MEETING AGENDA
ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES
March 30, 2020
Teleconference/WebEx

NOTE: Sessions of the meeting may be closed pursuant to 5 U.S.C. 552(b) to discuss organizational and personnel matters that relate solely to internal personnel rules and practices of the ACMUI; information the release of which would constitute a clearly unwarranted invasion of personal privacy; information the premature disclosure of which would be likely to significantly frustrate implementation of a proposed agency action; and disclosure of information which would risk circumvention of an agency regulation or statute.

MONDAY, MARCH 30, 2020
OPEN SESSION

	1.	**Opening Remarks** Mr. Einberg will formally open the meeting and Mr. Layton will provide opening remarks.	**C. Einberg, NRC** **M. Layton, NRC**
9:30 – 10:45	**2.**	**Old Business** Ms. Jamerson will review past ACMUI recommendations and provide NRC responses.	**K. Jamerson, NRC**
	3.	**Open Forum** The ACMUI will identify medical topics of interest for further discussion.	**ACMUI**
	4.	**Trends in Radiopharmaceuticals** Dr. Jadvar will provide a presentation on the status of emerging radiopharmaceuticals.	**H. Jadvar, ACMUI**
10:45 – 11:00		**BREAK**	
11:00 – 12:15	**5.**	**Patient Intervention Subcommittee Report** Mr. Sheetz will discuss the subcommittee's recommendations regarding the definition of patient intervention and other actions exclusive of medical events.	**M. Sheetz, ACMUI**
	6.	**NMED Overview** Mr. Sun will provide an overview of the NRC's Nuclear Material Events Database.	**R. Sun, NRC**
12:15 – 1:15		**LUNCH**	
1:15 – 2:30	**7.**	**ACMUI Reporting Structure** Members will discuss the reporting structure of the Committee and provide feedback to the NRC.	**K. Jamerson, NRC**
	8.	**ACMUI Bylaws Subcommittee Report** Dr. Wolkov will discuss the subcommittee's recommendations for changes to the bylaws, with focus on term limits for the ACMUI Chair and Vice Chair.	**H. Wolkov, ACMUI**
2:30 – 2:45		**BREAK**	
	9.	**Medical Related Events** Dr. Howe will provide an update on recent medical events.	**DB. Howe, NRC**

2:45 – 5:00	**10. Interventional Radiologist Subcommittee Report** Ms. Shober will discuss the subcommittee's recommendations on the need for an Interventional Radiologist on the ACMUI.	**M. Shober, ACMUI**
	11. Open Forum The ACMUI will discuss medical topics of interest previously identified.	**ACMUI**
	12. Administrative Closing Ms. Jamerson will provide a meeting summary and propose dates for the fall 2020 meeting.	**K. Jamerson, NRC**
5:00	**ADJOURN**	

	ITEM	DATE	STATUS		Target Completion Date for NRC
20	The ACMUI endorsed the Medical Event Reporting and Impact on Medical Licensee Patient Safety Culture Draft Report, as amended to support the concept of the pilot program with the total number of sites and duration to be determined at a later date and to include the Patient Intervention Subcommittee recommendations as an addendum .	9/11/2017	*Accepted*	*Closed**	12/02/2019
	*Action closed via 12/02/2019 NRC Response Memorandum (ADAMS Accession No. ML19232A141) - pending formal closure by ACMUI at Spring 2020 meeting.				

	ITEM	DATE	STATUS		Target Completion Date for NRC
1	The ACMUI recommended that there be no breast feeding cessation for ^{11}C, ^{13}N, ^{15}O, and ^{82}Rb; a 12-hours cessation for ^{18}F-labeled and 68Ga-labeled; a 24-hours cessation for ^{99m}Tc-labeled; 7-days cessation for ^{123}I-NaI and ^{111}In-leukocytes; 14 days cessation for ^{201}-Tl-chloride; 28 days cessation for ^{67}Ga and ^{89}Zr; 35 days for ^{177}Lu, diagnostic; and total stop of breastfeeding for ^{131}I-NaI, ^{177}Lu, therapeutic, ^{223}Ra and all alpha emitters.	2/15/2018	*Accepted*	Closed*	Apr. 2020
20	The Committee recommended for the NRC to draft an Information Notice on the best practices that could help prevent medical events.	9/21/2018	*Accepted*	Closed**	12/02/2019
	*Action complete via 8/23/2019 NRC Response Memorandum (ADAMS Accession No. ML19232A141)				
	**Action complete via 12/02/2019 NRC Response Memorandum (ADAMS Accession No. ML19325E235) - pending formal closure by the ACMUI at the Spring 2020 meeting.				

	ITEM	DATE	STATUS		Target Completion Date for NRC Action
1	The ACMUI recommended adding language into the draft *Training and Experience Requirements for All Modalities Subcommittee report* regarding the Committee's desire to work with the NRC staff to develop a curriculum for limited-scope authorized user pathway.	2/26/2019	*Accepted*	Open***	02/27/2020
2	The ACMUI endorsed the *Training and Experience Requirements for All Modalities Subcommittee Report,* and the recommendations included therein.	2/26/2019	*Accepted*	Closed***	02/27/2020
3	The ACMUI endorsed the Yttrium-90 Microspheres Brachytherapy Licensing Guidance, Rev. 10 Subcommittee Report, and the recommendations therein, with the caveat that the term "drug" be changed to "device."	4/3/2019	*Accepted*	Closed	12/16/2019
4	Dr. Palestro formed a subcommittee to re-evaluate the 1980 infiltration decision and report to the Committee at the fall 2019 meeting with any recommendations. Subcommittee members include: Dr. Vasken Dilsizian, Mr. Richard Green, Ms. Melissa Martin (Chair), Mr. Michael Sheetz, Ms. Megan Shober, and Ms. Laura Weil. The NRC staff resource is Maryann Ayoade.	4/3/2019	*Accepted*	Closed	09/10/2019
5	The ACMUI endorsed the Germanium-68/Gallium-68 Generator Licensing Guidance, Rev. 1 Subcommittee Report and the recommendations therein.	4/3/2019	*Accepted*	Closed	08/22/2019

6	The ACMUI endorsed the ACMUI Bylaws Subcommittee Report, with the following amendments: 1) amend the subcommittee's recommendation regarding the Chair's role on subcommittees in Section 1.3.6 to remove the phrase in the "in these instances"; 2) add language in Section 1.3.6 regarding the ACMUI Chairman serving on a subcommittee at the subcommittee's discretion; 3) amend the subcommittee's recommendation regarding explicit language defining Conflict of Interest in Section 4.1 to instead reference the appropriate OGE reference	4/4/2019	*Accepted*	Closed	07/10/2019
7	The ACMUI recommended that the NRC staff request a presentation from NNSA to review their plans for isotope utilization in the United States. The presentation will be given at the Fall 2019 ACMUI Meeting .	4/4/2019	*Accepted*	Closed	09/11/2019
8	The NRC staff will amend its Opening Remarks such that a statement regarding Conflict of Interest willl be included at every ACMUI Meeting.	4/4/2019	*Accepted*	Closed	06/10/2019
9	The ACMUI recommended that the NRC add a column to the Recommendation and Action Charts to include the date anticipated completion date for NRC staff action.	4/4/2019	*Accepted*	Closed	06/10/2019
10	Dr. Palestro formed a subcommittee to improve the ACMUI's institutional memory. Subcommittee members include: Dr. Ronald Ennis, Dr. Michael O'Hara, Dr. A. Robert Schleipman (chair), Ms. Megan Shober, and Ms. Laura Weil. The NRC staff resource is Ms. Kellee Jamerson.	4/4/2019	*Accepted*	Closed	09/10/2019
11	The ACMUI tentatively scheduled its fall 2019 Meeting for September 11-12, 2019. The alternate date is September 10-11, 2019.	4/4/2019	*Accepted*	Closed	09/10/2019

12	The Committee approved the proposed amendments to the ACMUI Bylaws, with specific changes to Sections 1.3.6 and 4.1, regarding the ACMUI Chairman's involvement in subcommittees and conflicts of interest, respectively.	6/10/2019	*Accepted*	Closed	09/10/2019
13	The ACMUI endorsed the Regulatory Guide 8.39, "Release of Patients Administered Radioactive Material" Subcommittee Report and the recommendations provided therein.	6/10/2019	*Accepted*	Closed	09/10/2019
14	The Committee recommended that the NRC's medical event Abnormal Occurrence criteria need to be reviewed and revised.	7/24/2019	*Accepted*	Closed	09/10/2019
15	Dr. Palestro amended the membership of the Training and Experience Requirements Subcommittee. Subcommittee membership now includes Dr. Schleipman as Chair and it is at the discretion of the subcommittee to allow Dr. Metter to continue to serve on the subcommittee.	9/10/2019	*Accepted*	Open*	12/02/2019
16	The ACMUI endorsed the Medical Events Subcommittee Report as presented.	9/10/2019	*Accepted*	Open*	12/02/2019
17	The ACMUI endorsed the Appropriateness of Medical Event Reporting Subcommittee report and the recommendations provided therein.	9/10/2019	*Accepted*	Open	Apr. 2020

18	The ACMUI endorsed the Evaluation of Extravasations Subcommittee Report, as amended, to note that under future revisions to Part 35 rulemakings, extravasations be captured as a type of passive patient intervention in the definition of patient intervention.	9/10/2019	*Accepted*	Open	Fall 2020
19	The ACMUI endorsed the Xcision GammaPod Licensing Guidance Subcommittee Report, as amended, to include the rationale that (1) the written directive should include dose and frequency and (2) replacing the chemical/physical form line to describe the sealed source and not the device.	9/10/2019	*Accepted*	Open**	02/26/2020
20	The ACMUI endorsed the Institutional Memory Subcommittee Report, as amended, to include the recommendation that a complete list of ACMUI members be updated and added to the webpage. The Subcommittee membership was amended to add Dr. Wolkov.	9/11/2019	*Accepted*	Open	Apr. 2020
21	Dr. Palestro formed a subcommittee to evaluate the definition of patient intervention and other actions and circumstances that are exclusive of medical events. Subcommittee membership includes: Dr. Dilsizian, Dr. Ennis, Mr. Sheetz (chair), and Mr. Bloom (pending verification of clearance). NRC staff resource is Ms. Maryann Ayoade. Subcommittee is expected to present a report at the spring 2020 meeting.	9/11/2019	*Accepted*	Open*	12/02/2019
22	Dr. Palestro charged the current Bylaws Subcommittee to determine (1) Should there be term limits for the ACMUI Chair & Vice Chair? If so, how long? and (2) Should the ACMUI Vice Chair automatically become the ACMUI Chair? The Subcommittee membership was amended to remove Dr. Schleipman and add Dr. Wolkov (chair). NRC staff resource will now be Ms. Kellee Jamerson. Subcommittee is expected to present a report at the spring 2020 meeting.	9/11/2019	*Accepted*	Open*	12/02/2019

23	Dr. Palestro formed a subcommittee to investigate the need for an Interventional Radiologist (IR) on the ACMUI, including whether an IR should be a non-voting consultant or full Committee member. Subcommittee membership includes Dr. Dilsizian, Dr. Ennis, Dr. Jadvar (pending security clearance), and Ms. Shober (chair). It is at the discretion of the subcommittee to allow Dr. Metter to serve on the subcommittee. The NRC staff resource is Dr. Katie Tapp. Subcommittee is expected to present an interim report at the spring 2020 meeting.	9/11/2019	*Accepted*	Open*	12/02/2019
24	The ACMUI tentatively scheduled its spring 2020 meeting for March 23-24, 2020. The alternate date is March 30-31, 2020.	9/11/2019	*Accepted*	Open*	12/02/2019
25	The ACMUI endorsed the Training and Experience Requirements Subcommittee Report and the recommendations provided therein.	10/17/2019	*Accepted*	Open***	02/27/2020
	*Action completed via 12/02/2019 NRC Response Memorandum (ADAMS Accession No. ML19325E235) - pending formal closure by the ACMUI at the Spring 2020 meeting.				
	**Action completed via 2/26/2020 NRC Response Memorandum (ADAMS Accession No. ML20043F492) - pending formal closure by the ACMUI at the Spring 2020 meeting.				
	***Action completed via 2/27/2020 NRC Response Memorandum (ADAMS Accession No. ML20058F039) - pending formal closure by the ACMUI at the Spring 2020 meeting.				

	ITEM	DATE	STATUS		Target Completion Date for NRC Action
1	The ACMUI endorsed the Regulatory Guide (RG) 8.39, "Release of Patients Administered Radioactive Material" Subcommittee report and the recommendations provided therein regarding the draft final RG 8.39, Revision 1, Phase 1.	3/11/2020	*Pending*	Open	Apr. 2020

OPEN FORUM

NO MEETING HANDOUT

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Protecting People and the Environment

Trends in Radiopharmaceuticals

Hossein Jadvar, MD, PhD, MPH, MBA

Advisory Committee on the Medical Uses of Isotopes

March 30, 2020

Trends in Radiopharmaceuticals
Outline

- Recent approvals
- Neuropsychiatric
- Cardiac
- Oncologic & Theranostics
- Summary

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Trends in Radiopharmaceuticals

Recent Approvals

YEAR	Neuropsychiatric	Oncologic
2012	^{18}F-florbetapir (*Amyvid*^{R})	^{11}C-choline
2013	^{18}F-futemetamol (*Vizamyl*^{R})	^{223}Ra dichloride (*Xofigo*^{R})
2014	^{18}F-florbetaben (*NeuraCeq*^{R})	
2016		^{18}F-fluciclovine (*Axumin*^{R}) ^{68}Ga-DOTATATE (*Netspot*^{R})
2018		^{177}Lu-DOTATATE (*Lutathera*^{R}) ^{131}I-Iobenguane (*Azedra*^{R})
2019	^{18}F-fluorodopa	^{68}Ga-DOTATOC

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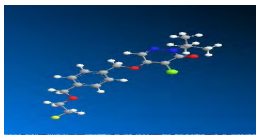
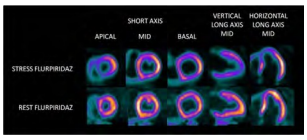
Trends in Radiopharmaceuticals

Cardiovascular



^{18}F-Flurpiridaz

Mitochondrial complex 1 (MC-1)



- 1st Phase 3 clinical trial (May 2015; Lantheus Medical Imaging)
  - 795 patients with known or suspected CAD
  - Compared with SPECT MPI and Coronary Angiography
  - > sensitivity than SPECT MPI (females, obese)
  - < radiation exposure than SPECT MPI by ~50%
  - Did not meet non-inferiority threshold for specificity in comparison to SPECT MPI
- 2nd Phase 3 international multicenter clinical trial (AURORA, 650 pts; ongoing since June 8, 2018; last pt. f/u anticipated August 2020)
  - Compared to Coronary Angiography

Berman DS et al. JACC 2013; Maddahi J, J Nucl Cardiol 2012; Yu M et al. Semin Nucl Med 2011

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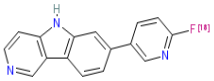
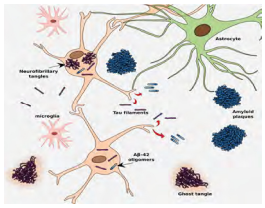
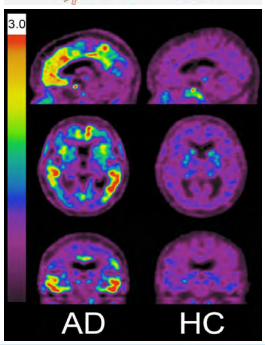
Trends in Radiopharmaceuticals



Neuropsychiatric
^{18}F-Flortaucipir



- Intracellular accumulation of hyperphosphorylated tau protein in neurons (a microtubule-associated protein)
- Associated with *Taupathies* including AD
- Binds to paired helical filaments (PHF) tau protein deposits
- Retention in medial temporal cortex in normal aging and very early AD
- Amount & location of tau may have implications for both spread of tau and cognitive deterioration
- Off-target binding in mid-brain, meninges, choroid plexus, striatum
- May be useful in assessing novel disease modifying anti-tau immunotherapies
- Owned by Eli Lilly and originally developed by Siemens



Saint-Aubert, Molecular Neurodegeneration 2017; Okamura, Clin Transl Imaging 2018; Pontecorvo, Brain 2019

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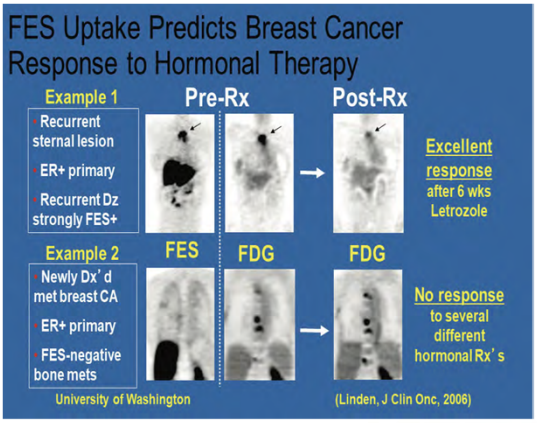
Trends in Radiopharmaceuticals

Oncologic & Theranostic
^{18}F-fluoroestradiol (EstroTep^{R})

- Estrogen Receptor
- Approved in France
- Zionexa filed NDA with FDA in May 2019
- Characterization of ER status and heterogeneity in metastatic breast cancer



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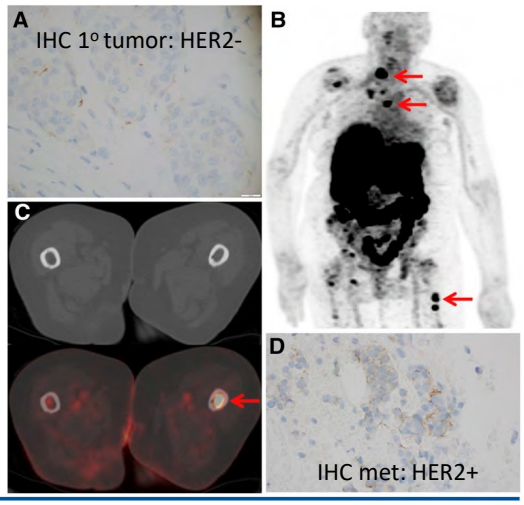
Trends in Radiopharmaceuticals: Oncologic & Theranostic
^{89}Zr-trastuzumab

- human epidermal growth factor receptor 2 (HER2)–targeted PET tracer
- HER2-positive metastases in patients with HER2-negative primary breast cancer
- HER2-targeted imaging can identify additional candidates for HER2-targeted therapy



