

Survey and Expert Interviews on European Legal Requirements

Session 3

15:45–17:45

Presentation of Survey Methodology and Results of Questionnaires and Expert Interviews

Jonathan Gear

Members

Lead: J. Gear

Co-leads: K. Herrmann, S. Peters

Contributors: C. Stokke, P. Covens, C. Decristoforo, R. Schulze,
B.J. Krause

Presentation of WP2

- Survey on **practical implementation** of the main requirements of European **pharmaceutical legislation** concerning therapeutic nuclear medicine
- Survey on **practical implementation** of the main requirements of **BSSD** concerning therapeutic nuclear medicine
 - Provision for individual dose planning
 - Provision for individual dosimetry verification
 - Involvement of the MPE
 - Release of patients
 - Management of radioactive effluents and waste
- Identify **gaps** in implementing the above requirements
- Identify **barriers** encountered by stakeholders in **development** of therapeutic radiopharmaceuticals
- Identify **barriers** encountered by stakeholders in the **use** of therapeutic radiopharmaceuticals

Presentation of WP2

WP2 structure

- Pre-survey: **Completed in July 2022**
- Expert interviews: **Completed in summer 2022**
- Main survey: **Closed at end of 2022**

Pre survey

WP2 established contact with competent authorities, regulators and stakeholders

Database created and contacts refined for more personal approach

Gathered relevant literature concerning national regulations and guidance to feed into WP1

Many thanks for distribution through **EIBIR**, **EANM**, **EFOMP** and **HERCA**

Pre survey

Pre-survey structure

- Radiation protection of the public
- Radiation protection of the patient
- Management of radioactive waste

- Pharmaceutical legislation concerning clinical use
- Pharmaceutical legislation concerning use in trials
- Pharmaceutical legislation concerning in-house preparation
- Pharmaceutical legislation concerning supply and distribution preparation
- Pharmaceutical legislation concerning marketing authorisation

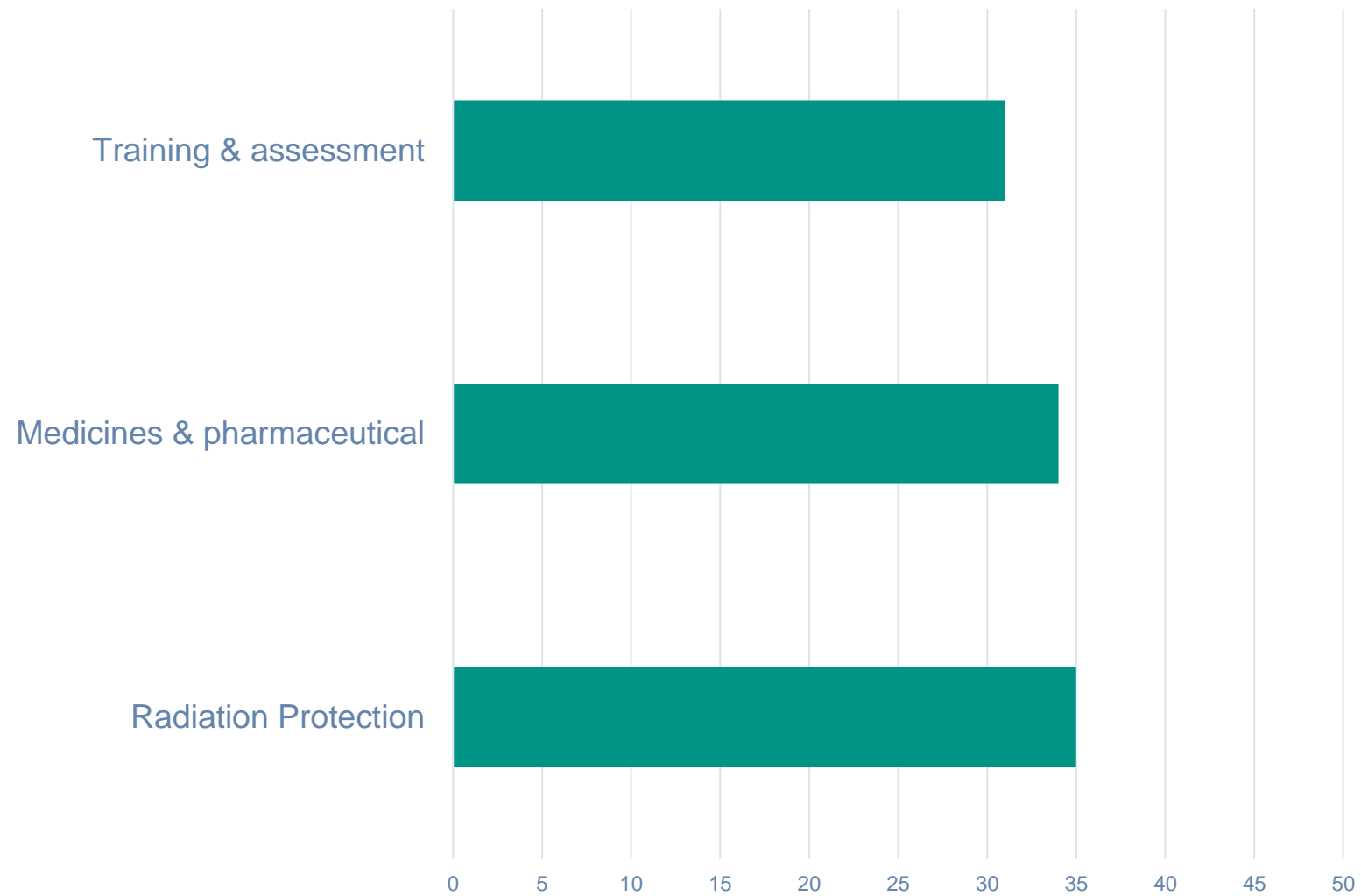
- National medical physics society
- National training school/programme for medical physics experts

