0	0	2
Wrong Drug	0	0	0	0	1	0	2	3
Total	4	2	9	2	10	10	11	48

Time out: 2021-5/10 (50%), 2022-3/10 (30%), 2023-10/11 (91%)
(Wrong Drug, Wrong Dosage & Wrong Patient)

35.400 Manual Brachytherapy

Medical Event Summary

	2017	2018	2019	2020	2021	2022	2023	Total
Applicator issue (e.g. jam, eye plaque dislodged)	0	0	0	2	0	1	1	4
Wrong site implanted (e.g. penile bulb, bladder)	1	1	1	2	2	0	0	7
Activity/prescription error (e.g. air kerma vs mCi, enter wrong activity in planning software)	1	0	1	0	1	0	0	3
Wrong Dose	5	11	3	0	0	0	2	21
New Device	0	1	0	0	0	0	0	1

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35.400 Manual Brachytherapy

Medical Event Summary

	2017	2018	2019	2020	2021	2022	2023	Total
Wrong Source	0	0	0	1	0	0	0	1
Patient Health (?patient intervention)	0	0	0	1	0	0	0	1
Wrong Patient	0	0	0	0	1	0	0	1
Total	7	13	5	6	4	1	3	39
"Time Out" may have prevented	1	0	5	1	2	0	0	9

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35.400 Manual Brachytherapy

Potentially ~23% (9/39) of ME from 2017 to 2023 may have been prevented with the use of a “Time Out” (wrong site, wrong source and wrong patient):

- “Time Out” or checklist for 2021 may have prevented: ¾ (75%)
- No benefit in 2022 or 2023

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35.600 Use of a sealed source in a remote afterloader unit, teletherapy unit, or gamma stereotactic unit

	2017	2018	2019	2020	2021	2022	2023	Total
Wrong position	2	3	4	7	0	1	3	20
Wrong reference length	2	1	4	2	2	2	0	13
Wrong plan	0	2	0	0	0	0	0	4
Wrong dose/source strength	0	1	0	0	0	0	2	1
Machine/applicator malfunction	2	3	1	1	1	2	2	12
Software/hardware failure	2 (9 patients)	0	1	1	0	0	0	4
Treatment planning	0	0	0	2	1	2	0	5
Human Error	0	0	0	0	1	4	1	6
Total	8	10	10	13	5	11	8	65

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35.600 Use of a sealed source in a remote afterloader unit, teletherapy unit, or gamma stereotactic unit

Medical Event Summary

	2017	2018	2019	2020	2021	2022	2023	Total
Location								
Breast	0	1	0	1	0	0	0	2
Gynecological	7	7	8	10	4	2	5	43
Skin/neck	0	1	0	2	1	5	1	10
Bronchus	0	0	0	0	0	0	0	0
Prostate	0	0	0	0	0	0	1	1
Brain	1	1	2	0	0	0	0	4
Unknown	0	0	0	0	0	4	1	5
Total	8	10	10	13	5	11	8	65

GYN tumors most common site of ME

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35.600 Use of a sealed source in a remote afterloader unit, teletherapy unit, or gamma stereotactic unit

MEs that may have been prevented by "timeout" (wrong plan or dose)

- 2017 0/8 events
- 2018 3/10 events
- 2019 0/10 events
- 2020 0/13 events
- 2021 0/5 events
- 2022 0/11 events
- 2023 2/8 events

Total 5/65 (8%)

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35.600 Use of a sealed source in a remote afterloader unit, teletherapy unit, or gamma stereotactic unit

MEs caused by "infrequent user/inattention"

This is difficult to determine based on information in NMED. For this assessment, assumed wrong position is a surrogate for "infrequent" user/inattention – improved training may be beneficial

- 2017 2/8 events
- 2018 3/10 events
- 2019 4/10 events
- 2020 7/13 events
- 2021 0/5 events
- 2022 1/11 events
- 2023 3/8 events

Total 20/65 (31%)

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35.1000 Radioactive Seed Localization

Medical Events Summary

	2018	2019	2020	2021	2022	2023
Total Medical Events	0	1	0	1	0	1
Cause:						
Delayed seed removal (patient intervention)	0	1	0	0	0	1
Lost seed	0	0	0	0	0	0
Wrong implant site	0	0	0	0	0	0
Seed migration	0	0	0	1	0	0