Ulaner GA, JNM 2016

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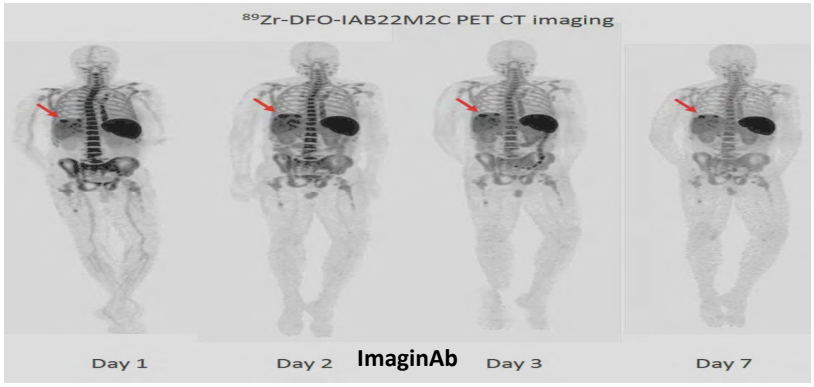
Trends in Radiopharmaceuticals: Oncologic & Theranostic
^{89}Zr-IAB22M2C anti-CD8 Minibody



ClinicalTrials.gov Identifier NCT03802123: Phase II, Open Label, Multi-Dose Study of ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) for PET/CT in Patients with Metastatic Solid Tumors; N=40 (recruiting); 3 mCi (±20%) IV before & 4-5 wks after Rx; RECIST 1.1/iRECIST

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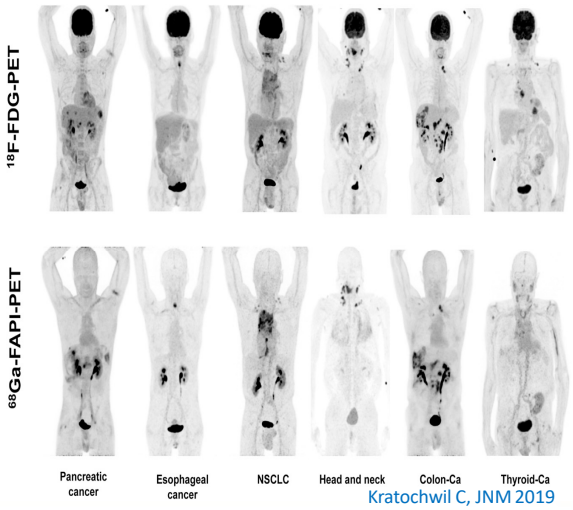
Trends in Radiopharmaceuticals: Oncologic & Theranostics

^{68}Ga-FAPI

- Fibroblast activation protein inhibitor (FAPI)
- FAP: type II membrane-bound glycoprotein enzyme with peptidase activity; highly expressed on cell surface of activated fibroblasts (wound healing, inflammation, fibrosis, *cancer associated fibroblasts*)
- **FAP-targeted theranostics**



Kratochwil C, JNM 2019

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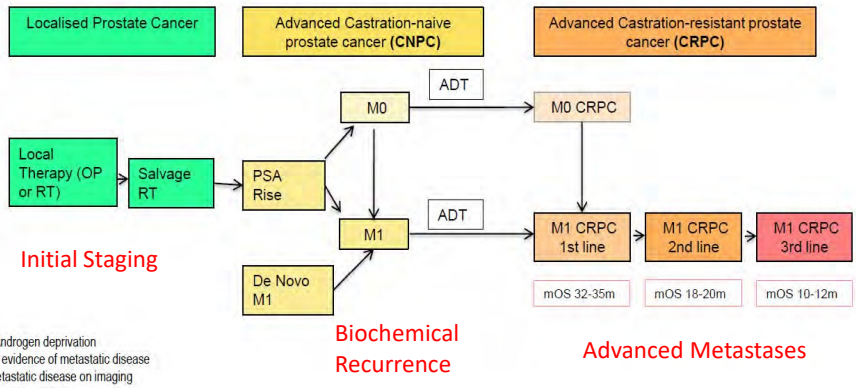
Trends in Radiopharmaceuticals

Oncologic & Theranostics

Prostate Cancer



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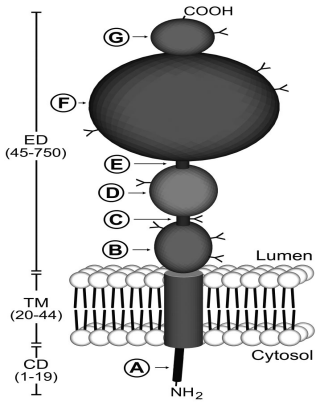
Trends in Radiopharmaceuticals

Oncologic & Theranostics

Prostate-Specific Membrane Antigen (PSMA)

- Transmembrane enzyme (folate hydrolase 1 (FOLH1); carboxypeptidase)
- Expressed in secretory cells of prostate epithelium, small bowel, proximal renal tubule, salivary glands, brain, neovasculature of many tumors
- Undergoes internalization constitutively
- Over-expressed in aggressive tumors, met/rec dz. (1000x nl./benign, ~2M/cell)



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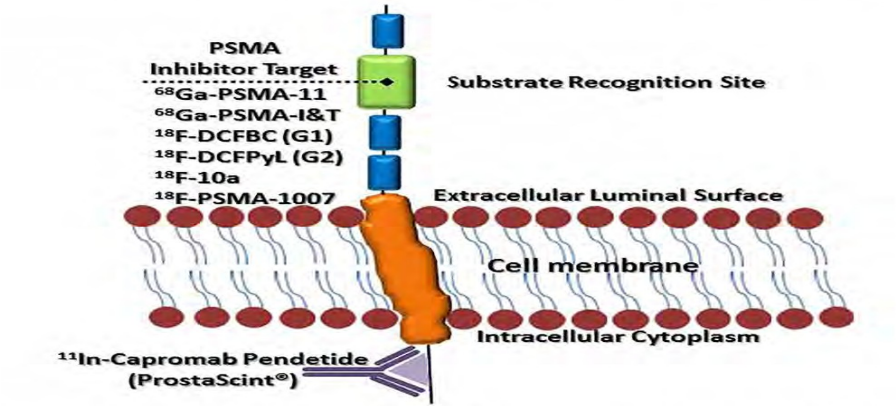
Trends in Radiopharmaceuticals

Oncologic & Theranostics

Prostate-Specific Membrane Antigen (PSMA)



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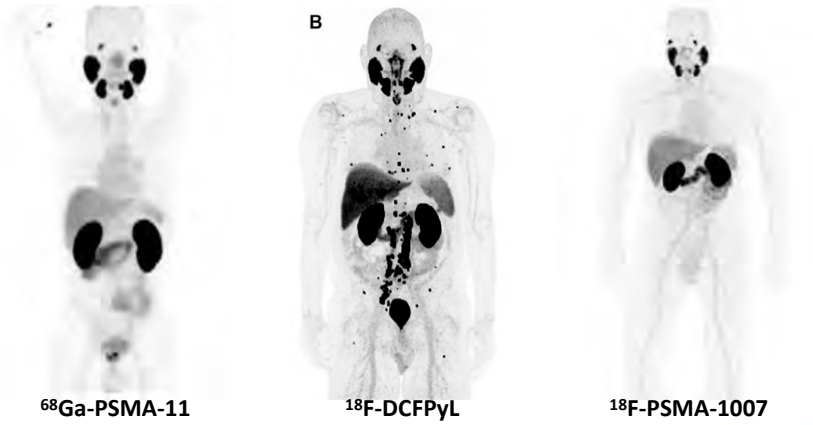
Trends in Radiopharmaceuticals

Oncologic & Theranostics

Prostate-Specific Membrane Antigen (PSMA)



^{68}Ga-PSMA-11 ^{18}F-DCFPyL ^{18}F-PSMA-1007

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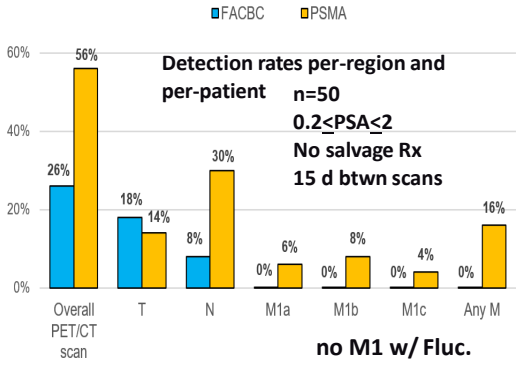
THE LANCET Oncology 2019

^{68}Ga-PSMA-11 PET/CT detects prostate cancer at early biochemical recurrence with superior detection rate and reader agreement when compared to ^{18}F-Fluciclovine PET/CT in a prospective head-to-head comparative phase 3 study

Calais J, Ceci F, Eiber M, Elashoff D, Grogan T, Dahlbom M, Slavik R, Gartmann J, Nguyen K, Lok V, Reiter RE, Rettig MB, Jadvar H, Bach-Gansmo T, Savir-Barush B, Nanni C, Rischpler C, Hofman M, Hope TA, Fendler WP, Czernin J



	Multi-rater Kappa (95% CI)		
Region	PSMA	^{18}F-fluciclovine	p
Tr	0.65 (0.49, 0.81)	0.43 (0.27, 0.59)	0.046
N	0.76 (0.60, 0.92)	0.05 (-0.11, 0.21)	<0.001
M1a	0.60 (0.44, 0.76)	-0.02 (-0.18, 0.14)	<0.001
M1b	0.46 (0.30, 0.62)	-0.03 (-0.19, 0.13)	0.003
M1c	0.65 (0.49, 0.81)	-0.01 (-0.17, 0.15)	0.004
Any M	0.60 (0.44, 0.76)	-0.07 (-0.23, 0.09)	<0.001
PET/CT scan	0.67 (0.51, 0.83)	0.20 (0.04, 0.36)	0.015

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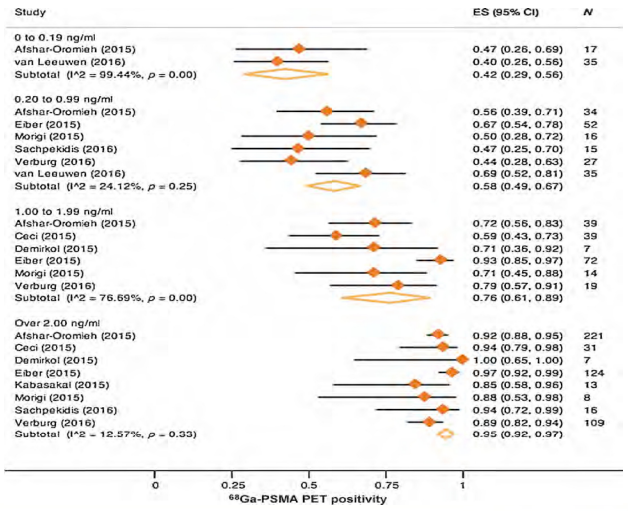
Systematic Review & Meta Analysis: ^{68}Ga-PSMA-11

Perera M et al. Eur Urol 2016

Biochemical Recurrence PSA

16 studies, 1309 pts.



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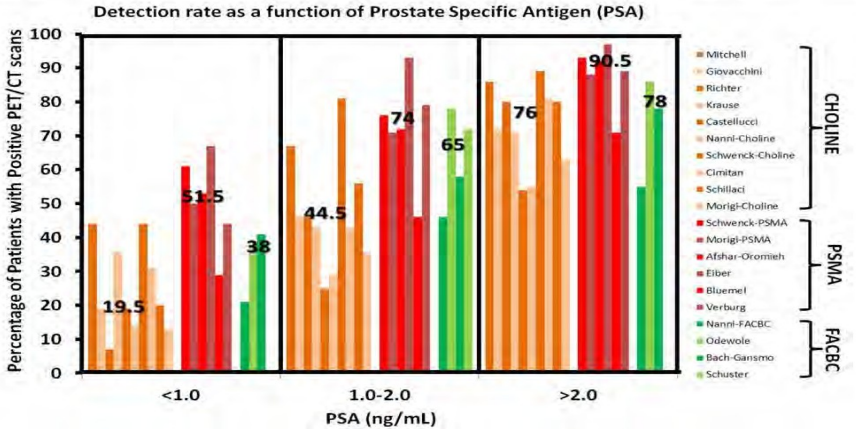
Trends in Radiopharmaceuticals

Oncologic & Theranostics



Evans JD et al. Precision Radiation Oncology 2018

FDA approval: ^{11}C-choline (2012), ^{18}F-fluciclovine (2016)

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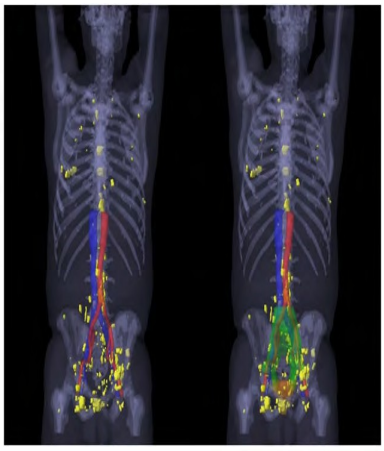
Trends in Radiopharmaceuticals

Oncologic & Theranostics

Prostate-Specific Membrane Antigen (PSMA)

^{68}Ga-PSMA-11 PET/CT Mapping of Prostate Cancer Biochemical Recurrence After Radical Prostatectomy in 270 Patients with a PSA Level of Less Than 1.0 ng/mL: Impact on Salvage Radiotherapy Planning JNM 2018

Jeremie Calais[1], Johannes Czernin[1], Minsong Cao[2], Amar U. Kishan[2], John V. Hegde[2], Narek Shaverdian[2], Kiri Sandler[2], Fang-I Chu[2], Chris R. King[2], Michael L. Steinberg[2], Isabel Rauscher[3], Nina-Sophie Schmidt-Hegemann[4], Thorsten Poeppel[5], Philipp Hetkamp[2], Francesco Ceci[1], Ken Herrmann[1,5], Wolfgang P. Fendler[1,6], Matthias Eiber[1,3], and Nicholas G. Nickols[2,7]



49% pts +PSMA

19% pts with at least 1+ lesion not covered by RTOG guidelines CTVs

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Calais *et al. BMC Cancer* (2019) 19:18
https://doi.org/10.1186/s12885-018-5200-1

PSMA-SRT Trial

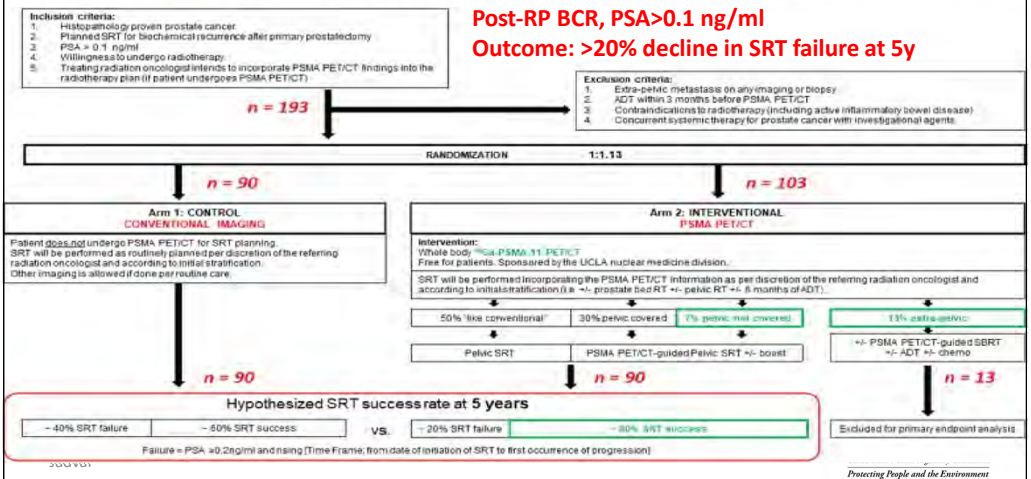
BMC Cancer

STUDY PROTOCOL Open Access

Randomized prospective phase III trial of ^{68}Ga-PSMA-11 PET/CT molecular imaging for prostate cancer salvage radiotherapy planning [PSMA-SRT]

Jeremie Calais[1*], Johannes Czernin[1*], Wolfgang P. Fendler[1,2], David Elashoff[3] and Nicholas Nicholas G. Nickols[4,5]

Post-RP BCR, PSA>0.1 ng/ml
Outcome: >20% decline in SRT failure at 5y

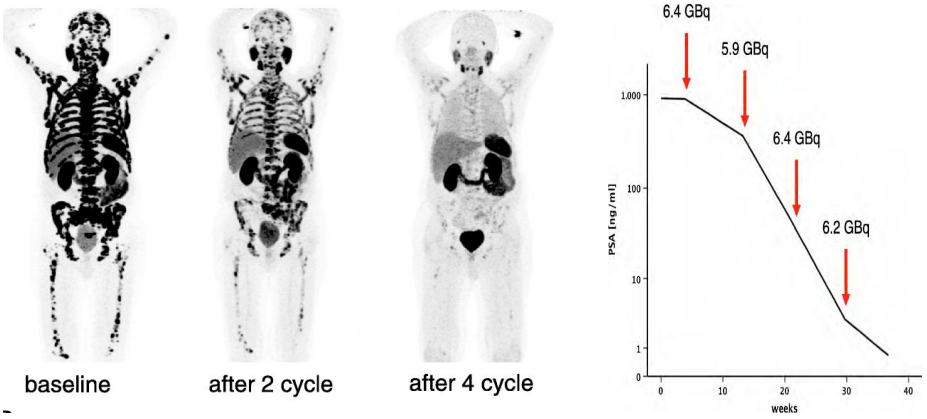


Protecting People and the Environment

Trends in Radiopharmaceuticals

Oncologic & Theranostics

^{177}Lu-PSMA-617



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[^{177}Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study

Lancet Oncol 2018

Michael S Hofman, John Violet*, Rodney J Hicks, Justin Ferdinandus, Sue Ping Thang, Tim Akhurst, Amir Iravani, Grace Kong, Aravind Ravi Kumar, Declan G Murphy, Peter Eu, Price Jackson, Mark Scalzo, Scott G Williams, Shahneen Sandhu*

- 30 men mCRPC
- Prior Rx: 87% chemo, 83% ADT
- PSMA+ / FDG-
- RLT: 7.5 GBq/cycle x 4 cycles q6w
- 57% PSA decline ≥50% from baseline
- 82% objective response
- 37% improvement in global health

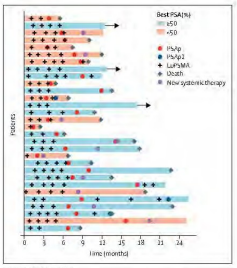

Figure 2: Patient events
Arrow indicates patients without PSA progression up to cut-off date. PSA=prostate-specific antigen. LuPSMA=lutetium-prostate-specific membrane antigen. PSAp2=second PSA progression in patients with initial response who progressed after trial completion and responded to further LuPSMA.

study was sponsored by the Peter MacCallum Cancer Centre (Melbourne, Australia). All authors had full access to all of the data. The corresponding author takes final responsibility for the analysis and decision to submit for publication.