Pre survey

Pre-survey results

- 61 responses received
- 2 EU countries did not respond
- Norway, Switzerland, UK, Bosnia & Herzegovina, North Macedonia and Serbia
- 150 different organisations identified
- 176 contact details were established
- 85 documents and 133 unique web links were gathered

Pre survey



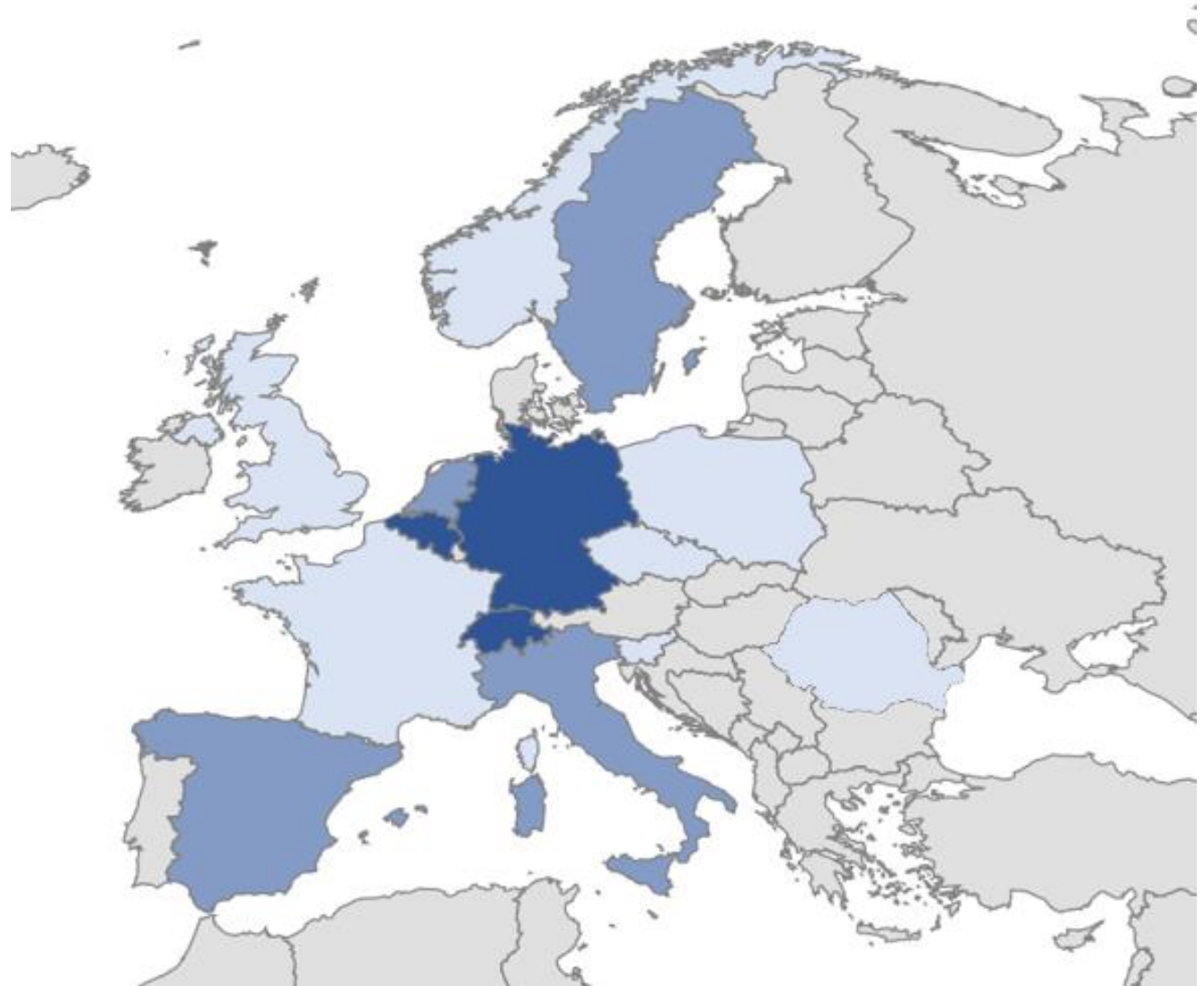
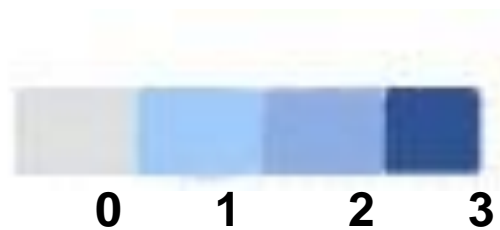
Expert interviews