35.1000 Intravenous Cardiac Brachytherapy

Medical Events Summary

	2017	2018	2019	2020	2021	2022	2023	Total
Did not follow proper procedure	0	0	1	0	0	0	0	1
Tortuous vessel anatomy	0	1	1*	0	0	0	0	2
Catheter issue	0	1	0	1	0	0	0	2
Wrong Site	0	0	0	0	0	0	1	1
Total	0	2	2	1	0	0	1	6

*AU felt this is “patient intervention”
No time out issues

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35.1000 Gamma Knife® Perfexion™, Icon™ and Esprit™

Medical Events Summary

	2017	2018	2019	2020	2021	2022	2023	Total
Total Medical Events	0	1	2	2	0	2	1	8
Cause:								
Back-up battery power source failure	0	1	0	0	0	0	0	1
Patient set-up error	0	0	0	1	0	0	0	1
Patient movement	0	0	2	0	0	0	0	2
Wrong site (treatment plan)	0	0	0	0	0	0	0	0
Wrong site (human error-shifting of co-registration images)	0	0	0	1	0	1	0	2
Patient motion management system failure	0	0	0	0	0	1	0	1
Device Malfunction	0	0	0	0	0	0	1	1

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35.1000 ^{90}Y Theraspheres

Medical Events Summary

	2017	2018	2019	2020	2021	2022	2023	Total
Total Medical Events	15	14	15	15	23	23	22	127
Cause:								
> 20% residual activity remaining in delivery device/leakage	7	11	9	12	10	2	11	62
Delivery device set-up error	2	2	1	1	1	0	2	9
Wrong dose (treatment plan calculation error)	4	0	1	0	0	3	1	9
Wrong site (catheter placement error & size)	2	0	0	2	1	7	3	15
Wrong dose vial selected*	0	1	4	0	1	1	1	8
Wrong dose (calibration error)*	0	0	0	0	3	1	0	4
Aggregation of microspheres	0	0	0	0	7	9	4	20

For 2021 - 2023: Time out 4/23 (17%), 2/23 (9%), 1/22 (5%) – Wrong Dose*
Infrequent/inattention 10/23 (43%), 2/23 (9%), 11/22 (50%) – > 20% Residual

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35.1000 ^{90}Y SirSpheres

Medical Events Summary

	2017	2018	2019	2020	2021	2022	2023	Total
Total Medical Events	8	7	11	8	18	9	9	70
Cause:								
> 20% residual activity remaining in delivery device/leakage	7	2	8	8	2	1	6	34
Wrong dose (treatment plan calculation error)	0	2	0	0	2	1	0	5
Wrong site (catheter placement error & defective catheter)	1	2	2	0	4	0	1	10
Wrong site (WD error)	0	1	1	0	1	1	2	6
Aggregation of microspheres	0	0	0	0	9	6	0	15

2021 - 2023: Time out: 1/18(6%), 1/9(11%), 2/9(22%) - Wrong Site (WD)
Infrequent/inattention: 2/18(11%), 1/9(11%), 6/9(67%) - >20% Residual

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Actions to Prevent 35.1000 ^{90}Y Microsphere Medical Events

- Ensure familiarity with the mechanics of ^{90}Y microsphere delivery device and setup procedures
- Confirm all data and calculations in treatment plan
- Perform “Time Out” to assure all elements of treatment are in accordance with Written Directive

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Possible Elements of a "Time Out"

- Identity of patient via two identifiers (e.g. name and DOB)
- Procedure to be performed
- Radiopharmaceutical
- Activity
- Dosage –second check of dosage calculation and that the WD and dosage to be delivered are identical
- Others as applicable
  - units of activity (LDR prostate)
  - anatomic location
  - patient name on treatment plan
  - treatment plan independent second check has been performed
  - reference length (HDR)
  - Implant site location (RSL)

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Acronyms

- 10 CFR – Title 10 of the *Code of Federal Regulations*
- AUs – authorized users
- FY – fiscal year
- GYN – gynecological
- HDR – high dose-rate
- LDR – low dose rate
- mCi – milliCurie
- ME – medical event
- RSL – radioactive seed localization
- WD – written directive
- Y – Yttrium