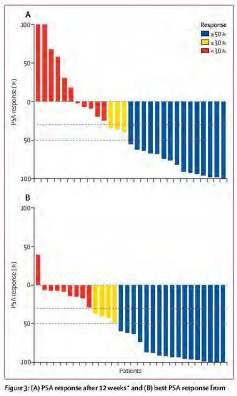

Figure 3: (A) PSA response after 12 weeks* and (B) best PSA response from

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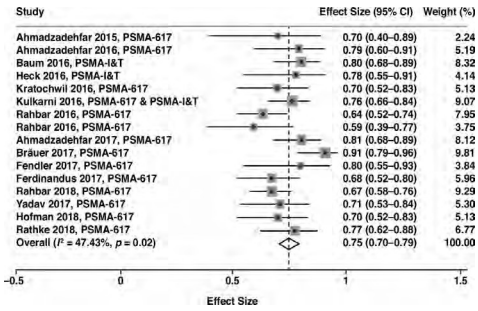
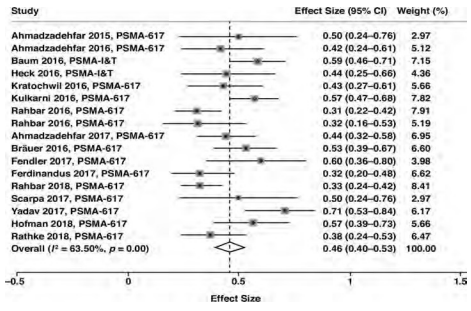
Systematic Review & Meta-Analysis: ^{177}Lu-PSMA-617

- 17 articles; 744 patients
- Pooled proportions
  - **any PSA decline – 75%** (95% CI, 70-79%)
  - **>50% PSA decline – 46%** (95% CI, 40-53%)
  - Toxicity: anemia (23%), leukopenia (14.2%), thrombocytopenia (15%), nephrotoxicity (0-9.5%), xerostomia (14.5%)

Yadav MP et al. AJR 2019



any PSA decline



>50% PSA decline

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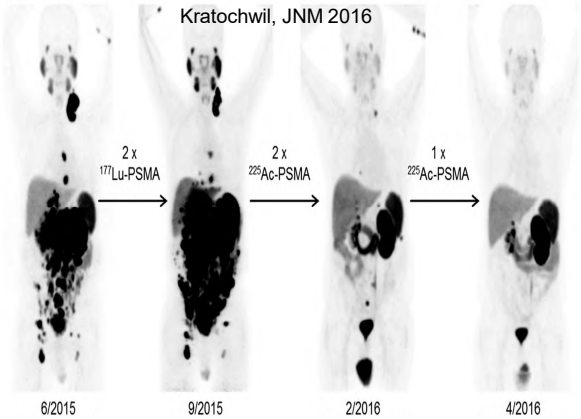
Trends in Radiopharmaceuticals

Oncologic & Theranostics

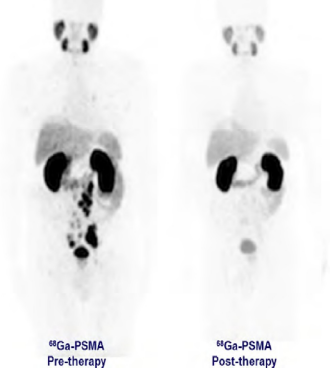
^{225}AC-PSMA-617

Kratochwil, JNM 2016



^{213}Bi-PSMA-617

Sathekge, EJNMMI 2018



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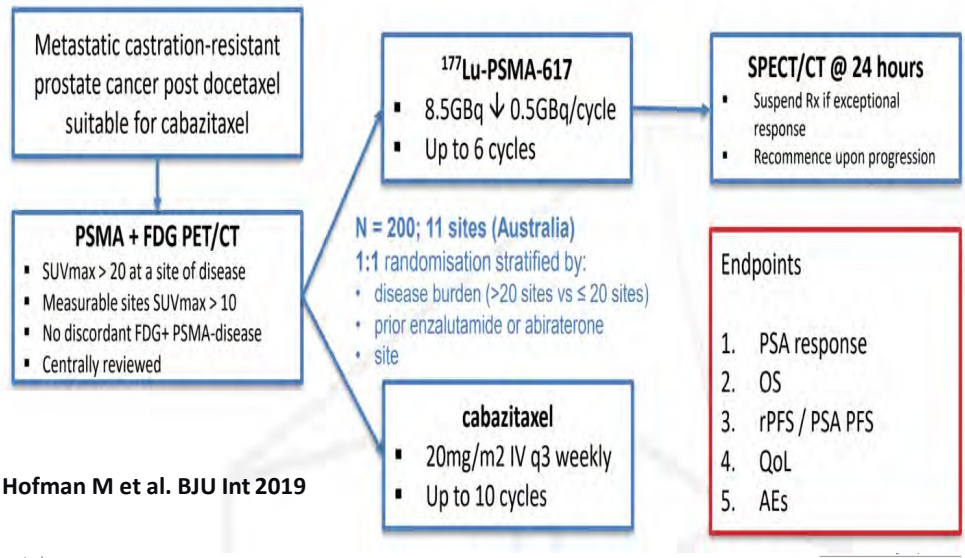
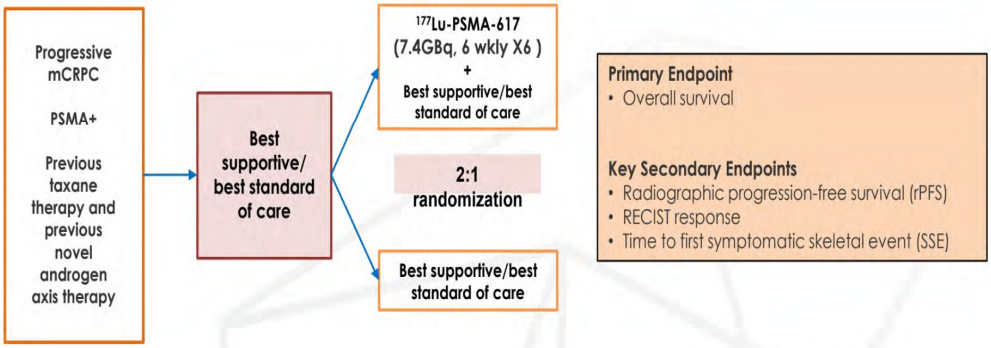
TheraP Trial: ^{177}Lu-PSMA-617 vs. cabazitaxel



Hofman M et al. BJU Int 2019

Jadvar

VISION Trial: ^{177}Lu-PSMA versus best supportive care



- 9 Countries (NA and EU)
- >750 patients recruited
- 12-14 months FU min 15 month

Jadvar

PRINCE Trial

PSMA-lutetium Radionuclide therapy and ImmuNotherapy in prostate CancEr

@UCSFImaging
NCT03805594
Dr Rahul Aggarwal
Dr Tom Hope

- Metastatic CRPC
- Progressed after enzalutamide, abiraterone or apalutamide

PSMA + FDG PET/CT

Pembroluzimab 200mg
3 weekly

+

^{177}Lu-PSMA-617
6 weekly, 4 cycles
Day 4 ± 2 days
8.5 GBq, ↓0.5 GBq/cycle

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LuPARP Trial

Phase 1 trial of ^{177}Lu-PSMA-617 therapy and Olaparib (PARPi)

- Metastatic CRPC
- Progressed after 2nd generation AR-targeted agent
- Post taxane chemotherapy

PSMA + FDG PET/CT

^{177}Lu-PSMA-617
6 weekly, 4 cycles
7.4 GBq

+

Olaparib day 2-15
3+3 dose escalation design
50mg to 300mg bd
(6 levels of increment)

clinicaltrials.gov: NCT03874884
PI: A/Prof Shahneen Sandhu

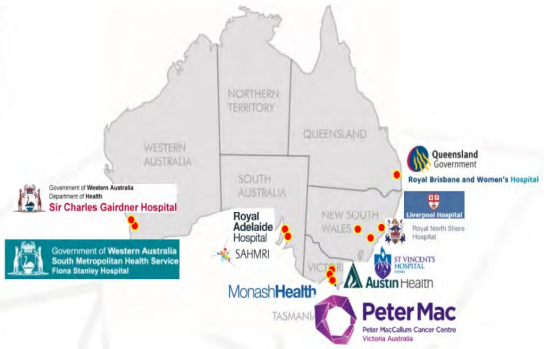
Jadvar

#UpFrontPSMA: high-volume metastatic hormone naïve PC

De novo High-Volume mHNPC
- ≥ 4 bone mets with ≥ 1 extra-axial AND/OR
- Visceral mets

ARM A (n = 70)
Upfront Lu-PSMA x 2-3 + ADT followed by Docetaxel x 6

ARM B (n = 70)
ADT + Docetaxel x 6



Primary endpoint: undetectable PSA at 12 months

Statistical assumptions
- P1 0.5, P2 0.25
- 2-sided alpha=0.05, beta=0.8

PI: A/Prof Arun Azad

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FUNDED BY MOVEMBER® FOUNDATION

Congressionally Directed Medical Research Programs CDMRP Department of Defense

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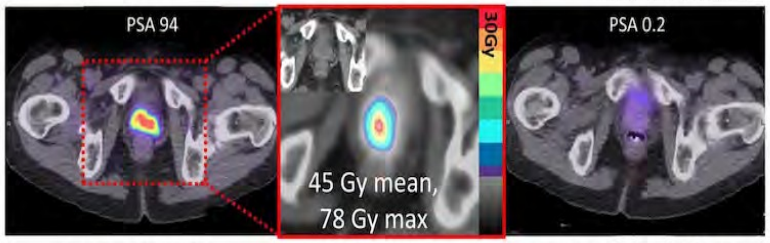
#LuTectomy: ^{177}Lu-PSMA prior to surgery

FUNDED BY MOVEMBER® FOUNDATION

Hofman et al (unpublished)

GG9 post docet, abi, enza & cabazitaxel



baseline PSMA PET | voxel dosimetry | post ^{177}Lu-PSMA$_{617}$ PSMA PET

High-risk localised prostate cancer ± N1

High PSMA Expression

→ **^{177}Lu-PSMA x 1-2 cycles**

→ **At 6-8 weeks:**
- **Prostatectomy + pelvic LN dissection**

Primary endpoints:
- **Dosimetry**

Key Secondary endpoints
- **Safety**
- **PSMA PET Response**

Correlative samples
- Tumour tissue
- PBMCs
- ctDNA, serum

PI: Prof Declan Murphy

Jadvar

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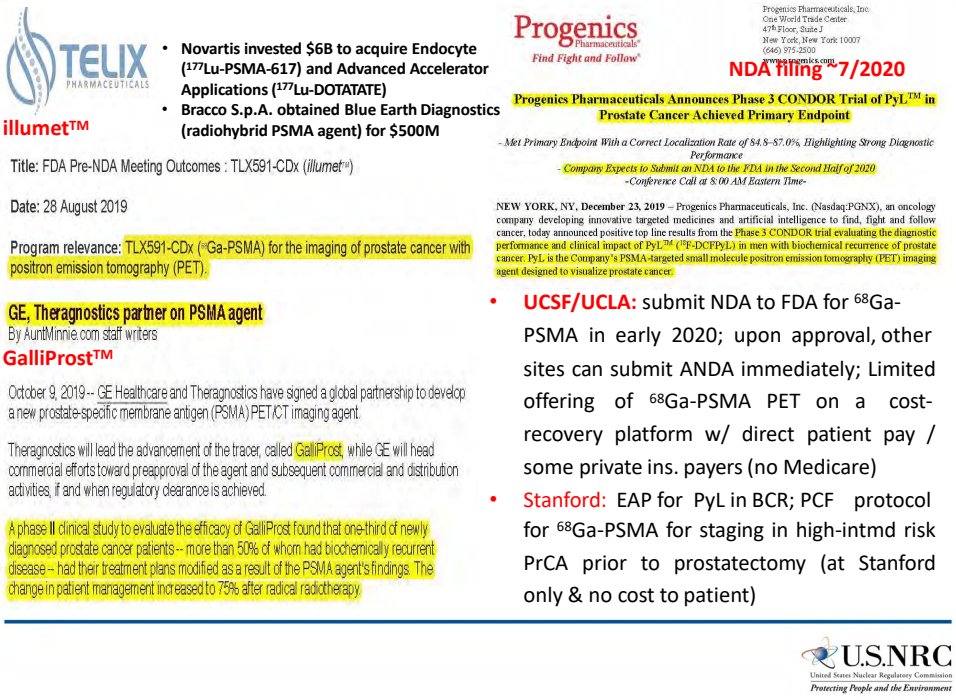

TELIX PHARMACEUTICALS

- Novartis invested $6B to acquire Endocyte (^{177}Lu-PSMA-617) and Advanced Accelerator Applications (^{177}Lu-DOTATATE)
- Bracco S.p.A. obtained Blue Earth Diagnostics (radiohybrid PSMA agent) for $500M

illumet™

Title: FDA Pre-NDA Meeting Outcomes : TLX591-CDx (*illumet™*)

Date: 28 August 2019

Program relevance: TLX591-CDx (^{68}Ga-PSMA) for the imaging of prostate cancer with positron emission tomography (PET).

GE, Theragnostics partner on PSMA agent

By AuntMinnie.com staff writers

GalliProst™

October 9, 2019 -- GE Healthcare and Theragnostics have signed a global partnership to develop a new prostate-specific membrane antigen (PSMA) PET/CT imaging agent.

Theragnostics will lead the advancement of the tracer, called GalliProst, while GE will head commercial efforts toward preapproval of the agent and subsequent commercial and distribution activities, if and when regulatory clearance is achieved.

A phase II clinical study to evaluate the efficacy of GalliProst found that one-third of newly diagnosed prostate cancer patients -- more than 50% of whom had biochemically recurrent disease -- had their treatment plans modified as a result of the PSMA agent's findings. The change in patient management increased to 75% after radical radiotherapy.

Progenics Pharmaceuticals

Find Fight and Follow®

Progenics Pharmaceuticals, Inc.
One World Trade Center
47th Floor, Suite 1
New York, New York 10007
(646) 975-2500
www.progenics.com

NDA filing ~7/2020

Progenics Pharmaceuticals Announces Phase 3 CONDOR Trial of PyL™ in Prostate Cancer Achieved Primary Endpoint

- Met Primary Endpoint With a Correct Localization Rate of 84.8-87.0%, Highlighting Strong Diagnostic Performance

- Company Expects to Submit an NDA to the FDA in the Second Half of 2020

-Conference Call at 8:00 AM Eastern Time-

NEW YORK, NY, December 23, 2019 – Progenics Pharmaceuticals, Inc. (Nasdaq:PGNX), an oncology company developing innovative targeted medicines and artificial intelligence to find, fight and follow cancer, today announced positive top line results from the Phase 3 CONDOR trial evaluating the diagnostic performance and clinical impact of PyL™ (^{18}F-DCFPyL) in men with biochemical recurrence of prostate cancer. PyL is the Company's PSMA-targeted small molecule positron emission tomography (PET) imaging agent designed to visualize prostate cancer.