- Identify **gaps** in implementing the requirements
- Identify **barriers** encountered by stakeholders in the **development** of therapeutic radiopharmaceuticals
- Identify **barriers** encountered by stakeholders in the **use** of therapeutic radiopharmaceuticals

7 national regulators, 5 from industry, 6 MPEs, 3 NM physicians,
4 radiopharmacists

Expert interviews

Distribution of interviews



Expert interviews

Interviews were conducted by different members of the WP (21 face-to-face, 4 written communication)

A written summary of interviewee answers were generated

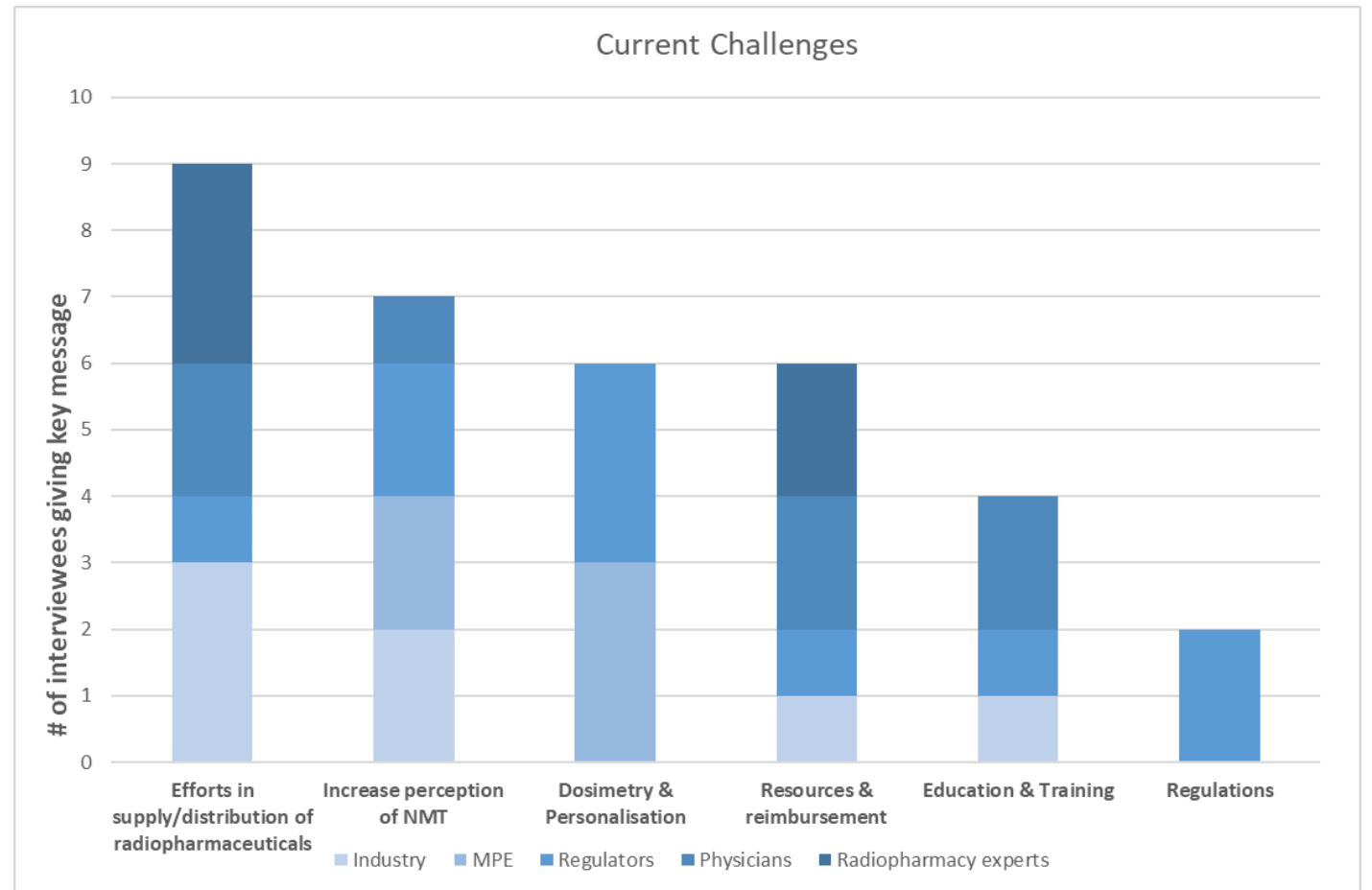
These were then cross compared for each question