ACMUI COMMENTS ON REVISIONS TO REGULATORY GUIDE 8.39

Commission Briefing | April 9, 2024 | Megan Shober

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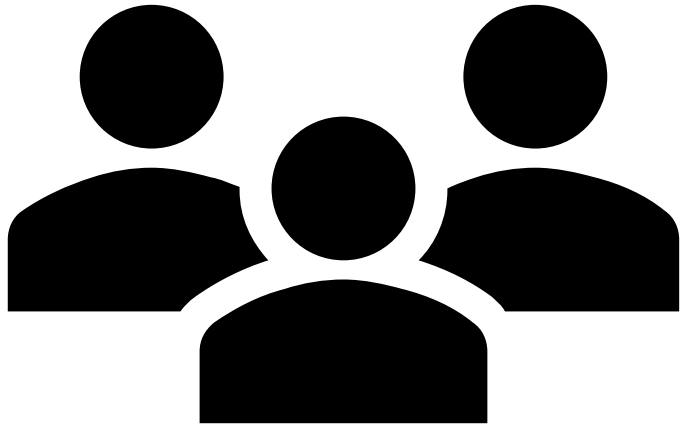
SUBCOMMITTEE MEMBERS

Hossein Jadvar
Josh Mailman
Melissa Martin
Megan Shober



NRC staff resource: Katie Tapp

PREVIOUS COMMISSION ENGAGEMENT

2011: Identify gaps in release data

2012: Revisit release calculations

2014: Revise Regulatory Guide 8.39

2018: Received staff evaluation of patient release program

TIMELINE

Regulatory Guide 8.39 “Release of Patients Administered Radioactive Material”

Revision 0
Issued 1997

Revision 1
Draft 2019
Draft Final 2019
Issued 2020

Revision 2
Draft 2021

REVISION 2 SCOPE

- ✓ Overhauled methodology to calculate dose to bystanders
- ✓ Updated release thresholds based on administered activity and dose rate
- ✓ Updated breastfeeding interruption times

TIMELINE-REVISION 2

8/11/2021
To ACMUI
for review

12/15/2021
ACMUI
approved
comments

7/14/2023
NRC response
to ACMUI
comments

4/21/2023
Public comment

REVISION 2 COMMENTS

Focused on external dose contribution

Significantly reduced threshold for patient-specific release calculations

No example for most common release scenario (i.e., I-131 patient going home)

REVISION 2 ISSUES

Overly complex model requires unrealistic knowledge of patient behavior.

ACMUI did not support:

- “Release of Patient after a Hold Time”
- “Material Separated from Patient”