- **UCSF/UCLA:** submit NDA to FDA for ^{68}Ga-PSMA in early 2020; upon approval, other sites can submit ANDA immediately; Limited offering of ^{68}Ga-PSMA PET on a cost-recovery platform w/ direct patient pay / some private ins. payers (no Medicare)
- Stanford: EAP for PyL in BCR; PCF protocol for ^{68}Ga-PSMA for staging in high-intmd risk PrCA prior to prostatectomy (at Stanford only & no cost to patient)

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Trends in Radiopharmaceuticals

Summary

- Anticipated availability of new PET radiotracers in the next few years in major clinical settings of cardiology, neurology, and oncology
- Theranostics will continue to grow with the clinical introduction of PSMA based agents for imaging and radioligand therapy of prostate cancer

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Acronyms

- CAD: coronary artery disease
- FAPI: fibroblast activation protein inhibitor
- FDG: fluorodeoxyglucose
- Lu-177: Lutetium-177
- MPI: myocardial perfusion imaging
- PET: positron emission tomography
- PHF: paired helical filaments
- PSA: prostate-specific antigen
- PSMA: prostate-specific membrane antigen
- SPECT: single-photon emission computed tomography

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Patient Intervention Subcommittee Report

Michael Sheetz

Advisory Committee on the Medical Uses of Isotopes

March 30, 2020

Subcommittee Members

- Gary Bloom
- Vasken Dilsizian, MD
- Ronald Ennis, MD
- Michael Sheetz (Chair)

- NRC Staff Resource: Said Daibes Figueroa, PhD

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Subcommittee Charge

- Evaluate the definition of “patient intervention” and other actions and circumstances that are exclusive of Medical Events
- Determine what types of events are intended to be captured by the term “patient intervention” and what should or should not be reported as a Medical Event

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History of Misadministration (Medical Event) Reporting Requirement

- First proposed by AEC in 1973
- NRC establishes reporting criteria in 1980
  - Wrong radionuclide
  - Wrong patient
  - Wrong route of administration
  - Diagnostic dose differing by > 50%
  - Therapeutic dose differing by >10%

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Purpose of Misadministration (Medical Event) Reporting

- Allow NRC to investigate the incident to:
  - Evaluate the corrective action taken by the licensee to minimize the chance for recurrence
  - Take generic corrective action to inform other licensees if they could make the same errors

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Exclusion to Misadministration Reporting Requirement (1980)

- Extravasation - the infiltration of injected fluid into the tissue surrounding a vein or artery
- Reason: Extravasation frequently occurs in otherwise normal intravenous or intra-arterial injections and is virtually impossible to avoid

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Revised NRC Medical Use Policy Statement (2000)

- Continue to regulate the medical use of radionuclides as necessary to provide for radiation safety of workers and general public
- Not intrude into the medical judgements affecting patients, except as necessary to provide for radiation safety of workers and general public
- When justified by risk to patients, regulate radiation safety of patients primarily to assure use of radionuclides is in accordance with the physician's direction
- In developing a specific regulatory approach, consider industry and professional standards that define acceptable approaches of achieving radiation safety

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Revised Misadministration Reporting Requirement (2002)

- Term "Misadministration" changed to "Medical Event"
- ME criteria included a dose threshold
- Purpose of reporting Medical Event
  - To evaluate if there was a breakdown in the licensee's program
  - Take corrective action If there was a generic issue that should be reported to other licensees

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Exclusions to Medical Event Reporting Requirement (2002)

- Brachytherapy sources implanted in the correct site but migrated outside the treatment site
- Patient Intervention - actions by the patient, whether intentional or unintentional, such as dislodging or removing treatment devices or prematurely terminating the administration
- Events involving patient intervention that result in permanent functional damage must be reported

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Previous ACMUI Recommendations Regarding Patient Intervention

- 2017 Patient Intervention Subcommittee:
  - Introduced the concept of "passive" rather than "active" patient intervention related to unintentional treatment outcomes with Y-90 microsphere therapy
- 2019 Extravasation Subcommittee:
  - Recommendation extravasation be considered a type of "passive" patient intervention, so that extravasation causing permanent functional damage be reportable as a Medical Event

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What Should or Should Not be Considered a Medical Event

- Physical action taken by patient
- Physiological changes in patient's medical condition
- Condition for licensee inability to control patient intervention event
- What benefit to reporting patient intervention events

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Specific Exemptions to Medical Event Reporting in 10 CFR 35.1000

- RSL Licensing Guidance, Revision 1
  - Patient fails to return for explant surgery
  - Determination not to explant seed due to various patient conditions
- Y-90 Microsphere Licensing Guidance, Revision 10
  - Emergent patient conditions (artery spasm or sudden change in blood pressure)
  - Stasis or dose to wrong treatment site due to shunting

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Examples of Medical Events Not Due to Patient Intervention

- NRC IN 2006-11 "Applicability of Patient Intervention in Determining Medical Events for Gamma Stereotactic Radiosurgery.."
  - Concluded licensee did not provide sufficient evidence to exclude equipment set-up error as cause of Medical Event, rather than patient intervention
- Y-90 Microsphere Licensing Guidance, Revision 10
  - Incomplete administration due to clogging or kinking of catheter not considered stasis, and therefore needs to be reported as Medical Event

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Subcommittee Position on Medical Events and Patient Intervention

- Purpose of ME reporting is to evaluate error or problem in licensee program, or generic issue that should be reported to other licensees
- Unanticipated event that occurs during properly performed clinical procedure, that results from actions taken by the patient which could not have been reasonably prevented, or from anatomical or physiological condition of the patient, should not need to be reported as a ME
- Reporting such unavoidable patient specific events will not help to prevent such events in the future, and doing so would potentially infringe on the practice of medicine

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Subcommittee Position on Medical Events and Patient Intervention

- The term “patient Intervention” should be interpreted to include:
  - Intentional or “voluntary” physical actions taken by the patient, such as removing an implanted brachytherapy source or applicator, or refusing to continue with a prescribed course of treatment
  - Unintentional or “involuntary” actions resulting from the anatomical or physiological conditions of the patient, such as extravasation, migration of implanted radioactive seeds, arterial spasm, and the onset of other underlying medical diseases and disorders which interfere with the prescribed treatment

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Subcommittee Position on Medical Events and Patient Intervention

- Expansion of the term “patient intervention” is consistent with the original objective for which it was developed in 2002
- Event resulting from patient intervention which results in unintended permanent functional damage to an organ or physiological system should be reported as a ME
- ME resulting from patient intervention (whether it causes permanent functional damage or not) should still be reported to institution’s Patient Safety Committee

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Subcommittee Position on Medical Events and Patient Intervention

- ME due to device failure or equipment malfunction, with no error on part of licensee, still need to be reported, as it may indicate a generic defect or problem that would be of benefit to other licensees

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Subcommittee Recommendations

- Current definition of "patient Intervention" should be interpreted to include both intentional (or voluntary) actions taken by the patient, and unintentional (or involuntary) actions
- Medical Events resulting from "patient intervention" should not need to be reported as it would potentially infringe on the practice of medicine, and it will not help to prevent such events in the future
- Medical Events resulting from patient intervention which result in unintended permanent functional damage to an organ or a physiological system should be reported as required by 10 CFR 35.3045(b)

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Acronyms

- ACMUI – Advisory Committee on the Medical Uses of Isotopes
- AEC – Atomic Energy Commission
- IN – Information Notice
- ME – Medical Event
- RSL – Radioactive Seed Localization

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U.S. Nuclear Regulatory Commission
Advisory Committee on the Medical Use of Isotopes

Subcommittee on Patient Intervention

Draft Report
Submitted: March 5, 2020

Subcommittee Members:
Gary Bloom
Vasken Dilsizian, MD
Ronald Ennis, MD
Michael Sheetz (Chair)

NRC Staff Resource: Said Daibes Figueroa, PhD

Subcommittee Charge:

During the September 10-11, 2019 Advisory Committee on the Medical Uses of Isotopes (ACMUI) Meeting, ACMUI Chairman, Dr. Christopher Palestro, established a subcommittee to evaluate the definition of "patient intervention" and other actions and circumstances that are exclusive of Medical Events.

As part of its evaluation, the subcommittee looked at the different aspects of patient intervention, discussed below, such as 1) active actions taken by the patient to interrupt treatment delivery, 2) anatomical, physiological, or changing medical conditions which cause a deviation in the administration, and 3) extravasation. It also looked at the applicability of these events with respect to the Medical Event reporting requirement.

Background:

A medical misadministration reporting rule was first proposed by the Atomic Energy Commission (AEC) in response to an August 1972 Government Accounting Office (GAO) report, which identified 20 cases of wrong doses or overdoses between 1961 and 1972, which involved human error. In March 1973, the AEC published a proposed misadministration rule that would have required licensees to notify the AEC of misadministrations which may result in a demonstrable effect on the patient.[1] The Nuclear Regulatory Commission (NRC) was established as the AEC's regulatory successor in 1975, and in July 1978, it published a proposed Misadministration Reporting Requirement that noted, "The purpose of a misadministration reporting requirement is to allow NRC to investigate the incident; evaluate the corrective action taken by the licensee to minimize the chance for recurrence; and, if other licensees could make the same errors, begin generic corrective action which would, as a minimum, inform other

licensees of the potential problem".[2] A final rule was published in May 1980 which included criteria for misadministration reporting at 10 CFR 35. 41.[3] For this Part, a misadministration was defined as the administration of:

> (a) A radiopharmaceutical or radiation from a sealed source other than the one intended;
> (b) A radiopharmaceutical or radiation, to the wrong patient;
> (c) A radiopharmaceutical or radiation by a route of administration other than that intended by the prescribing physician;
> (d) A diagnostic dose of a radiopharmaceutical differing from the prescribed dose by more than 50 percent;
> (e) A therapeutic dose of a radiopharmaceutical differing from the prescribed dose by more than 10 percent; or
> (f) A therapeutic radiation dose from a sealed source such that errors in the source calibration, time of exposure and treatment geometry result in a calculated total treatment dose differing from the final prescribed total treatment dose by more than 10 percent.

At that time, the NRC did however specifically exclude extravasation, or the infiltration of injected fluid into the tissue surrounding a vein or artery, as a misadministration. It stated, "Extravasation frequently occurs in otherwise normal intravenous or intra-arterial injections. It is virtually impossible to avoid. Therefore, the Commission does not consider extravasation to be a misadministration."

In August 2000, the NRC issued a revised Medical Use Policy Statement, to focus its regulatory emphasis on those medical procedures that pose the highest risk.[4] The policy statement outlined the intent of the NRC to regulate the medical use of radioisotopes based on the following four guiding principles:

1. The NRC will continue to regulate the medical use of radioisotopes as necessary to provide for the radiation safety of workers and the general public.
2. NRC will not intrude into the medical judgements affecting patients, except as necessary to provide for the radiation safety of workers and the general public.
3. NRC will, when justified by the risk to patients, regulate the radiation safety of patients primarily to assure the use of radionuclides is in accordance with the physician's direction.
4. NRC, in developing a specific regulatory approach, will consider industry and professional standards that define acceptable approaches of achieving radiation safety.

In April 2002, the regulations in 10 CFR 35 were revised to be more risk-informed and performance-based, in alignment with the revised Medical Use Policy Statement.[5] The term "Misadministration" was changed to "Medical Event", and the reporting criteria was revised to include different types of deviations from that which was prescribed (wrong dose or dosage, wrong radioactive drug, wrong route of administration, wrong patient, wrong mode of treatment, wrong treatment site, or implant of leaking sealed source) and to also include a dose threshold that must exceed 0.05 Sv (5 rem) effective dose equivalent, 0.5 Sv (50 rem) to an organ or tissue, or 0.5 Sv (50 rem) shallow dose equivalent to the skin (10 CFR 35.3045a). It was stated again that the purpose of reporting Medical Events was for the NRC to evaluate if there was a breakdown in the licensee's program for ensuring that byproduct material or radiation from byproduct material was administered as directed by the Authorized User (AU), or if there was a generic issue that should be reported to other licensees, thereby reducing the likelihood of other medical events. A specific exclusion was listed for permanent implant brachytherapy for sources that were implanted in the correct site but migrated outside the treatment site. There was also an exclusion from the Medical Event reporting requirement for an event that results from "patient intervention", where "patient intervention" is defined as: "actions by the patient or human research subject, whether intentional or unintentional, such as dislodging or removing treatment devices or prematurely terminating the administration" (10 CFR 35.2) However, a licensee must report any event resulting from intervention of a patient or human research subject in which the administration of byproduct material or radiation from byproduct material results or will result in unintended permanent functional damage to an organ or a physiological system, as determined by a physician (10 CFR 35.3045(b)).

In the 2018 amended 10 CFR 35 regulations for the reporting and notification requirements for a Medical Event, no changes were made to the patient intervention exclusion.

Previous ACMUI Subcommittee Recommendations Regarding Patient Intervention:

A previous 2017 ACMUI Patient Intervention Subcommittee, looking into unintentional treatment outcomes with Y-90 microsphere therapy, introduced the concept of "passive" rather than "active" patient intervention.[6] It stated, "Unintentional treatment outcome due to anatomic or physiologic anomaly and/or imaging uncertainty falls into the category "the Art of Medical Practice" provided that the standards of medical practice are met. Reporting such unpredictable and unavoidable patient-specific medical events will not help to prevent such events in the future, and therefore cannot be regulated". This type of "passive" patient intervention was intended to address situations where there was a stasis of arterial flow or shunting of microspheres through aberrant vessels, resulting in a medical event for the Y-90 microsphere therapy. The subcommittee also recommended that such unintentional treatment

outcome exceptions should apply to ALL current and future treatments, and not limited to Y-90 microspheres.

A 2019 ACMUI Subcommittee on Extravasation reviewed the NRC decision in 1980 to exclude extravasation, or the infiltration of injected fluid into the tissue surrounding a vein or artery, from being considered a misadministration (Medical Event).[7] The subcommittee agreed with the 1980 assessment that extravasation frequently occurs in otherwise normal intravenous or intra-arterial injections and is virtually impossible to avoid, and concluded that extravasation is a practice of medicine issue and not an item that needs to be regulated by the NRC. The subcommittee reconfirmed that the exclusion of extravasation from Medical Event reporting was appropriate for both diagnostic and therapeutic procedures. However, one of its recommendations was for extravasation to be considered a type of passive "patient intervention" and that extravasation that leads to "unintended permanent functional damage" be reportable as a Medical Event under 10 CFR 35.3045(b).

Discussion of Issue:

At issue is what types of events are intended to be captured by the term "patient intervention" and what should or should not be considered a Medical Event. As noted by the definition of "patient Intervention", it was intended to address physical action taken by the patient (intentional or unintentional) which caused a deviation in the administration of byproduct material or radiation from byproduct material, from that which was directed by the AU. It is also assumed that the licensee did everything it should to prevent patient intervention during the treatment that resulted in a Medical Event, and that the actions taken by the patient were practically out of the licensee's control. For example, a patient pulls out a vaginal applicator during an HDR treatment, and then refuses completion of the treatment. However, there could also be a situation where physiological changes in the patient's medical condition causes a deviation in the administration of byproduct material or radiation from byproduct material, from that which was directed by the AU. For example, a patient experiences severe cardiac arrhythmias half-way through a gamma knife treatment, requiring urgent medical care, thus preventing completion of the treatment. In both cases, the patient caused a deviation from the prescribed treatment which would meet the medical event reporting criteria; and in both cases, the events could not have been reasonably prevented by the licensee. Therefore, it would seem reasonable for both of these examples to be considered a type of patient intervention.

A reportable Medical Event is meant to be an event that occurred due to treatment errors on the part of the licensee. If the Medical Event criteria are met due to a patient death, patient choice, or because of a changing medical condition that is out of the control of the licensee, it should not be reportable as a Medical Event, however, the licensee should note the reason in

the patient's record. Reporting such unavoidable patient specific Medical Events will not help to prevent such events in the future. The subcommittee recognized that the condition "that is out of the control, or that could not have been reasonably prevented by the licensee" is subjective and may result in varying interpretations. However, decisions on what constitutes reasonable medical practice for the level of patient control should be left to the physician's professional judgement, as they have the primary responsibility for the protection of their patients. The NRC's responsibility, as part of its charge to provide for the radiation safety of patients, is to regulate against unacceptable risks from improper procedures or careless use, while avoiding intrusion into the practice of medicine. Medical Events resulting from intervention of a patient that result in unintended permanent functional damage to an organ or a physiological system should still be reported by the licensee.

It should be noted that a Medical Event may also be due to a device failure or equipment malfunction, with no error on the part of the licensee. These events still need to be reported as a Medical Event, as it may indicate a generic defect or problem that would be of benefit for other licensees to know.

Specific Exemptions to Medical Event Reporting in 10 CFR 35.1000:

Several patient specific events have been incorporated in Part 35.1000 licensing guidance which are also exempt from the Medical Event reporting requirement. Each of these events or situations involves an anatomical, physiological, or changing medical condition, which could cause a deviation in the administration of radioactive material from that prescribed by the AU, resulting in a Medical Event. The events are appropriately excluded from the Medical Event reporting requirement because they cannot be controlled by the licensee and fall into the category of "the practice of medicine".

In the "Low Activity Radioactive Seeds Used for Localization of Non-Palpable Lesions and Lymph Nodes" Licensing Guidance, October 07, 2016, Revision 1,[8] there is an exemption from Medical Event reporting for cases involving: (a) intervention of a patient, (b) the patient failing to return for his/her explantation by the scheduled surgery appointment date and time, and (c) a physician determination not to explant the seed due to various patient conditions (e.g. doing so would jeopardize the patient's well-being). Here, "various patient conditions" is intended to address situations where either the implanted seed may have migrated close to sensitive nerves or vessels where surgical removal may cause significant patient harm (e.g. brachial plexus), or the patient's medical condition has changed such that the patient may be at a high risk to physically tolerate the surgical procedure.

In the "Yttrium-90 Microsphere Brachytherapy Sources and Devices TheraSphere® and SIR-Spheres®" Licensing Guidance, November, 8, 2019, Revision 10,[9] there is an exemption from

Medical Event reporting if the procedure must be modified due to emergent patient conditions that prevent administration in accordance with the written directive (e.g., artery spasm or sudden change in blood pressure). There is also an exemption if the total dose or activity administered was less than that prescribed due to stasis, or if a dose to the wrong treatment site is due to shunting, when shunting was evaluated prior to the treatment in accordance with the manufacturer's procedures. All of these exemptions are intended to address an anatomical or physiological condition of the patient that may affect the administration of the therapy in accordance with written directive, and are out of the control of the AU or licensee.

Examples of Medical Events Not Due to Patient Intervention:

There have been two Medical Events that were discovered by the NRC during routine inspections where the licensee initially determined it to be the result of patient intervention and therefore did not report the event. These are described in NRC Information Notice 2006-11 "Applicability of Patient Intervention in Determining Medical Events for Gamma Stereotactic Radiosurgery and Other Therapy Procedures".[10] In both cases, which involved a Gamma Knife, the patient's head frame had moved during treatment resulting in a dose to the wrong treatment site. In both cases, the licensee attributed the movement as a result of "patient intervention", and since it did not result in permanent functional damage, the licensee concluded that it did not meet the reporting criteria for a Medical Event. However, the NRC concluded that neither licensee provided sufficient evidence to exclude equipment set-up error as the cause of its Medical Event, rather than patient movement.

There have been multiple cases involving Y-90 microsphere treatments where the micro-catheter becomes occluded and prevents complete administration of the prescribed dosage from the delivery device. This has created confusion among some licensees as to whether this type of event is reportable as a Medical Event, or it constitutes a type of stasis or patient intervention. However, in the most recent Y-90 microsphere licensing guidance document[9], it states that "The inability to complete administration due to clogging or kinking of the catheter is not considered stasis.", and therefore this would need to be reported as a Medical Event.

Recommendations:

The purpose of the Medical Event reporting rule is to evaluate if there was an error or problem in the licensee's program for ensuring that byproduct material or radiation from byproduct material was administered as directed by the AU, or if there was a generic issue that should be reported to other licensees, thereby reducing the likelihood of other Medical Events. If a Medical Event occurs during a properly performed clinical procedure, and results from actions taken by the patient which could not have been reasonably prevented by the licensee, or from an anatomical or physiological condition of the patient which falls into the realm of the practice

of medicine, then it should not need to be reported. Reporting such unavoidable patient specific medical events will not help to prevent such events in the future, and doing so would potentially infringe on the practice of medicine. The term "patient Intervention" should be interpreted to include all such events. Intentional or "voluntary" actions would include physical actions taken by the patient, such as removing an implanted brachytherapy source or applicator, or refusing to continue with a prescribed course of treatment. Unintentional or "involuntary" actions would include medical outcomes resulting from the anatomical or physiological conditions of the patient, such as extravasation, migration of implanted radioactive seeds, arterial spasm, and the onset of other underlying medical diseases and disorders which interfere with the prescribed treatment. This expansion of the term "patient intervention" is consistent with the original objective for which it was developed in 2002.