Summaries compared and conclusions reported in D2.2

Summaries, conclusions and key points discussed in D2.3 alongside main survey results

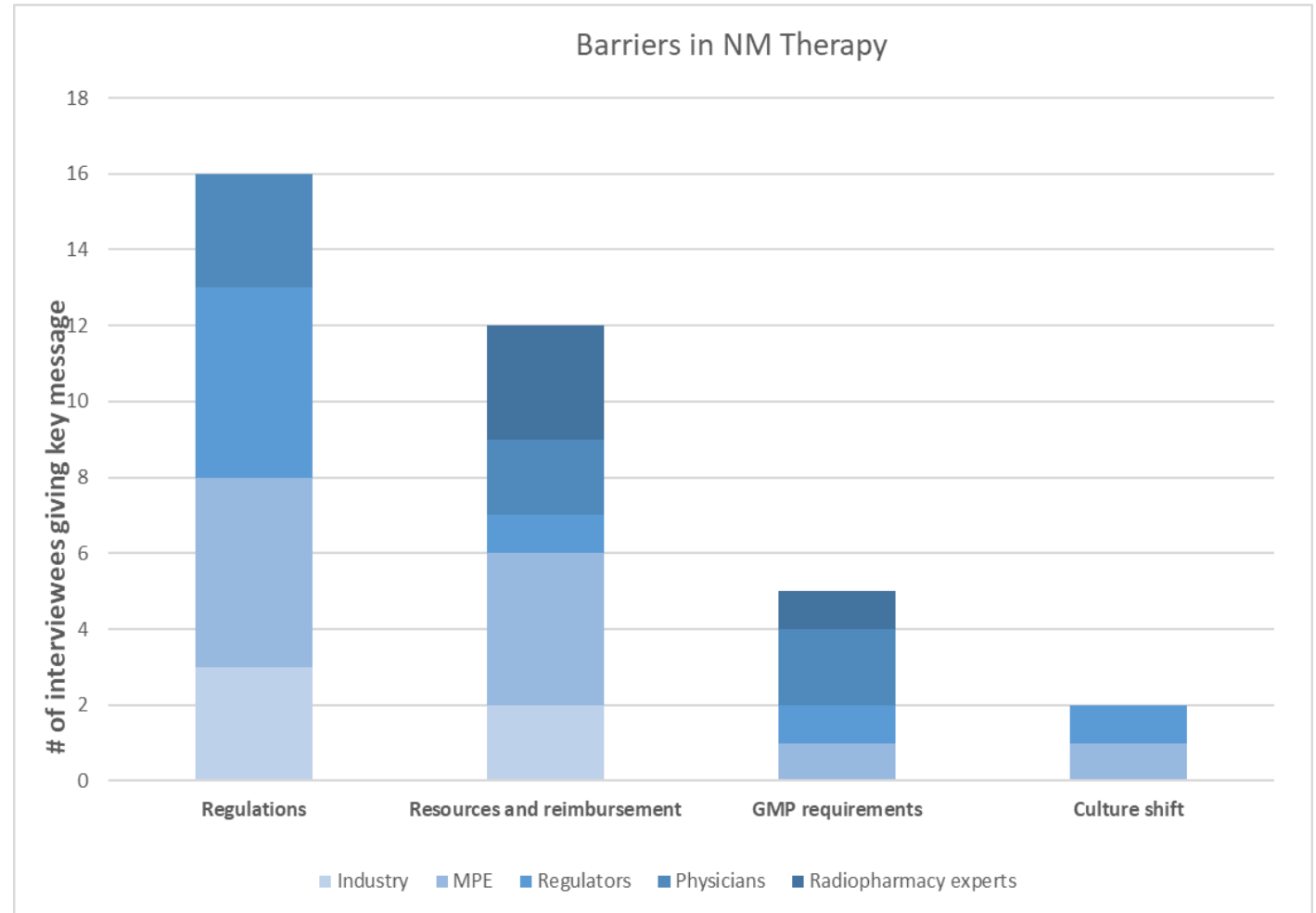
Interview questions

- What do you believe is the biggest challenge facing NMT at the present time and why?