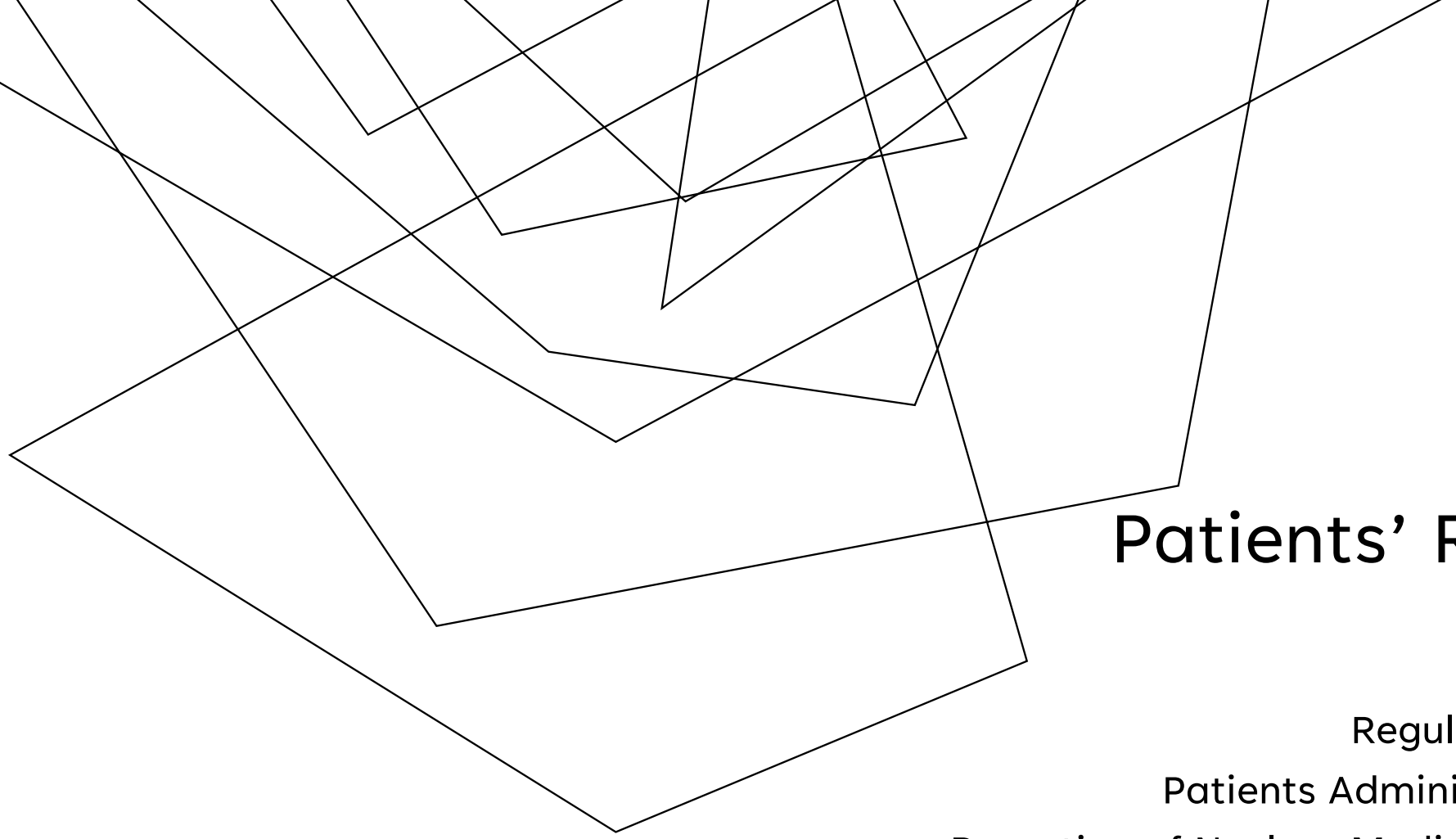
NEXT STEPS

When requested by NRC staff, review draft final Revision 2 and provide recommendations.

ABBREVIATIONS

ACMUI: Advisory Committee on the Medical Uses of Isotopes

I-131: iodine-131



Patients' Rights Advocate Perspectives on

Regulatory Guide 8.39, Release of Patients Administered Radioactive Material

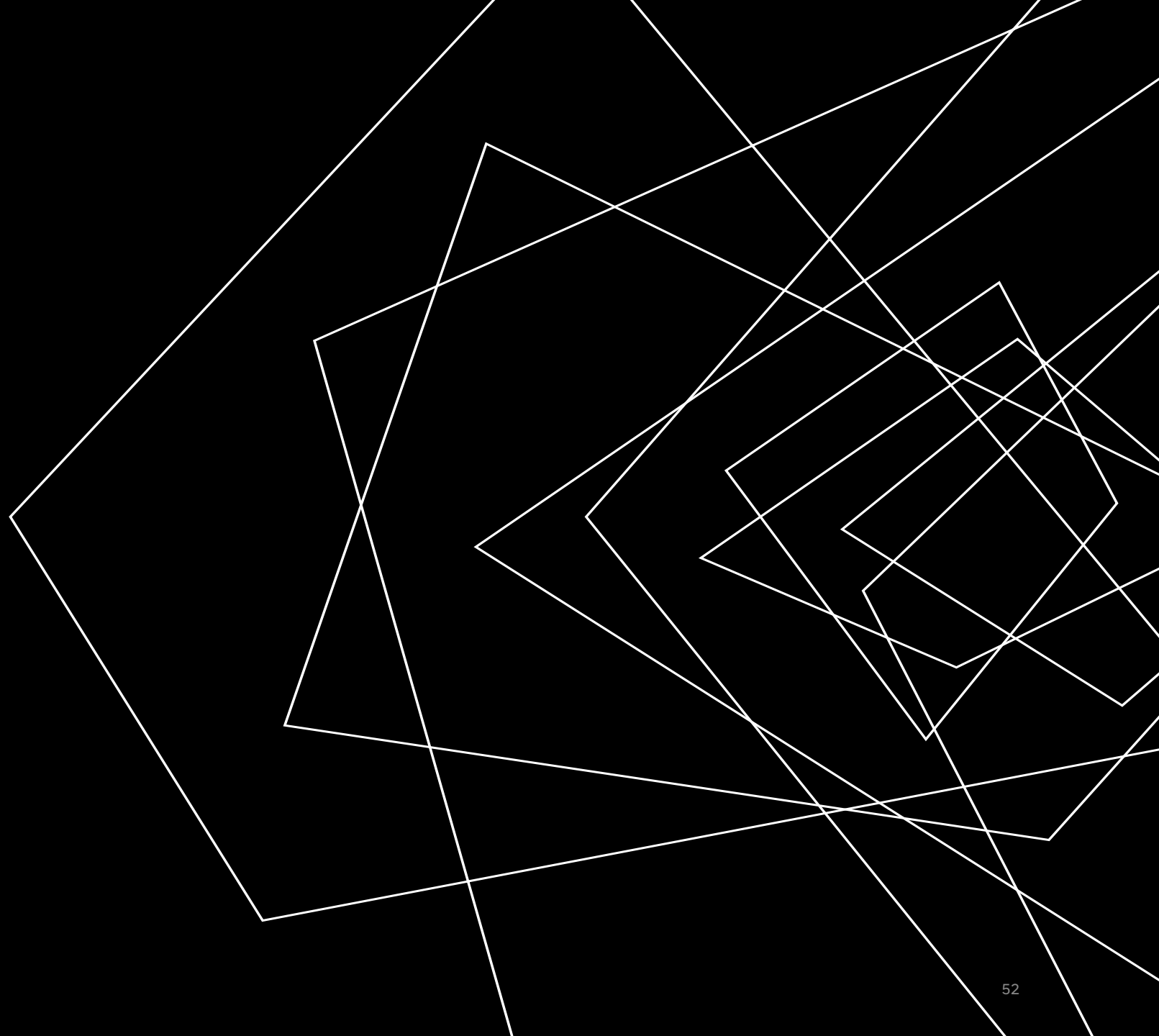
Reporting of Nuclear Medicine Injection Extravasations