Medical Events resulting from patient intervention in which the administration of byproduct material or radiation from byproduct material results or will result in unintended permanent functional damage to an organ or a physiological system, as determined by a physician, should be reported as required by 10 CFR 35.3045(b). This will allow for those events resulting in serious patient harm to be evaluated for any program deficiencies in the safe use of radioactive material, help ensure that corrective actions are taken, where possible, to prevent recurrence, and identify any generic issues or concerns that may be of benefit to other licensees.

A Medical Event resulting from patient intervention (whether it causes permanent functional damage or not) should still be internally reported to the institution's Patient Safety Committee in accordance with the institutional patient safety reporting and review process. This review is both appropriate and important in ensuring a strong patient safety culture.

Summary of Recommendations:

1. The current definition of "patient Intervention" in 10 CFR 35.2 should be interpreted to include both intentional (or voluntary) actions taken by the patient, such as removing an implanted brachytherapy source or applicator, or refusing to continue with a prescribed course of treatment; and unintentional (or involuntary) actions which would include medical outcomes resulting from the anatomical or physiological conditions of the patient, such as extravasation, migration of implanted radioactive seeds, arterial spasm, and the onset of other underlying medical diseases and disorders which interfere with the prescribed treatment.

2. The subcommittee agrees that Medical Events resulting from "patient intervention" should not need to be reported as it would potentially infringe on the practice of medicine, and it will not help to prevent such events in the future.

3. Medical Events resulting from patient intervention in which the administration of byproduct material or radiation from byproduct material results or will result in unintended permanent functional damage to an organ or a physiological system, as determined by a physician, should be reported as required by 10 CFR 35.3045(b).

References:

1. History of the NRC's Misadministration Reporting Rule, Norman L. McElroy, J Nuc Med. 1986;27:1104
2. Federal Register, 29297, July 7, 1978, Volume 43, Nuclear Regulatory Commission, Misadministration Reporting Requirements, Proposed Rule
3. Federal Register, 31701, May 14, 1980, Volume 45, Nuclear Regulatory Commission, Misadministration Reporting Requirements, Final Rule
4. Federal Register, 47654, August 3, 2000, Volume 65 Nuclear Regulatory Commission, Medical Use of Byproduct Material, Policy Statement; Revision
5. Federal Register, 20330, April 24, 2002, Volume 67, Nuclear Regulatory Commission, Medical Use of Byproduct Material, Final Rule
6. ACMUI, Subcommittee on Patient Intervention, Draft Report, Part II, April 27, 2017
7. ACMUI, Subcommittee on Extravasation, Final Report, October 23, 2019
8. Nuclear Regulatory Commission, "Low Activity Radioactive Seeds Used for Localization of Non-Palpable Lesions and Lymph Nodes" Licensing Guidance, October 07, 2016, Revision 1
9. Nuclear Regulatory Commission, "Yttrium-90 Microsphere Brachytherapy Sources and Devices TheraSphere® and SIR-Spheres®" Licensing Guidance, November, 8, 2019, Revision 10
10. Nuclear Regulatory Commission, Information Notice 2006-11 "Applicability of Patient Intervention in Determining Medical Events for Gamma Stereotactic Radiosurgery and Other Therapy Procedures", June 12, 2006

Respectfully submitted,
Subcommittee on Patient Intervention
Advisory Committee on the Medical Use of Isotopes
U.S. Nuclear Regulatory Commission

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Overview of Nuclear Material Events Database (NMED)

Robert Sun
Medical Safety and Events Assessment Branch
March 30, 2020

1

NMED Background Info

What is NMED?

- NRC database for tracking nuclear material events.
- Contains over 23,000 records of events submitted to the NRC and Agreement States since 1990.
- Contains Nuclear Material Events related to: Loss/Abandonment/Theft, Medical Events, Overexposure, Release/Contamination, Equipment Failure, etc.
- Data is updated daily, using event data based on NRC reporting requirements as well as Agreement State reporting.

NMED Project Objectives

- Collect, review, and compile material event reports into NMED
- Develop and maintain NMED website for NRC and State agencies
- Develop NMED software for State agencies
- Provide event analysis and assessment support
- Provide technical assistance to NRC and States

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NMED Background Info

Who has access?

- Login access - users include Federal and State regulators, or their contractors (with sponsorship and need to know).
- Current users: Primarily NRC (including ACMUI) and Agreement State users. Other agencies include: DHS, CBP, DOT, FBI, DOE, Navy, Air Force

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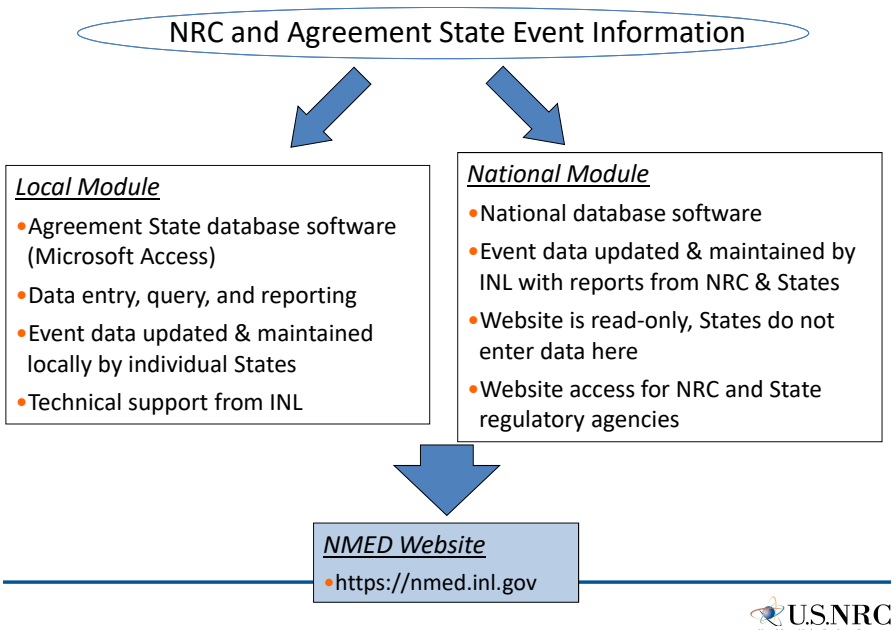

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NMED National Module Data Collection and Coding

Data Collection

- Agreement State-Regulated Events
  - States collect data and submit to the NRC/INL.
- NRC-Regulated Events
  - INL collects data from the NRC daily reports (ENs and PNs) and public ADAMS (inspection reports, licensee reports, consultant reports, etc.). Also requests for clarifying information via RAIs
- Only publicly available information is used.
- For consistency, event report abstracts are entered manually (reports are not just copied/pasted into the national module).

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NMED National Module Data Collection and Coding

INL Event Coding:

- Event date - the most conservative date is used
- Event reportability - in a few cases, does not strictly match the CFR
- Reporting requirements - NMED lists the "equivalent" CFR for Agreement State events
- Multiple event types in a single event record
- Abnormal Occurrences (AOs) marked as "Potential" and provided to AO working group, in support of Annual Report to Congress on AOs (NUREG-0090)

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Event Reporting Schedule (SA-300 Appendix C)

Event Reporting Schedule for Agreement States			
	Reportable Event Notification[1]	**Agreement State Reporting Schedule to NRC**	**Reporting Methods to NRC[4]**
IMMEDIATE	**Significant** reportable events requiring **immediate notification (i.e., within 4 hours or less[2])** by Agreement State licensees.	Agreement State should report to NRC immediately of notification by an Agreement State licensee.	Report initial information to the NRC Operations Center[5] (301) 816-5100 Fax #: (301) 816-5151 Email: HOO.HOC@nrc.gov
24 HOURS	**Significant** reportable events requiring notification within **24 hours or less, or next calendar day**, by Agreement State licensees.	Agreement States should report to NRC within 24 hours of notification by an Agreement State licensee.	
	Events involving **theft or terrorist** activities should be reported to the **FBI[3]**.	Agreement States should consider reporting to the FBI within 24 hours of notification.	
5 - 60 DAYS	**5 - 60 day reportable events** requiring **greater than 24 hour** notification by Agreement State licensee and event follow-up reports.	Agreement States should provide 5 - 60 day notification within the same timeframe licensees must report the event to the Agreement State, and any follow-up reports should be provided in a timely manner[6].	NMED Local Agreement State Software or NMED website at http://nmed.inl.gov or Mail: U.S. NRC, Branch Chief of NMSS/MSST/MSEB, Mail Stop T-5B60 Washington, DC 20555
VOLUNTARY	Lost, stolen, or abandoned sources reported to the Agreement and non-Agreement States that are non-AEA or unlicensed material and not covered by the above two categories.	Voluntary reporting by the Agreement States and non-Agreement States[7].	

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NMED Website

- https://nmed.inl.gov
- NMED is an *events* database.
- Generally, only reportable material events are included.
- Complete vs Closed Events
  - Complete
    - Events are only marked “Complete” if they contain all of the information required by SA-300 (Appendix E).
    - INL uses SA-300 to determine if an event is “Complete”.
  - Closed
    - Events can be “Closed” when the regulatory agency plans no further action.
    - The regulatory agency determines if an event is “Closed” and notifies INL.

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NMED Website

- Incomplete Events
  - Requests for additional information (RAIs) are sent for events that are still incomplete 57 days after the event was reported to the regulatory agency.
  - Typical information requested includes:
    - Cause
    - Corrective Action (actions taken to prevent recurrence, not how the facility mitigated the event)
    - Final Dose Assessment
    - Radionuclide & Activity
    - Device manufacturer, model number, and serial number
    - Source manufacturer, model number, and serial number

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NMED Website Uses

- Develop and save advanced searches.
- Library of Quarterly Newsletters and Quarterly/Annual Reports.
- Check a licensee's event history prior to inspection.
- Check a prospective company's event history prior to authorizing reciprocity work.
- Research similar events for generic issues.
- Locate owner of a "found" source.
- Review events involving a state/region.
  - Find incomplete events.
  - Find open events.
  - Find events for which a RAI was sent but no response received.
- Prepare for an IMPEP review.

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NMED - What it Does and Doesn't Do

- During the September 2019 ACMUI meeting, the Appropriateness of Medical Event Reporting Subcommittee reported on a number of findings regarding the Nuclear Material Events Database (NMED).
- "Gaps" with the NMED database were discussed.
- These findings are generally outside the scope of NMED's intended function.

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NMED - What it Does and Doesn't Do

NMED Does:

1. Provide access to Federal and State regulators, or their contractors.
2. Serve as a tool to assist regulators in identifying generic trends or problems.
3. Include a narrative and summarizes the event using publicly available information.
4. Capture critical event information and requests for additional information within the scope of the reporting requirements.
5. Operate within the confines of the 10 CFR.

NMED Does NOT:

1. Provide access to general members of the public.
2. Serve as a platform for sharing operating experience with licensees or members of the public.
3. Include a narrative that includes all of the details, discussion, and causes. These can be found in the inspection report.
4. Have the authority to dictate level of detail or information provided in event reports beyond what is required in 10 CFR.
5. Establish new reporting criteria.

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Contact Information

NRC NMED Project Manager
- Robert Sun: 301-415-3421
- nmednrc@nrc.gov

NMED INL Team
- Tom Smith, Dante Huntsman, Robert Sant
- nmed@inl.gov

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Acronyms

ACMUI – Advisory Committee on the Medical Uses of Isotopes
AO – abnormal occurrences
CBP – U.S. Customs and Border Protection
CFR – Code of Federal Regulations
DHS – U.S. Department of Human Services
DOE – U.S. Department of Energy
DOT – U.S. Department of Transportation
EN – event notifications
FBI – Federal Bureau of Investigations
IMPEP – Integrated Materials Performance Evaluation Program
INL – Idaho National Laboratory
NMED – Nuclear Material Events Database
PN – preliminary notifications
RAI – requests for additional information

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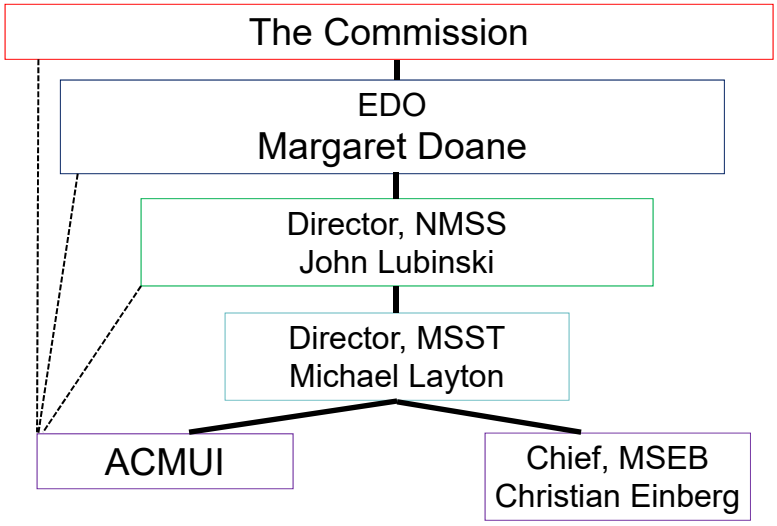
Committee Reporting Structure

Kellee Jamerson, ACMUI Coordinator
Medical Radiation Safety Team
March 30, 2020

Outline

- **Current Reporting Structure**
- **Annual Review**
- **Meetings**
- **Discussion**

Current Reporting Structure



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Annual Review

In September 2012, the ACMUI recommended to have an annual review of reporting structure.

4

Meetings

Two meetings at Headquarters each year

- **March/April**
- **September/October**

Approximately 2-3 teleconferences (as needed)

5

ACMUI Discussion

6

Points of Contact

- **Michael Layton– MSST Director**
  - **301-415-0321; Michael.Layton@nrc.gov**
- **Christian Einberg – Designated Federal Officer (DFO), Chief, MSEB**
  - **301-415-5422; Christian.Einberg@nrc.gov**
- **Kellee Jamerson – DFO, ACMUI Coordinator**
  - **301-415-7408; Kellee.Jamerson@nrc.gov**

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Acronyms

- **ACMUI – Advisory Committee on the Medical Uses of Isotopes**
- **DFO – Designated Federal Officer**
- **EDO – Executive Director for Operations**
- **MSST – Division of Materials Safety, Security, States, and Tribal Programs**
- **MSEB – Medical Safety and Events Assessment Branch**
- **NMSS – Office of Nuclear Material Safety and Safeguards**

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ACMUI Bylaws Subcommittee

Harvey B. Wolkov, M.D.
Advisory Committee on the Medical Uses of Isotopes
March 30, 2020

Subcommittee Members

- Michael Sheetz, M.S.
- Megan Shober, M.S.
- Harvey Wolkov, M.D. (Chair)

- NRC Staff Resource: Kellee Jamerson

Subcommittee Charge

- Review and comment on term limits for ACMUI Chair and Vice Chair
  - If term limits, how long?
- Review succession of ACMUI Vice Chair to Chair

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Advantages of Term Limits

- Bring new ideas and initiatives for Committee review, including opportunities to increase the diversity of committee perspectives.
- Low turnover rate causes a foundation of stale ideas, new perspectives inspire change that can prevent the committee from becoming stagnant.
- Motivation may decrease with prolonged leadership.
- Stop political power maneuvering.

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Advantages of Term Limits (cont'd)

- Easier to remove passive, ineffective, or troublesome leaders.
- Allows leadership opportunities for other committee members.
- Members may not be willing to take a Chair position with no end date.
- Board Chairs require an intensive commitment of time and energy; helps prevent board chairs from burning out by shortening the duration of their commitment.

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Advantages of Term Limits (cont'd)

- Allows the committee to adjust leadership to suit changing organizational needs
- BoardSource's Nonprofit Governance Index (2007) demonstrated that boards with term limits are more effective than those without
  - This can be extended to leadership – there is no perpetual concentration of power and the group dynamic is constantly changing, preventing stagnation.

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Disadvantages of Term Limits

- Good, hard working leaders would be forced to leave the committee
- Creates leadership vacancies that must be filled. The organization will spend more time and resources to recruit and educate a new chair.
- Changes the learning curve – "It takes 6 months to learn a job and another 6 months to be good at it."
  - Longstanding chair may bring invaluable knowledge such as institutional memory and/or knowledge of process and procedure.

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Disadvantages of Term Limits (cont'd)

- Loss of networking benefits.
  - Assumes leadership develops a professional network from other government agencies (Ethics committee, staff, industry leaders, and others with niche expertise).
- A chair may be willing and highly motivated to continue to serve
- Term limits could create professional disappointment
- Creates the potential closing off of leadership development and opportunity

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Disadvantages of Term Limits (cont'd)

- Members may take their skills and interest to other organizations resulting in a loss of expertise.
- Loss of cohesion to the team/committee.

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Term Limits – Duration of Service

According to BoardSource's Leading with Intent: National Index of Nonprofit Board Practices (2015):

71% of organizations have term limits for Board Chairs
- 38% serve a one-year term
- 31% serve a two-year term
- 18% serve a three-year term
- Only 4% serve four or more years

Most commonly, chairs serve 2 consecutive terms
[19% serve one term and 17% serve three or more terms]

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Automatic Succession

Advantages

- Allows for smooth transition of leadership
- The organization will spend less time and resources to recruit and educate a new committee chair
- Vice Chair has time to be groomed for the position

Disadvantages

- Other committee members may be more suited for a leadership position

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Subcommittee Deliberations

The current ACMUI bylaws state "the Chair and Vice Chair will be appointed by the Director, NMSS. The Chair and Vice Chair will serve at the discretion of the Director, NMSS."

- When considering term limits for ACMUI leadership, the Subcommittee did not feel most of the theoretical arguments, pro and con, were particularly applicable.

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Subcommittee Deliberations

- The Subcommittee felt that the current structure defined in the current bylaws was working successfully and did not need to be changed.
- The Subcommittee felt that the relative short tenure of each of the Subcommittee's members created uncertainty regarding our recommendation.
- Subcommittee members recommended that we canvass the opinions of two more senior members of the ACMUI regarding term limits and succession.

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Subcommittee Deliberations

- Drs. Ronald Ennis and Vasken Dilsizian were provided the Subcommittee's working materials and they were interviewed by the Subcommittee chair.
- There was concordance of opinion of the two more senior ACMUI members and the Subcommittee with respect to both term limits and succession.

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Subcommittee Recommendations

The Subcommittee recommends no changes to the existing ACMUI bylaws.

Term Limits

The Subcommittee agrees that the ACMUI Chair and Vice Chair should be appointed by the Director of NMSS and the Director should determine the duration of the term, as currently stated in the bylaws.