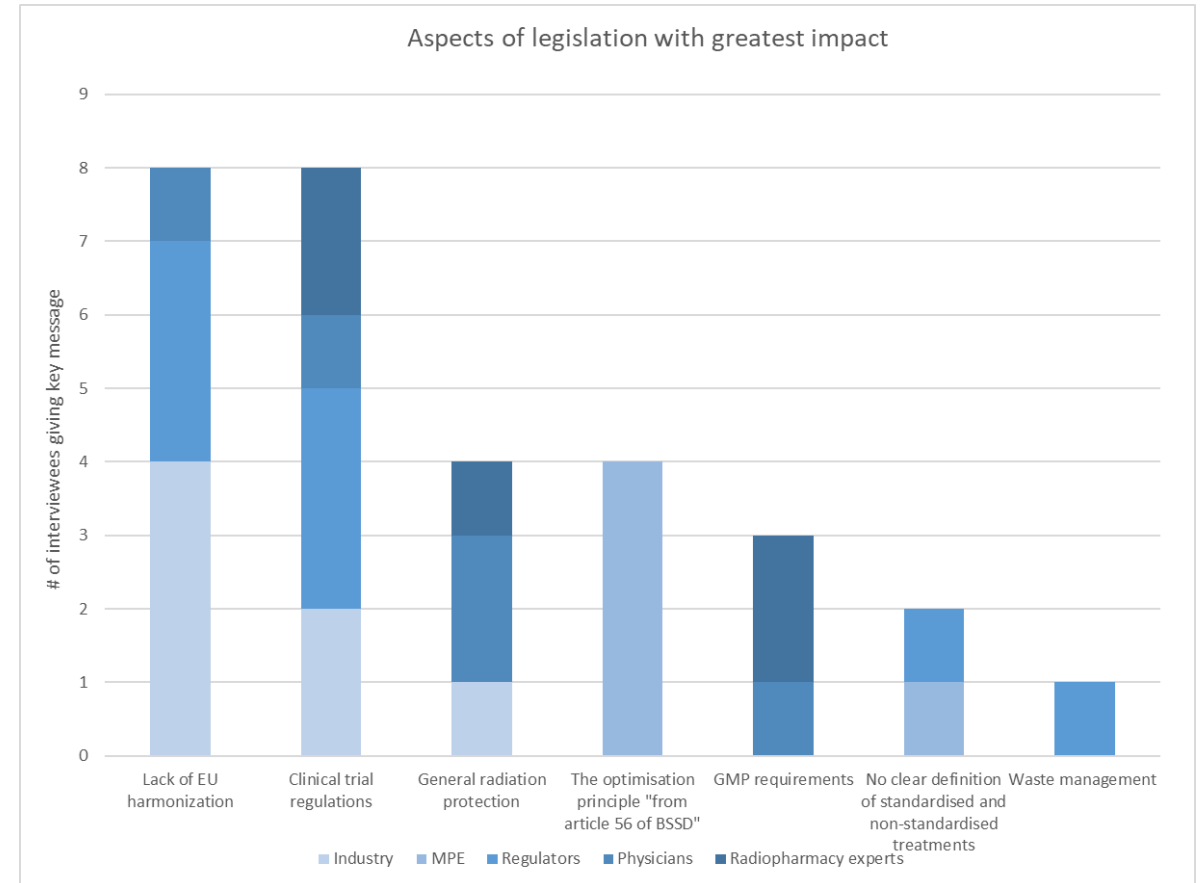


What are the barriers that you face in your work implementing/developing NMT or NMT products?