Josh Mailman

AGENDA

Extravasations

Reg Guide 8.39



EXTRAVASATIONS

WHAT HAS CHANGED SINCE OUR LAST PUBLIC MEETING IN FALL 2023

- There has been no update since our last meeting
- Current recommendation has patients being part of the reporting process
  - In general patients don’t know what an extravasation means
- Education will need to be done
  - How often does this happen and how does this impact safety and efficacy
  - Can we use other data to help us determine this

ARE PATIENTS DISCUSSING THIS

- **Clearly there are some patient organizations that are.**
- **In the NET Community which has been using Dota Imaging since 2017 and Dota Therapy – this topic has rarely if ever been discussed without me initiating conversation on the topic. I have talked to 100s if not 1,000s of NET patients and this issue is rarely if ever raised.**
- **Top topics**
  - Will / how does this imaging work?
  - How long do I need to be off long-acting therapy?
  - How do I deal with some of the side effects that are presented on the label (extravasations and injection site issue did not make the label)?
  - How do I travel safely home?
  - What precaution do I take around loved ones (partners, children and animals)?

IS THERE OTHER DATA THAT CAN GUIDE OUR GUIDANCE

- **We have seen data that significant Extravasations can occur in 1 out of 30 or 1 out of 300.000.**
  - If it was 1 out of 30 and had a patient impact, I would assume we should have seen it in FDA Phase 3 reporting for NETTER-1, NETTER-2, or Vision Trials.
  - If it impacted the efficacy of treatment, the manufacturer would have an incentive to require this during the trial, as it would improve efficacy and potentially the guideline placement.
  - Many centers are performing post-therapy SPECT scans. Some at 3 to 4 hours post treatment and others at 24 hours. We may be able to capture data from those centers that can help us better understand the real-world impact of this.

REGULATORY GUIDE 8.39

RELEASE OF PATIENTS ADMINISTERED RADIOACTIVE MATERIAL

WHAT HAS CHANGED SINCE OUR LAST PUBLIC MEETING IN FALL 2023

- There has been no update since our last meeting
- ACUMI Committee is awaiting staff update for new rounds of comments
- In general, I have not been able to engage the patient community to get feedback.

ARE PATIENTS DISCUSSING THIS

- **For the most part, patients and referring oncologists have very little any insight into Reg 8.39, yet many of their conversations revolve around the topic**
- **Top topic For NET Patients as pertains to Patient Release Criteria**
  - How do I travel safely home?
  - What precautions do I take around loved ones (partners, children, and animals)?
- **Why does one center's instructions differ from another**
- **Do the "examples" take into account different ligands, chelators, and isotopes?**
  - Is a PSMA Alpha patient sweat radioactive?

THANK YOU

Josh Mailman

Josh@norcalcarcinet.org