Succession

The Subcommittee agrees that officer succession should be at the discretion of the Director of NMSS, as currently stated in the bylaws.

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Acronyms

- ACMUI – Advisory Committee on the Medical Uses of Isotopes
- NMSS – Office of Nuclear Material Safety and Safeguards

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Advisory Committee on the Medical Uses of Isotopes

Bylaws Subcommittee
Draft Report

Submitted on March 2, 2020

Subcommittee Members

Michael Sheetz, M.S.
Megan Shober, M.S.
Harvey Wolkov, M.D. (Chair)

NRC Staff Resource: Kellee Jamerson

Subcommittee Charge

The Subcommittee and its Chair were appointed by Chairman, Dr. Christopher Palestro, on September 11, 2019. The Subcommittee charge was to 1) review and comment on term limits for the Advisory Committee on the Medical Uses of Isotopes (ACMUI) Chair and Vice Chair. If term limits were recommended, what would be the duration of the term; and 2) review the automatic succession of the Vice Chair to Chair.

Introduction

The ACMUI bylaws state the Chair and Vice Chair of the ACMUI are appointed by the Director of the Office of Nuclear Material Safety and Safeguards (NMSS). The Director of NMSS will determine the duration of the officer's term.

The Subcommittee reviewed arguments in support of term limits and succession and against term limits and succession. The arguments in support of term limits include:

- New leadership brings new ideas and initiatives for committee review, including opportunities to increase the diversity of committee perspectives;
- Low turnover creates a foundation of stale ideas; abrogate political maneuvering;
- Allows for easier removal of ineffectual leaders;
- Allows leadership opportunities for other committee members;
- Helps prevent leadership burn out by shortening the duration of the officer's commitment; and
- Allows the Committee to adjust leadership to suit changing organizational needs.

Some of the arguments against term limits include:

- Forcing hard working, effective leaders to leave the Committee;
- The creation of leadership vacancies that must be filled creates inefficiencies for the organization in terms of time and resources to recruit and educate a new leader;

- Longstanding Chair brings invaluable knowledge such as institutional memory and/or knowledge of process and procedure; recognition of the steep learning curve faced by new leadership;
- A Chair may be highly motivated to continue to serve; and
- Loss of potential networking benefits (Ethics Committee, staff and others with niche expertise).

Discussion

The main arguments in favor of automatic leadership succession is it allows for a smooth transition of leadership and allows time for the Vice Chair to be groomed for the position. The main argument against automatic succession is there may be other committee members more suited for the Chair leadership position.

When considering term limits, the Subcommittee did not feel most of these theoretical arguments, pros and cons, were particularly applicable to the ACMUI leadership. It was the consensus of the Subcommittee that the current structure defined by the bylaws was working successfully and did not need to be changed. The Subcommittee expressed concern that our deliberations on the matter of term limits and succession could be biased by the short tenure of each of the Subcommittee members.

The Subcommittee also canvassed the opinions of two more senior members of the ACMUI regarding term limits and succession. To this end, the Chair of the Subcommittee sent its working materials to Drs. Ronald Ennis and Vasken Dilsizian for review. The two members were interviewed by the Subcommittee Chair. There was concordance of opinion of the two more senior ACMUI members and the Subcommittee with respect to both term limits and succession.

Subcommittee Recommendations

The Subcommittee recommends no changes to the existing bylaws.

The Subcommittee agrees that the ACMUI Chair and Vice Chair should be appointed by the Director of NMSS and the Director should determine the duration of the term as currently stated in the bylaws.

The Subcommittee agrees that Officer succession should be at the discretion of the Director of NMSS, as currently stated in the bylaws.

Respectfully Submitted on March 2, 2020,

Bylaws Subcommittee
Advisory Committee on the Medical Uses of Isotopes

U.S.NRC
United States Nuclear Regulatory Commission
Protecting People and the Environment

Status of Medical Events FY 2019

Donna-Beth Howe, Ph.D.
Medical Radiation Safety Team
March 30, 2020

1

Medical Events

The dose threshold for diagnostic events precludes reportable events most years.

Each year, there are approximately 150,000 therapeutic procedures performed utilizing radioactive materials.

2

Medical Events FY 2014 - 2016

- **46 Medical events reported - FY 2014**
- **57 Medical events reported - FY 2015**
- **50 Medical events reported - FY 2016**

	FY14	FY15	FY16
35.200	1	3	4
35.300	3	8	4
35.400	5	9(10*)	6 (18)
35.600	10	17	6
35.1000	27	20(30)	30

* The total number of patients involved if greater than the number of reports

3

Medical Events FY 2017 - 2019

- **43 Medical events reported - FY 2017**
- **48 Medical events reported - FY 2018**
- **56 Medical events reported - FY 2019**

	FY17	FY18	FY19
35.200	0	0	1(8)
35.300	4	2	9
35.400	7	11(13)	5
35.600	8 (14)	10	9(10)
35.1000	24	25(26)	32

4

Medical Events 2019

35.200 Medical events **1**

Sr-82/Rb-82 Generator 1 (8)

5

35.200 Medical Events

Sr-82/Rb-82 Generator **1**

- **8 patients - 100.7 to 256.9 cGy (rad) to the red marrow, 117.12 to 299.36 cGy (rad) to the bone surface, and 27.02 to 68.4 cGy (rad) effective dose.**
  - Excess Sr-82 and Sr-85 breakthrough for 3 days.
  - Breakthrough test performed by three different individuals, each recorded no breakthrough values.
  - Unknowingly eluted generator on day one with Ringer's Lactate.
  - Discovered from unexpected waste survey results.

6*

Sr-82/Rb-82 Generator (cont.)

- Primary Failures
  - Human error in the inadvertent use of Ringer's Lactate to elute the Rb-82 generator.
  - Inadequate practices in conducting the QC strontium breakthrough analyses.
- Corrective Actions
  - Immediately stopped the Rb-82 generator program.
  - Automated medication dispensing system with medication scanning prior to each administration.
  - Daily audits of the IV fluid, modify the forms, obtain new equipment, and train personnel.

7

Medical Events 2019

35.300 Medical events		**9**
Iodine -131	3	
Na I-131	2	
I-131 Iomab-B	1	
Samarium-153	1	
Radium-228	2	
Lutetium-177	3	

8

35.300 Medical Events

NaI-131 **2**

Liquid I-131 - spill from feeding tube **1**

- Administered 2.73 GBq (73.8 mCi) of prescribed 6.48 GBq (175 mCi) of liquid I-131.
- Patient unable to swallow pill, so administered through a feeding tube inserted into the patient's gastric tube.
- Pool of radioactive liquid next to the patient on a disposable drape, on the patient, and on the imaging table after flushing the feeding tube with saline.
- Feeding tube removed from the gastric tube and flushed, no further leakage.

9*

35.300 NaI-131 Spill (cont.)

Spill from feeding tube (cont.)

- Spill contained; patient and site decontaminated; no hospital personnel contaminated.
- Determined spill activity 3.74 GBq (101.2 mCi) by surveying all contaminated items in storage drum and conservative decay calculations.
- Concluded cause was a feeding tube failure.
- Do not plan to perform any more administrations of I-131 through a feeding tube.

10

35.300 Na I-131 Capsule

Wrong patient 1

- **Prescribed 0.518 GBq (14 mCi) [40,000 cGy (rad)] for hyperthyroidism, but administered 1.221 GBq (33 mCi) [96,500 cGy (rad)].**
- The wrong I-131 capsule was administered - did not verify it was for the patient.
- Techs were re-educated on the importance of following procedures for administration of radiopharmaceuticals.

11

35.300 I-131 Iomab-B

I-131 Iomab-B 1

- **Administered 17.13 GBq (462.92 mCi) I-131 Iomab-B 42% less than prescribed 29.415 GBq (795 mCi).**
- Clinical trial for acute myeloid leukemia - used delivery system under research and development.
  - Delivery system design was cause - it did not permit visualization of the dosage vial and required the manufacturer to set the infusion time.
  - Manufacturer was present and assisted in setting up the delivery system and infusion time.
- Refused to continue in trial until development of a system with visualization of the dose.

12

35.300 Sm-153 Leak

Sm-153 Quadromet 1

- **Administered 86.95 MBq (2.35 mCi) but prescribed to 2,146 MBq (58 mCi).**
- Sm-153 leaked – initially thought a crack in the locking assembly of the IV tubing caused the leak.
- Concluded from location of the spill that IV tubing itself failed.
  - Abraded at the time of needle insertion.
  - Added pressure from the dosage administration caused the tube wall to fail and the leakage.

13

35.300 Ra-223 Xofigo

Ra-223 Xofigo 2

Incorrect written directive 1

- **Administered 3.07 MBq (83 µCi) per but standard dosage protocols that was dispensed correctly by the pharmacy and administered to the patient.**
- Licensee assayed dosage vial using an incorrect setting on the dose calibrator – displayed dosage of 2.07 MBq (56 µCi).
- The written directive filled out according to the incorrectly assayed dosage resulting in incorrect written directive.

14*

35.300 Ra-223 Written Directive (cont.)

Incorrect written directive (cont.)

- Future written directives will receive the physician's signature and approval prior to assaying the dosage.
- Discovered during a routine written directives audit.
- Written directives will be audited quarterly by the RSO or designee.

15

35.300 Ra-223

Received half of 2 administration

- **Prescribed 8.65 MBq (233.69 µCi) of Ra-223 Xofigo, received 4.41 MBq (119.19 µCi)**
- Dosage was divided into 2 syringes - size of the patient and doses typically arrive in 10 cc syringes.
- After first syringe, patient was discharged.
- Patient returned the following day and received the second syringe of 4.24 MBq (114.5 µCi).
- Corrective actions included additional training and supervision to personnel.

16

35.300 Lu-177 Lutathera

Lu-177 Lutathera **3**

Infusion pump issue

- **Prescribed 7.4 GBq (200 mCi) of Lutathera, received 4.99 GBq (134.9) - 32.55% of dosage**
- Infusion method had potential for small bubbles to develop in the infusion line, causing the pump to alarm.
- Technologist was aware of issue, knew how to prevent it, called away, and instructed the other technologist to pause the infusion and contact her if the pump alarmed.

17*

35.300 Lu-177 Infusion Pump Issue (cont.)

- Pump alarmed - other technologist tried to restart - a larger bubble formed in the line.
- Nurse asked to assist in purging the line but drained Lu-177 into an emesis basin, thinking it was saline.
- Contaminated staff and patient clothing, and areas of the treatment bay; clothing held for decay and treatment bay decontaminated.
- Make-up dose administered the next day to complete the patient's planned therapy.
- Retraining applicable staff members and modifying the Lu-177 infusion method.

18

35.300 Lu-177 Lutathera

Vial Issue 1

- **Administered 5.39 GBq (145.7 mCi) of Lu-177 intended 7.4 GBq (200 mCi)**
- Loss of integrity of the air seal on the Lutathera vial caused the fluid level to rise within the vial.
  - Positive pressure cap on the peripherally inserted central catheter (PICC) offered resistance to the flow, and led to the fluid level rise in the vial.
  - Height of the vial possibly too low relative to the entry point in the patient, affecting gravity influence on the flow.

19*

35.300 Lu-177 Vial Issue (cont.)

Corrective actions:

- Written procedures require replacing a positive pressure cap on the line from the vial to the patient with a free-flow cap to reduce backpressure on the line.
- Increase height of the dose vial above the patient catheter input port to provide added gravity assist.
- Inserting needles into the vial septum at an angle to keep needles from moving and cause stretching of the rubber cap from weight of attached tubing
- Revising the written directive form.

20

35.300 Lu-177 Lutathera

FDA Protocol and Medical license restrictions 1

- **Intended four treatments of Lu-177 at 7.4 GBq (200 mCi) each to the midgut.**
- Physician changed the dosage of the fourth and final treatment to 3.7 GBq (100 mCi).
  - Per FDA protocol, commercial nuclear pharmacy could only ship full vials of Lutathera at 7.4 GBq (200 mCi).
  - If the physician wanted to administer half the dose, medical facility would have to do it. Medical use RSO informed medical physicist and physician that they were not licensed to split doses.

21*

35.300 Lu-177 Protocol/License Restrictions (cont.)

- Patient agreed to full dosage of 7.4 GBq (200 mCi).
- RSO stated that both the prescribing physician and the patient were notified that the written directive was not updated.
- The highest critical organ doses in excess of the prescribed written directive were the spleen at 304 cGy (rad) and the kidneys at 235 cGy (rad).
- Licensee will consult with the primary physician and update the written directive if the dose in the written directive cannot be provided by the radiopharmacy.
- No adverse effects are expected to the patient.

22

Medical Events 2019

35.400 Medical events **5**

Prostate 5

One licensee, 2 reports	2
Wrong site	1
Source activity error	1
No post implant procedures	1

23

35.400 Medical Events

Prostate **9 (11)**

One licensee, 2 separate reports, 2 patients

- Report 1 - prescribed 10,000 cGy, 82 Pd-103 seeds (59.57 MBq (1.61 mCi) each) to the prostate.
  - Preplanned treatment plan revised periodically during implantation using ultrasound images of seed positions – D90 of 102%.
  - 30 day post implant CT scan dosimetry evaluation D90 was determined to be 74.8% intended dose.
  - Prostate gland larger at the 30-day CT scan compared to the day of the implant (46.4 cm3 vs. 39.7 cm3).
  - Caused post-operative swelling.
  - Identified on inspection.

24*

35.400 One licensee, 2 reports (cont.)

- Report 2 - prescribed 10,000 cGy, 52 Pd-103 seeds (56.6 MBq (1.5 mCi) each) to the prostate
  - Preplanned treatment plan revised periodically during implantation using ultrasound images of seed positions – D90 determined to be 82%.
  - 30 day post implant CT scan dosimetry evaluation D90 was determined to be 62.4% of the intended dose.
  - Cause - post-operative swelling.
  - Identified on inspection.

25

35.400 Wrong Site

Wrong Site

- Prescribed 10,000 cGy (rad) to the patient's prostate gland, 52 seeds (2,486.4 MBq (1.292 mCi each).
  - All implanted inferior to the prostate by 4 cm in penile bulb misread ultrasound image.
  - Discovered 42 days later during the post-implant dosimetry review.
  - The estimated dose to the prostate was 0 cGy (rad) exposure to 90% of the penile bulb was 7,399 cGy (rad).
  - Second implant planned.
  - Cause - human error. Corrective actions included providing additional instruction to personnel.

26

35.400 Wrong Activity

Wrong seed activity

- Prescribed an activity of 6.1 GBq (164.85 mCi) for a dose of 14,100 cGy (rad), but was administered 7.89 GBq (213.15 mCi) for a dose of 17,540 cGy (rad)
  - Dosimetrist entered an incorrect source strength (weaker seeds) into the planning system.
  - Total source strength 29% greater than intended and dose 24.4% greater than prescribed.
  - Discovered during post treatment review and CT scan.

27*

35.400 Wrong Activity (cont.)

- Corrective Actions:
  - During receipt and assay, highlight source strength on manufacturer's data sheet.
  - Physician and dosimetrist/physicist will ensure prior to implantation that the correct seed strength is being used and has been input in the planning system.

28

35.400 No Procedures

- **No post implant procedures**
  - Prescribed 16,000 cGy (rad) (1.512 GBq (40.875 mCi) I-125), received a dose of 12,070 cGy (rad) or 24.5% less dose.
  - Discovered during inspection.
  - Licensee did not have written procedures for prostate seed therapies that ensure the administrations are in accordance with the written directive.
  - Two other patient records had no post operational dosimetry report.
  - Licensee no longer actively engaged in brachytherapy and the authorized user is no longer with licensee.

29*

35.400 No Procedures (cont.)

- Appropriate nomogram and/or procedures referenced are no longer available.
- Corrective actions:
  - Will ensure that either procedures are established or modality authorization is removed from license.
  - The authorized user moved to another facility and utilized the same procedures.
  - Regulator is following to ensure that procedures are adequate and implemented at that new facility.

30

Medical Events 2018

35.600 Medical events **9**

HDR

- Gynecological 9(10)
  - Device malfunction 1
  - Wrong site 5
  - Wrong plan 1
  - Catheter 1
  - Unidentified human error 1

31

35.600 Wrong site - Guide Tube

Wrong site - guide tube lengths

- Prescribed 2,400 cGy (rad) to the uterus in three equal fractions using three guide tubes – received 1,600 cGy (rad).
- All three source guide tubes in final fraction were too long (132 cm instead of 120 cm in length) and the entire 800 cGy (rad) was delivered to the vagina.
- The patient returned for monitoring - very mild skin reaction that resolved without any major intervention.

32*

35.600 Wrong site - Guide Tube (cont.)

- Cause - human error
- Corrective Actions:
  - Store the black end guide tubes (120 cm) on the wall and the green end guide tubes (132 cm) on a different rack, instead of the same storage rack.
  - Doctor will also use a ruler to verify the length of the guide tubes before each treatment.

33

35.600 HDR Events

Wrong site - did not correct catheter length

- Prescribed three fractions - intended target receiving 50% of the prescribed 1,400 cGy (rad) and unintended tissue (thighs) received 700 cGy (rad).
- Catheter length should have been 1500 mm, the planner noticed length incorrectly set at 1293 mm and changed the setting to 1500 mm, but failed to press the enter key.
- Plan approved with incorrect setting and first and second fractions completed.
- Another physicist reviewed the plan and discovered the error before third fraction.

34*

35.600 Did Not Correct (cont.)

- Error was due to the failure of the technician to correctly change the distance in the treatment plan.
- Failure of individuals who reviewed the first two treatments to catch the error.
- Corrective Actions:
  - Treatment plan developed to correct the exposure to the intended tissue.
  - Individuals received additional instruction on performing thorough reviews of treatment plans prior to performing a treatment.

35

35.600 Wrong site

- **Prescribed two fractions at 500 cGy (rad) to the vaginal cuff per fraction**.
- In first fraction, a vaginal cylinder was placed in the vaginal canal and the positioning was verified with a cone beam CT scan and cylinder was then connected to the afterloader.
- After completing the treatment, the vaginal cylinder was discovered dislodged from the initial position and between the patient's legs, estimated 500 cGy (rad) skin dose – no erythema at discovery.

36*

35.600 Wrong site (cont.)

- The patient indicated that she had coughed at some point during the treatment, which may have contributed to the dislodgement of the cylinder.
- Corrective actions:
  - Purchasing a more rigorous immobilization device for the applicator.
  - Research/review and update the brachytherapy monitoring procedures and devices throughout the system.