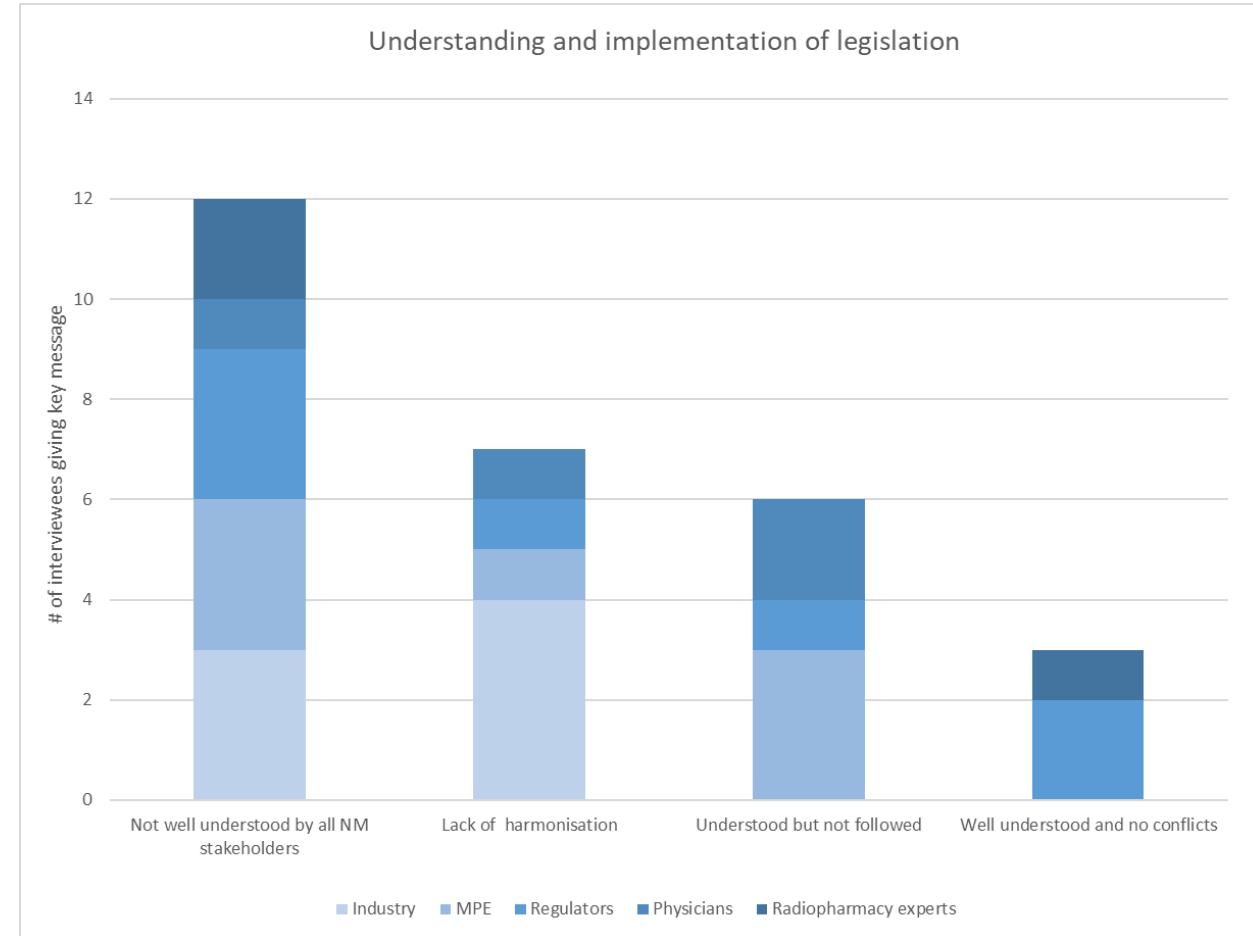
For regulators: What are the main issues you find in your regulatory role pertaining to NMT, and as a regulator how do you help tackle those issues?



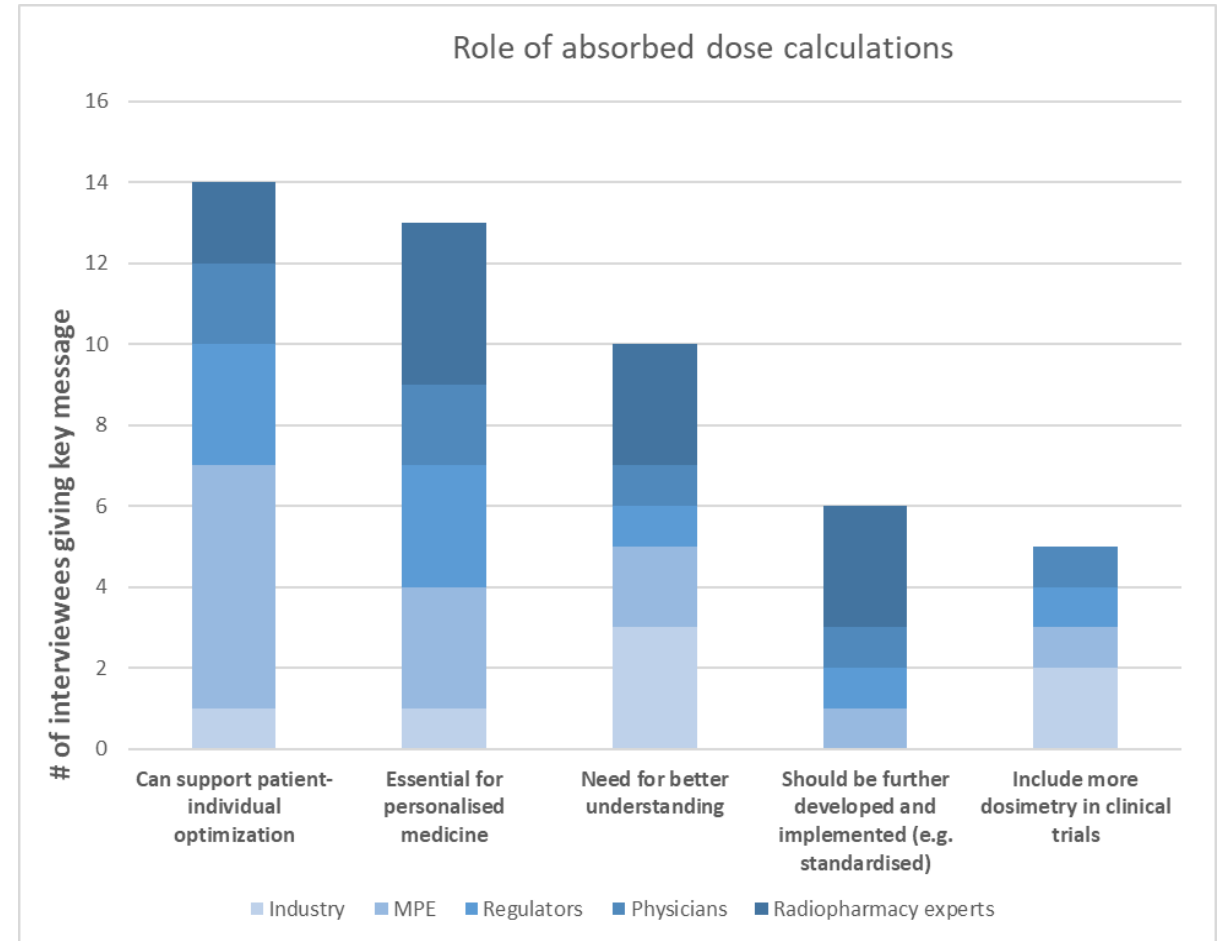
In your work relating to NMT, which aspects of national and internal legislation have the greatest impact?