37

35.600 Wrong Site - 2 patients

Wrong Site - 2 patients

- Both patients - prescribed 1,000 cGy (rad) to the vaginal cavity across two fractions, but only received 5% of dose at the target area.
- Both received 1,000 cGy (rad) to distal part of the vaginal wall instead of 200 cGy (rad) for first patient and 50 cGy (rad) for second patient.
- Technician entered applicator length of 120 cm into the device console, instead of 125 cm; caused 5 cm offset.

38*

35.600 Wrong Site - 2 patients (cont.)

- Two years earlier, the length of the vaginal applicator changed from 120 cm to 125 cm.
- Corrective Actions:
  - Reorganized applicator and catheter storage – separate cabinet for applicator using different treatment length.
  - Added and posted time out procedure with items to be verified before treatment.
  - Quality Management Program form - added total length of the rigid tube connected to the transfer tube verification and color coded high-risk items

39*

35.600 Wrong Site - 2 patients (cont.)

- Corrective Actions (cont.):
  - Annual review training by physicist for AUs, AMPs, and therapists emphasizing the importance of time out and verifying planned parameters versus delivery parameters and that rigid guide tube and the transfer guide tube total length can differ between applicators.
  - Conducted risk management meeting to further analyze their workflow in place.

40

35.600 Applicator Position

Wrong site - applicator position

- Prescribed four fractions - bowel (non-target) tissue received in excess of 50 cSv (rem) and 150% of the expected dose from all fractions.
- Cause - positioned the uterus/ovary applicator in the wrong location on last fractions.
- Intended target tissue received the intended dose in each fraction.
- Did recalculation with larger volume below reporting level.

41

35.600 Copied Wrong Length

Copied wrong length for catheter

- Prescribed 550 cGy (rad) over five fractions for a total dose of 2,750 cGy (rad) to the cervix.
- Using a Syeb-Neblett Template and seven catheters (two being 25 cm in length and five being 30 cm in length).
- Inferior surface of the right vaginal wall (2 cc volume and approximately 5 cm from the cervix) received total of 726 cGy and 236 cGy from later make up treatment - intended to receive 590 cGy (rad) over the five fractions - Difference of 372 cGy (rad) or 63%.

42*

35.600 Copied Wrong Length (cont.)

- Physicist copied the catheter length from one of the 25 cm catheters in first fraction plan and pasted it into two of the 30 cm catheter locations in second, third, and fourth fraction plans.
- Error identified prior to administering fifth fraction.
- Patient ultimately received the full intended dose to the tumor.
- Corrective Actions:
  - Updated procedures to record catheter lengths in a separate document during measurement.
  - No longer use different catheter lengths.

43

35.600 Equipment Failure

Equipment failure - Varian model GammaMed Plus

- Intended to receive the last of three HDR treatment fractions, with a total treatment time of 222.6 seconds divided through eight source positions.
- 25 seconds into the treatment, the HDR unit issued an inactive source error and retracted the source.
- The physicist confirmed that the source had retracted.
- Manufacturer recommended to turn console key off and then back on - failed 25 seconds into reset treatment.

44*

35.600 Equipment Failure (cont.)

- Remaining treatment plan saved.
- Patient - applicator removed and sent home.
- Varian service representative replaced the Geiger Muller board and verified functionality.
- The final portion of the treatment delivered a few days later without incident.
- The patient was informed at the time. The attending physician was notified 6 months later.

45

35.600 wrong treatment plan

Wrong treatment plan 1

- Prescribed 10 fractions of 625 cGy (rad) per fraction for five days (total of 6,250 cGy (rad)) – one fraction received 187% of fractional dose (1,167.3 cGy (rad)).
  - Pretreatment setup - satisfactory, included time out.
  - Test run of the dummy source for clearance of each channel – resulted in "electronic defective" error - treatment was aborted.
  - Physicist confirmed no dose delivered.
- Physicist loaded first treatment plan in the list (not the correct plan), looked at pre-treatment report, and got treatment code needed to start.

46*

35.600 Wrong Treatment Plan (cont.)

- Doctor started treatment – doctor and physicist monitored patient by closed circuit TV but not treatment console.
  - Physicist did not hear the system change to a different channel – looked at treatment console – recognized something was wrong -all the dwell times were in channel one.
  - Physicist stopped treatment; informed doctor of wrong treatment plan.
- Cause – after aborted test there was neither a time out or plan verification and treatment console wasn't monitored.

47*

35.600 Wrong Treatment Plan (cont.)

- Corrective Actions:
  - For aborted treatment - entire review process to be re-done to confirm no changes to the patient setup or treatment plan parameters.
  - Pretreatment report to be printed out, reviewed, and compared to the approved treatment plan.
  - Both treatment console and TV to be monitored at all times during treatment.
  - Training in updated time out and plan verification process.

48

35.600 HDR Events

Error not identified

- Prescribed 700 cGy (rad) per fraction - received a total of 467 cGy (rad) in first two fractions - identified before finishing scheduled third fraction.
- Cause - human error.
- Corrective Actions:
  - Amend written directive to give additional fractions to administer original dose to treatment area.
  - Update procedures and providing retraining.

49

Medical Events 2018

35.1000 Medical events		**32**
Perfexion	**2**	
Intervascular Brachytherapy	**2**	
Y-90 Microspheres	**28**	
Unidentified	1	
Therasphere ®	15	
SirSphere ®	12	

50

35.1000 Perfexion

- **Perfexion - Head frame slipped 2**
- **First** - patient's head may have slipped forward in the stereotactic frame by two millimeters.
- Collimator collision error during the treatment.
- Treatment halted - patient removed from the gamma knife.
- AU quickly looked at the frame, didn't see anything wrong, and the treatment was resumed.

51

35.1000 Perfexion Head Frame (cont.)

- **First** (cont.)
- After the treatment, the neurosurgeon noticed when removing the frame that the frame had shifted.
- Did not know when the slippage happened - dose could be 50% of the prescribed dose if during treatment.
- Licensee intended to use follow-up MRI scheduled 51 days later to help determine if medical event occurred.
- Patient died before the MRI date.

52

35.1000 Perfexion Head Frame (cont.)

- **Second** -The planned 2,500 cGy (rad) for 36.8 minute 0.1 cc. trigeminal neuralgia treatment at single position.
- Eight to nine remaining - significant patient movement but complied when asked to hold still.
- 4.04 minutes remaining - treatment stopped when the head fixation frame had shifted.
- Anterior pins almost touching the skin two inches above the original pin sites.

53

35.1000 Perfexion Head Frame (cont.)

- **Second (cont.)**
- Estimated doses:
  - Unintended 0.1 cc target volume received approximately four to five minutes of dose or roughly 270 to 340 cGy (rad).
  - The intended treatment site received between 2,230 and 2,160 cGy (rad).
- Incident to be covered in annual training review.
- Elekta contacted to assess possibilities for managing the frame fixation issue.

54

35.1000 Intravascular Brachytherapy

Wrong site – same licensee 2

- **First** - prescribed to receive 1,840 cGy (rad) to a coronary artery – received 0. Regulator estimated aorta 60 mm proximal to the intended target received 66 cSv (rem).
- Aborted after attempting to reach treatment site three times.
  - The source train retracted without complication
  - No procedural or regulatory violations and no equipment failures.

55

35.1000 Intravascular Brachytherapy

- **First** (cont.) -
- License discussion on general reporting requirements.
  - Desire to classify torturous anatomy as patient intervention.
  - Desire to convert tissue equivalent dose to a whole body effective dose.
- Regulator clarification – agreed the root cause was torturous patient anatomy but disagreed that it is classifiable as patient intervention.

56

35.1000 Intravascular Brachytherapy

- **Second** - prescribed 1,840 cGy (rad) to the circumflex artery - received 0. Unintended site received 98 cGy (rad).
- Attempted procedure three times - source stopped 10 mm proximal to the treatment site - junction between the left coronary and circumflex artery.
- Aborted treatment - source retracted - no indication of delivery catheter kinks.

57

35.1000 Intravascular Brachytherapy

- **Second (cont.)**
- Root cause:
  - Tortuous patient anatomy
  - Failure to follow procedure of inserting the delivery catheter, then withdrawing the guide wire and then extending it back down the catheter tubing as a "dummy run" to check for restrictions prior to sending the source train.
- Corrective Actions:
  - Additional personnel receiving training and commit to follow previously submitted procedures.

58

35.1000 Medical Events

Y-90 Microspheres	**33**
Unknown	1

59

35.1000 Unknown Y-90 Events

Unknown **1**

- Received 76% of the planned dose
- Remainder of activity leaked out because of a faulty stopcock assembly.
- The affected area was contained and decontaminated.

60

35.1000 Medical Events

Y-90 Microspheres **28**

Therasphere ®		**15**
– Overdose	3	
– Wrong lobe	1	
– Air bubbles	2	
– Kink	2	
– Stasis	1	
– Catheter diameter	2	
– Calibration date	1	
– Equipment failure	3	

61

35.1000 Y-90 Therasphere® Events

Over dose – no procedures or not followed

- Prescribed 12,000 cGy (rad); Received 69,800 cGy (rad)
  - The correct dose order either was never received by Nordion/BTG or was never ordered.
  - Staff did not properly assay the microspheres in the hot laboratory and did not reconcile it with the prescribed dosage.
  - Dosage was not confirmed prior to administration. Did not perform additional time-out to use the usual time-out checklist in addition to confirming the prescribed and assayed dose to be infused.

62

35.1000 Y-90 Therasphere® Events

Over dose – no procedures or not followed (cont.)

- Adequate documentation process did not exist - needed document retention for dose orders.
- Now a formal time-out in the procedure room when a dosage is brought into treatment room - includes the same checklist as the original procedural time-out, in addition to the prescribed and assayed dosage.
- Dosage assay process and documentation requires two nuclear medicine technologists.
- Enhanced radiopharmaceutical ordering and shipment tracking and reconciliation process.

63

35.1000 Y-90 Therasphere® Events

Over dose – no procedures or not followed (cont.)

- Retain all radiopharmaceutical ordering forms and written directives.
- Revise Written directive worksheet to differentiate between prescribed and administered dosage.
- Used patient identifiers in the Nordion/BTG order reference number field.
- Add administered dosage in standard radiology report template.
- Provide training to interventional nursing and associates in post procedural care and radiation safety for microsphere patients.

64

35.1000 Y-90 Therasphere® Events

Over dose - wrong patient

- **Prescribed 25,100 cGy (rad) to the liver, recieved 56,200 cGy (rad).**
  - Dose intended for a different patient.
  - Cause: human error
  - Corrective actions: procedural review and revision and personnel retraining.

65

35.1000 Y-90 Therasphere® Events

Over dose - vial labeling error

- Two liver lesions - treatment with two vials.
- One vial contained an activity of 7 GBq (189.19 mCi) and the other contained 9 GBq (243.24 mCi).
- Doctor reviewed the treatment records and discovered labeling error and vials may have been switched.
- Smaller lesion received the larger dose and the larger lesion received the smaller dose.

66

35.1000 Y-90 Therasphere® Events

Two lobes - dose to wrong one

- Prescribed 584.6 MBq (15.8 mCi) to the left lobe (230 cc volume) and 3,996 MBq (108 mCi) to the right lobe (1,600 cc volume).
- Left lobe's dose was delivered to the right lobe.
- Right lobe received 1,760 cGy (rad) 15 % of prescribed 12,000 cGy (rad) dose.
- Corrective actions: generating a new procedure and providing new training to personnel.

67

35.1000 Y-90 Therasphere® Events

Air bubbles

- Prescribed 12,700 cGy (rad), received 5,980 cGy (rad) - 47% of dose.
- Two vials – no issues with first; second was relatively full when returned for disposal and activity higher than expected.
- Physician saw multiple air bubbles trapped in the line After connecting line between the microcatheter and the delivery vial.

68

35.1000 Y-90 Therasphere® Events

Air bubbles (cont.)

- Three-way stopcock and syringes used to bleed out air and flush back dose to the patient
  - Prevented spillage or contamination and residual dose was retained in the syringes and stopcocks.
  - Activity remained in delivery equipment and did not go into the patient.
- The root cause: human error.
- Corrective Actions: refresher training and change procedure to confirm no air is not in the line between the microcatheter and the dose vial prior to connection.

69

35.1000 Y-90 Therasphere® Events

Air bubbles - possible kink

- Prescribed 1.232 GBq (33.3 mCi) to the right lobe of the liver, received 451 MBq (12.19 mCi) 36% to the right lobe and planned 42 MBq (1.14 mCi) to the lungs.
- No issues with catheter placement, position verification, flow during contrast and normal saline phases,
- Administration started - interventional radiologist saw several small air bubbles in the delivery line, experienced high resistance (saline went into vented vial), and stopped procedure.

70

35.1000 Y-90 Therasphere® Events

Air bubbles - possible kink (cont.)

- Used PET scanner to evaluate the activity in patient and delivery system.
- The cause: either a small air pocket or kink in the catheter - delivery system and catheter were sent to the vender for evaluation.
- Corrective Actions: proper setup of the delivery system retraining.
- Procedures modified - to check for air bubble before piercing the dose vial, and perform wet connection when connecting the catheter to the delivery system.

71

35.1000 Y-90 Therasphere® Events

First kink

- Prescribed 13,500 cGy (rad), received 4,900 cGy (rad) - 36.3% of dose.
- Not sure if caused by patient stasis or delivery system.
- Authorized user physician had used a thinner micro-catheter (2.4 French Maestro) but manufacturer indicated catheter size commonly used
- Tortuous path caused resistance in the circuit higher than the administration box could tolerate and delivery system could not work properly.
- Concluded problem was not due to patient stasis.

72

35.1000 Y-90 Therasphere® Events

First kink (cont.)

- Manufacturer evaluated the Y-90 kit for cause.
  - Microspheres found from outlet tubing to microcatheter.
  - Location of observed kinks had elevated radiation readings.
  - Pressure/Flow tests confirmed set functioned as expected.
  - Septum fragment in the dose vial did not block the flow path.
  - Obstruction within the microcatheter.
- Root cause: obstruction within the microcatheter due to a kink.
- Difficulty placing the catheter before the treatment may have increased likelihood of a kink.

73

35.1000 Y-90 Therasphere® Events

Second kink

- Prescribed 12,300 cGy (rad) to segment II of the left hepatic lobe, received 2,950 cGy (rad).
- Back pressure during the treatment with significant flow of saline into the pressure relief vial.
- Procedural images reviewed to look for failure.
  - Catheter was kinked and likely created the blockage.
  - Catheter moved between verification and administration from manipulation of the system connected to the catheter.

74

35.1000 Y-90 Therasphere® Events

Second kink (cont.)

- Delivery system sent to manufacturer for evaluation - no problem identified.
- Corrective Actions:
  - Physician and RSO will monitor the pressure relief vial for increased back pressure.
  - Have verbal countdown for administration pressure during the administration.
  - Terminate procedure when excessive back pressure cannot be corrected by simple catheter manipulation.

75

35.1000 Y-90 Therasphere® Events

Resistance - complex hepatic arterial system (stasis)

- Prescribed 12,000 cGy (rad) to segment four of the left lobe of the liver, received 640 cGy (rad) - 5% of dose.
- All pre-procedural safety checks conducted and appropriate imaging (cone beam CT) performed for catheter position and lesion location.
- High resistance felt on the syringe during the first set of infusions, and continued for the next few infusions.
- Stopped the treatment - risk of inadequate delivery of the microspheres due to possibility of stasis and concern for non-target embolization to other sites.

76

35.1000 Y-90 Therasphere® Events

Resistance - complex hepatic arterial system (cont.)

- PET CT post procedure for microsphere distribution - no non-targeted deposition.
- Undelivered microspheres were in the catheter.
- Licensee concluded incident due to emergent patient conditions and resistance of the patient's complex hepatic arterial system (stasis).
  - No evidence of catheter misplacement.
  - No non-target disposition.
  - No mechanical failure of the microsphere delivery system.
  - No evidence of any non-compliance with NRC guidelines.

77

35.1000 Y-90 Therasphere® Events

Catheter diameter

- Prescribed 2.29 GBq (62 mCi), received 1.37 GBq (37 mCi) 40% of dose.
- Two vials – no issues with first; 51% of second vial microspheres stuck in the catheter.
- Primary cause was equipment malfunction.
  - Catheter and device tubing sent to manufacturer.
  - Manufacturer concluded microspheres remained in the catheter because the catheter used had a internal diameter (0.4 mm) smaller than manufacturer requirements (> or = 0.5 mm).
- Will use larger diameter catheters in future.

78

35.1000 Y-90 Therasphere® Events

Catheter diameter too small

- Prescribed 22,000 cGy (rad), received 10,710 cGy (rad).
  - Particularly tortuous anatomy - after consulting with manufacturer and used a smaller 2.0 Fr catheter.
  - Microspheres stuck in the micro-catheter.
  - Delivery kit and catheter sent to the manufacturer - visual investigation, radioactive measurement, and digital microscope/flow tests - results in line with licensee's initial conclusion.
- Later procedure with larger microcatheter successful.
- Physician will continue to use larger microcatheters.

79

35.1000 Y-90 Therasphere® Events

Calibration date error

- Prescribed 11,000 cGy (rad) to the right lobe, administered 1,790 cGy (rad) - 16% of dose.
  - Administered microspheres with calibration date of 7/28/2019 instead of a calibration date of 8/4/2019.
  - Technologist and AU reviewed the ordering paperwork but failed to identify the incorrect calibration date prior to ordering.
  - Compared the dose activity to the order form instead of the written directive.
  - Used vender provided locked spreadsheet to determine ordering dose but it does not flag when a dose varies significantly from the prescribed dose.

80

35.1000 Y-90 Therasphere® Events

Calibration date error (cont.)

- TheraSphere doses must be ordered in GBq, but licensee is more familiar with mCi; technologist and AU did not recognize that the activity was abnormally low.
- Corrective Actions:
  - Modified the spreadsheet to flag doses not within 10% of the prescribe dose on the day of administration.
  - Technologist and AU will review the written directive and ordering form together prior to administration to ensure that there are no discrepancies with the prescription or dose.

81

35.1000 Y-90 Therasphere® Events

Leak at injector needle/septum interface

- Prescribed 12,000 cGy (rad) to the left lobe of the liver, received 8,090 cGy (rad) - 67.42% of dose.
- Delivery system sent to manufacturer - visual inspection, radiation measurement, digital microscopy, and pressure/flow testing.
  - Microspheres were in the acrylic vial shield indicating a leak at the injector needle/septum interface.
  - Thought to be from product defect - routine administration pressures do not produce this kind of leak.
  - No damage or visible defect was observed on the delivery system or dose vial.

82

35.1000 Y-90 Therasphere® Events

Tubing defect

- Prescribed 20,800 cGy (rad), received 14,500 cGy (rad) 69.7% of intended dose.
- Two vials – no issues with first; second vial failed to empty into the administration catheter further attempts were unsuccessful.
- The vial and administration kit sent to manufacturer for analysis.
  - The tubing had a manufacturing defect that restricted flow and eventually caused the blockage.
  - The defect could not be seen or felt by inspection.

83

35.1000 Y-90 Therasphere® Events

Microspheres tubing/catheter connector

- Prescribed 14,300 cGy (rad), received 5,434 cGy (rad) - 38.5% of dose.
- Dose stayed in the connector of the tubing and catheter.
- Manufacturer tested tubing and catheter; found flow through the catheter insufficient possibly from:
  - Overall length and inner diameter of the microcatheter.
  - Septum fragments from the dose vial.
  - Possible changes from time of treatment to inspection (e.g., dried saline, coiled in tight bends for extended time, etc.).
- AU did not use manufacturer's recommended size microcatheter.

84

35.1000 Y-90 Therasphere® Events

Microspheres tubing/catheter connector (cont.)

- Several potential causes and contributing factors – no definitive root cause.
- Corrective Actions:
  - Continue to follow their standard operating procedure of performing three flushes, ensuring the electronic dosimeter is reading zero, and surveying the patient.
  - Flush an additional time with 20 ml of saline after the electron dosimeter reads zero.
  - Use a catheter with a diameter greater than or equal to 0.02 inches.

85

35.1000 Medical Events

SirSphere ®	12
– Wrong site	4
– Measurement issue	1
– Equipment	1
– Catheter	5
– No information	1

86

35.1000 Y-90 SirSphere® Events

Wrong site – other lobe and stomach

- Prescribed 1.16 GBq (31.3 mCi) to the right lobe of the liver, received 2,900 cGy (rad) to the right lobe of the liver - 63.2% of the dosage, 2,170 cGy (rad) to the left lobe - 33.5% of the dosage, and 9,190 cGy (rad) to the stomach - 3.3% of the dosage.
  - Post-treatment Bremsstrahlung scan - microspheres in left lobe and stomach.
  - Prescribed prophylactic medication to help prevent ulceration.
  - Subsequent nausea and vomiting.

87

35.1000 Y-90 SirSphere® Events

Wrong site other lobe and stomach (cont.)

- Endoscopy 24 days later - mild to moderate erythema in the gastric antrum - expected to resolve in one to two weeks with continued treatment.
- Most likely cause:
  - Undetected movement of the catheter tip.
  - Possibly from patient movement.
  - Movement exacerbated by reduced slack in the catheter after pulling it back to correct its initial position.
- Corrective Actions: updating procedures and retraining personnel.

88

35.1000 Y-90 SirSphere® Events

Wrong site – spleen

- Prescribed to receive 779.22 MBq (21.06 mCi) to the liver, received 114.7 MBq (3.1 mCi) – 15% of dosage
- 259 MBq (7 mCi) [10,648 cGy (rad)] delivered to the patient's spleen.
  - Felt syringe pressure - using smaller gauge syringe made no difference – stopped treatment.
  - Microspheres clumping in the catheter and obstructing flow.
  - Suspected during catheter withdrawal the microspheres flowed into the larger splenic artery.
- Three days later reported observed uptake in spleen.

89

35.1000 Y-90 SirSphere® Events

Wrong site – spleen (cont.)

- Results of investigation - no physical obstruction, catheter placement was correct, no errors in the administration, no other causes identified.
- Patient monitored for any adverse impacts developed.
- Possible ways to prevent recurrence were identified and detailed in licensee's report. Corrective actions included generating a new written procedure.

90

35.1000 Y-90 SirSphere® Events

Wrong site – work around

- Patient scheduled for treatment to segments 7 and 8 of the right lobe of the liver, followed by second administration to segments 5 and 6 of the right lobe.
- Written directive - first treatment to left lobe, but already surgically removed.
  - Manufacturer's calculation sheet did not allow two treatments to the same lobe.
  - Authorized user put one treatment in each lobe to get activity for each part of the right lobe.
  - Not corrected when going from planned treatment to written directive.

91

35.1000 Y-90 SirSphere® Events

Wrong site - work around (cont.)

- Radiation Safety Office prepares the written directive for signature of the authorized user.
- Authorized user failed to correct the written directive error but realized after first treatment.
- Intended for the right lobe and administered correct dosage to the right lobe.
- Discovered 22 days later.

92

35.1000 Y-90 SirSphere® Events

Wrong site - work around (cont.)

- Corrective Actions:
  - Revised written directive preparation procedures.
  - Added another time-out for treatment details.
  - Trained all authorized users on modifications.
  - The authorized user not Radiation Safety Office to complete the written directive.
- Radiation Safety personnel present before procedure start to verify the correct patient is treated, the proper dose is administered, and the proper site is treated.

93

35.1000 Y-90 SirSphere® Events

Wrong lobe

- Prescribed 647.87 MBq (17.51 mCi) to the left lobe of the liver and 777 MBq (21 mCi) to the right lobe at a later date.
  - Facility typically treats right lobe before the left.
  - Failed to follow the written directive and recognize for this case, the left lobe was to be treated first.
  - Dosage administered to the right lobe was less than 20 percent of the planned later dosage.
  - The interventional radiologist discovered the error shortly after the procedure but did not think it had to be reported.

94

35.1000 Y-90 SirSphere® Events

Wrong lobe (cont.)

- Event discovered during routine inspection.
  - The written directive was not followed.
  - Dosage was delivered to an unintended site, this event should have been reported.
- Corrective Actions:
  - Revised policy and procedures.
  - Will prominently note the treatment lobe and stating the Y-90 procedure in the interventional radiology schedule and procedure board.
  - Time-out prior to the procedure start will include stating the laterality of the lobe.

95

35.1000 Y-90 SirSphere® Events

Licensee 1, Issue 1 - Aliquot

- Prescribed 429.2 MBq (11.6 mCi), received 316.72 MBq (8.56 mCi) - 74% of dosage.
- Dosage of 425.5 MBq (11.5 mCi) was small portion of the 7.13 GBq (192.6 mCi) in the unit vial.
- Microspheres remained in the administration system.

96

35.1000 Y-90 SirSphere® Events

Licensee 1, Issue 1 – Aliquot (cont.)

- Corrective Actions:
  - Order a dosage calibrated to give an activity closer to that needed for the date and time of administration.
  - Draw 10% greater than prescribed dosage for low administration activity.
  - Flushed system more in hopes of pushing more of the residual activity into the patient.

97

35.1000 Y-90 SirSphere® Events

Licensee 1, Issue 2 - Equipment

- Prescribed 1.2 GBq (32.43 mCi), received 0.46 GBq (12.43 mCi) – 38 % of dosage and less than 20% of dose.
- Interventional radiologist reported resistance in the line, with microspheres appearing to come out the top of the vial.
- Consulted with onsite manufacturer's representative.

98

35.1000 Y-90 SirSphere® Events

Licensee 1, Issue 2 – Equipment (cont.)

- The vial and administration kit sent to manufacturer for analysis.
  - Cause was failure of the administration equipment setup.
- Corrective Actions:
  - Use an updated administration set up for all future administrations.
  - Completed the patient administration - new written directive and new administration kit.

99

35.1000 Y-90 SirSphere® Events

Licensee 2, Issue 1 – Catheter backflow

- Two administrations – no issues with first – backflow into administration vial seen in second.

- Prescribed 453.99 MBq (12.27 mCi) to the right lobe in second administration, received 28% of the dosage.

100

35.1000 Y-90 SirSphere® Events

Licensee 2, Issue 2 – Catheter clogged

- Prescribed 1,100 cGy (rad) to segments 5 and 8 of the liver, received 250 cGy (rad) - 23%.
- Cause: a clog or other issue with either the stopcock or the microcatheter.
- Corrective action: procedure updates

101

35.1000 Y-90 SirSphere® Events

Catheter – Clogged/tip

- Received 31,500 cGy (rad) - 65% of dose
  - Issues with the delivery catheter during the procedure - catheter clogged, removed, and replaced during the procedure.
  - Thought Direxion HI-FLO microcatheter and angled tip was root cause of the clog.
- Manufacturer indicated all types of catheters can clog in normal use - plan other following up.
- Authorized user will use a microcatheter without the angled tip to avoid a similar event.

102

35.1000 Y-90 SirSphere® Events

Catheter - Occluded

- Prescribed 1.5 GBq (40.541 mCi), received 0.07 GBq (1.892 mCi) - 4.7% of dosage.
- The catheter could not be flushed - procedure stopped.
- First time using Embolx Sniper Microcatheter lot #EMB112818-05.
  - Uses a balloon to prevent potential backflow of the dose.
  - Smaller lumen than the catheters routinely used for this purpose.
- Catheter model will not be used for future treatments.

103*

35.1000 Y-90 SirSphere® Events

Patient movement dislodged IV

- Prescribed to receive 579.42 MBq (15.66 mCi), received 358.16 MBq (9.68 mCi).
- It was stated that the patient moved during the procedure and dislodged the IV.
- Licensee concluded no corrective actions needed to prevent recurrence.
  - Incident did not result in permanent functional damage to an organ.
  - Unavoidable due to patient movement.

104

35.1000 Y-90 SirSphere® Events

Prescribed dosage, received 68% of the drawn activity.

105

Acronyms

- µCi – microcurie
- AMP – authorized medical physicist
- AU – Authorized User
- cGy – centiGray
- CT – computed tomography
- FY – Fiscal Year
- GBq – Giga Becquerel
- HDR – High Dose Rate Remote Afterloader
- I-124 – Iodine-124
- I-131 – Iodine-131
- IVB – Intravascular Brachytherapy

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Acronyms

- Lu-177 – Lutetium-177
- MBq – Mega Becquerel
- mCi – millicurie
- MIBG - Metaiodobenzylguanidine
- Pd-103 – Palladium-103
- PET – positron emission tomography
- Ra-223 – Radium-223
- RSO – radiation safety officer
- SI units – International System of Units
- Sm-153 – Samarium-153
- Y-90 – Yttrium-90

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United States Nuclear Regulatory Commission
Protecting People and the Environment

QUESTIONS?

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U.S.NRC
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Protecting People and the Environment

Interventional Radiologist Subcommittee Report

Megan Shober
Advisory Committee on the Medical Uses of Isotopes
March 30, 2020

Subcommittee Members

- Vasken Dilsizian, MD
- Ronald Ennis, MD
- Hossein Jadvar, MD
- Darlene Metter, MD
- Megan Shober (Chair)

NRC staff resource: Dr. Katie Tapp

U.S.NRC
United States Nuclear Regulatory Commission
Protecting People and the Environment

Why?

- Concerns over yttrium-90 (Y-90) medical events
- Licensing issues with Y-90 microspheres
- Other emerging radiotherapies involving interventional radiologists (IR)
- Relative lack of IR expertise among present ACMUI members

Subcommittee Charge

- Investigate the need for an IR on the ACMUI.
- Determine whether this position should be a non-voting consultant or full ACMUI member.

ACMUI Membership

- Currently 13 members
- ACMUI positions last amended in 2009
  - Added Diagnostic Radiologist
- Changes to ACMUI positions require Commission approval.

Considerations

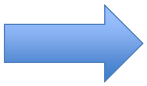
- ACMUI already has a diagnostic radiologist, a nuclear medicine physician, and two radiation oncologists.
  - Can be authorized users for microsphere therapy
  - Have skill sets that partly overlap with IR
  - Are not IR subject matter experts

Considerations

- Y-90 microspheres are the modality with the greatest number of reported medical events.
- Many Y-90 medical events are due to problems with interventional equipment (i.e., tubes, catheters).
- The IR is responsible for the equipment in the treatment room.

Considerations

- IR-administered radiotherapies are likely to increase in the future.



An IR expert could provide valuable perspective to ACMUI.

Membership?

- Is the value of the IR expertise significant enough to permanently add the position to the ACMUI?
- If considering a consultant:
  - How long?
  - Should the IR expert be an authorized user?

Recommendations

1. The Subcommittee *does not recommend* adding an IR as a full voting member of ACMUI at this time.
2. The Subcommittee *recommends* inviting an IR to be a consulting (non-voting) member of the ACMUI for a trial period of 2-3 years, after which this issue should be re-assessed.

Recommendations

3. This invitation should be extended to a practicing IR who regularly uses both types of Y-90 microspheres and who is an authorized user.

Questions?

Acronyms

- ACMUI: Advisory Committee on the Medical Uses of Isotopes
- IR: Interventional Radiologist
- Y-90: yttrium-90

U.S. Nuclear Regulatory Commission
Advisory Committee on the Medical Uses of Isotopes

Interventional Radiology Subcommittee

Draft Report

Submitted on: February 25, 2020

***Subcommittee membership**:*
Dr. Vasken Dilsizian, Dr. Ronald Ennis, Dr. Hossein Jadvar, Dr. Darlene Metter, and Ms. Megan Shober (chair). The NRC staff resource is Dr. Katie Tapp.

***Subcommittee charge**:*
At the Fall 2019 Advisory Committee on the Medical Uses of Isotopes (ACMUI) meeting, Chairman Dr. Christopher Palestro, created a subcommittee to investigate the need for an interventional radiologist on the ACMUI and to determine whether this position should be a non-voting consultant or full ACMUI member. This question was raised due to the ongoing licensing issues involving yttrium-90 (Y-90) microspheres, concerns over medical events resulting from the administration of Y-90 microspheres, the potential for other emerging radiotherapies to be administered by interventional radiologists, and a relative lack of expertise among present ACMUI members regarding interventional radiology.

***Background**:*
The ACMUI's role is to provide advice on policy and technical issues that arise in regulating the medical use of radioactive material for diagnosis and therapy, to comment on changes to NRC's regulations and guidance, to evaluate non-routine uses of radioactive material, to provide technical assistance when requested by NRC staff, and to bring key issues to the attention of the Commission for appropriate action.

The ACMUI reviews its charter on a biannual basis. In preparation for a charter review, ACMUI considers the balance of its membership. At the September 2019 ACMUI meeting, members identified a potential knowledge gap in interventional radiology.

The composition of ACMUI membership was last changed in 2009, when the ACMUI was expanded by one position to include a diagnostic radiologist[1]. Such a change in ACMUI membership requires Commission approval. For approximately one year prior to the Commission approval, the NRC staff invited a diagnostic radiologist to serve as a consultant (non-voting member) to the ACMUI.

Discussion:
The Subcommittee considered the areas of expertise of current ACMUI committee members. In 2009, when the Diagnostic Radiologist position was added to ACMUI, it was thought that this position could provide expertise in the area of existing and emerging diagnostic and image-guided therapeutic techniques, including interventional radiology. Over the past ten years, the field of interventional radiology has continued to mature and specialize. Practicing diagnostic

[1] ML092290414, SECY-09-0170, "Addition of a Diagnostic Radiologist on the Advisory Committee on the Medical Uses of Isotopes."

radiologists may not be able to provide the detailed knowledge on microspheres and other emerging technologies designed for therapeutic use by interventional radiologists.

Subcommittee members noted:

- Diagnostic radiologists and nuclear medicine physicians have familiarity with and may be part of the team that participates in microsphere therapies. However, it is the interventional radiologist who places the catheter for the intravascular administration of the dose to the treatment site.
- Radiation oncologists have training and experience to perform general intravenous radiation delivery and image-guided brachytherapy and may be part of the team that delivers microsphere therapies. Radiation oncologists typically have less experience with complex vascular liver infusions and procedures. Therefore, it is the interventional radiologist who is generally responsible for placing the catheter so the dose can be delivered to the treatment site.
- Of all medical uses of radioactive material, administration of Y-90 microspheres continues to have the greatest number of reported medical events[2].
- Many Y-90 medical events are due to problems with interventional equipment (i.e., tubes, catheters), and interventional radiologists are the subject matter experts with this equipment.
- Y-90 microspheres have the most complicated authorized user training requirements of any medical modality[3].

Subcommittee members also discussed the relative merits of adding an interventional radiologist as a consulting (non-voting) member versus adding this position as a full ACMUI member. At this time, the Subcommittee does not know whether the value of the interventional radiologist expertise is significant enough to seek Commission approval to permanently add the position to the ACMUI. However, the Subcommittee acknowledges the expertise gap currently present on the ACMUI with respect to microsphere therapy.

Recommendations:

1. The Subcommittee does not recommend adding an interventional radiologist as a full voting member of ACMUI at this time.
2. The Subcommittee recommends inviting an interventional radiologist to be a consulting (non-voting) member of the ACMUI for a trial period of 2-3 years, after which this issue should be re-assessed.
3. This invitation should be extended to a practicing interventional radiologist who regularly uses both types of Y-90 microspheres and who is an authorized user.

Respectfully submitted,
Megan Shober for the Interventional Radiology Subcommittee
Advisory Committee on the Medical Uses of Isotopes
U.S. Nuclear Regulatory Commission

[2] There were 47 medical events in calendar years 2017 and 2018 involving ytttrium-90 reported to the Nuclear Material Events Database (NMED), https://nmed.inl.gov/.

[3] ML15350A099, "Yttrium-90 Microsphere Brachytherapy Sources and Devices TheraSphere® and SIR-Spheres® Licensing Guidance," Rev. 9, February 2016.

OPEN FORUM

NO MEETING HANDOUT

September 2020

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
30	31	1	2	3	4	5 X
6 X	7 LABOR DAY	8	9	10	11	12 X
13 X	14	15	16	17	18	19 ROSH HASHANA
20 ROSH HASHANA	21	22	23	24	25	26 X
27 X	28 YOM KIPPUR	29	30	1	2	3 SUKKOT
4 SUKKOT	5	Notes				

October 2020

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
27	28	29	30	1	2	3 SUKKOT
4 SUKKOT	5	6	7	8	9	10 SHEMINI ATZERET
11 SIMCHAT TORAH	12 COLUMBUS DAY	13	14	15	16	17 X
18 X	19	20	21	22	23	24 X
25 ASTRO ANNUAL MEETING	26 ASTRO ANNUAL MEETING	27 ASTRO ANNUAL MEETING	28 ASTRO ANNUAL MEETING	29	30	31 X
1	2	Notes				