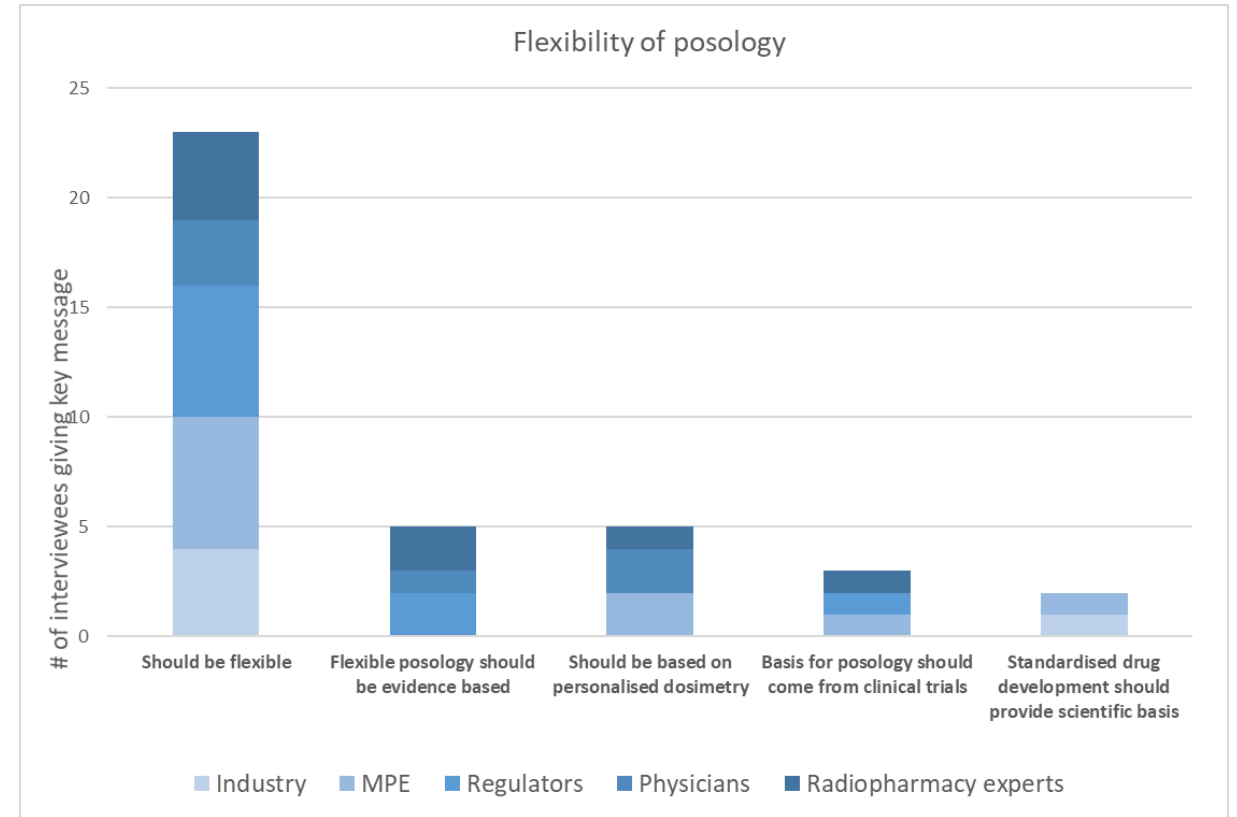
Do you think legislation is clearly understood and interpreted across all NMT stakeholders?



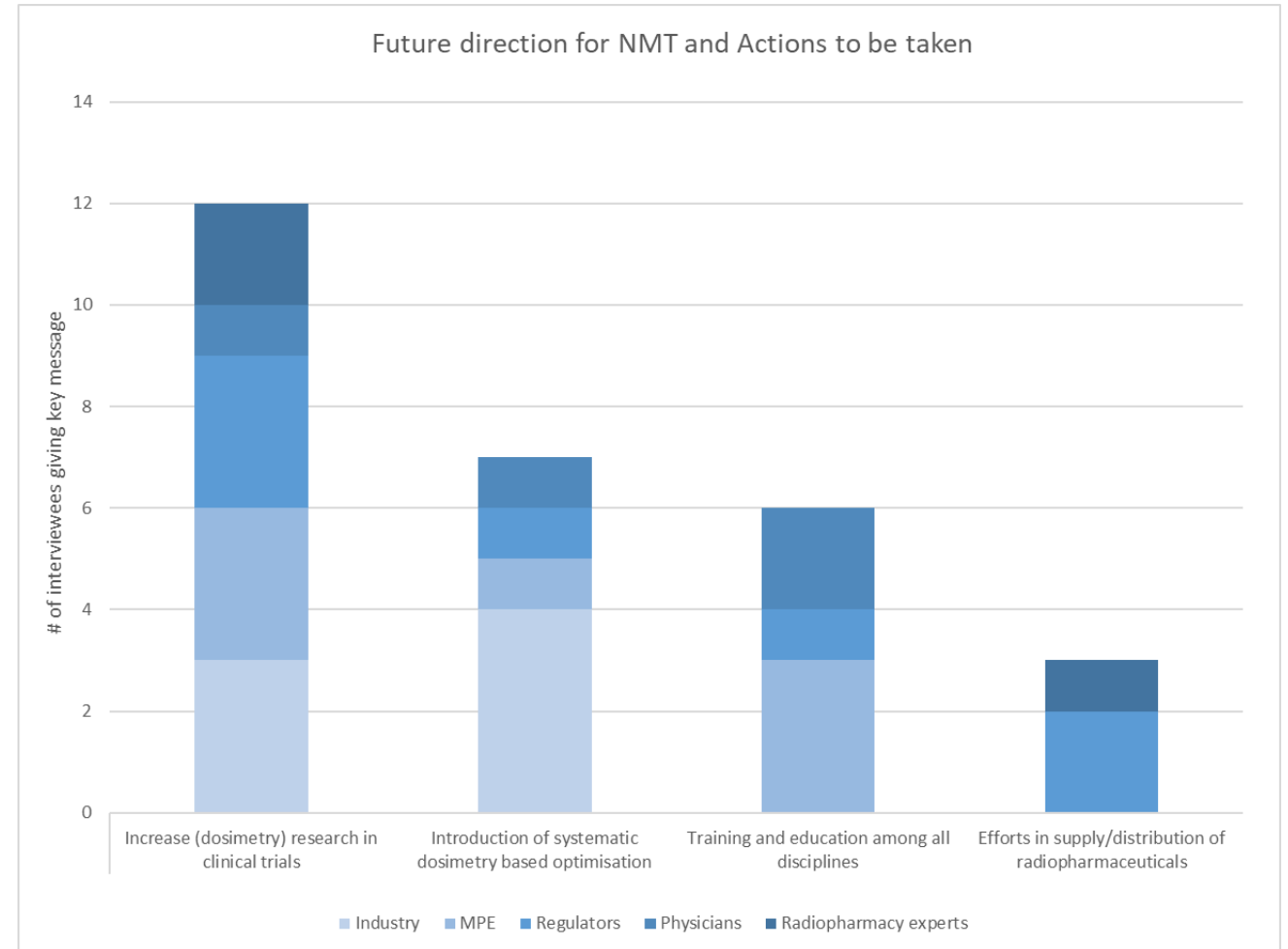
What role do you think absorbed dose calculations should play in NMT, both now and in the future?



How much flexibility in the SmPC should be available for the prescribing practitioner to personalise the administered activity?



What do you believe the future direction should be for NMT and what action should be taken to fulfil those aims??



Presentation of WP2

Main survey

Questions developed in June and July, then reviewed by EC

Programmed in SurveyMonkey

Distributed again through consortium networks
& pre-survey contacts

Open until end of 2022



Presentation of WP2

The main requirements of the BSSD and pharmaceutical legislation to be considered in the survey are the following

- Relevant provisions for **individual patient dose planning and dosimetry**
- Relevant provisions for **dosimetry verification**
- Authorisation and **conditions** for use that may or may not **restrict** potential **personalisation** in clinics
- Provisions for radiopharmaceutical **preparation, distribution** and **dispensing**
- Provision, training and involvement of **MPEs**
- Selected **dose constraints** for comforters, carers and the public
- Criteria used for **the release of patients** from hospitals
- Implemented strategies for **radioactive waste** management
- Practical aspects regarding the **use and marketing of radiopharmaceuticals**
- **Requirements** needed to achieve **marketing**

Response metrics

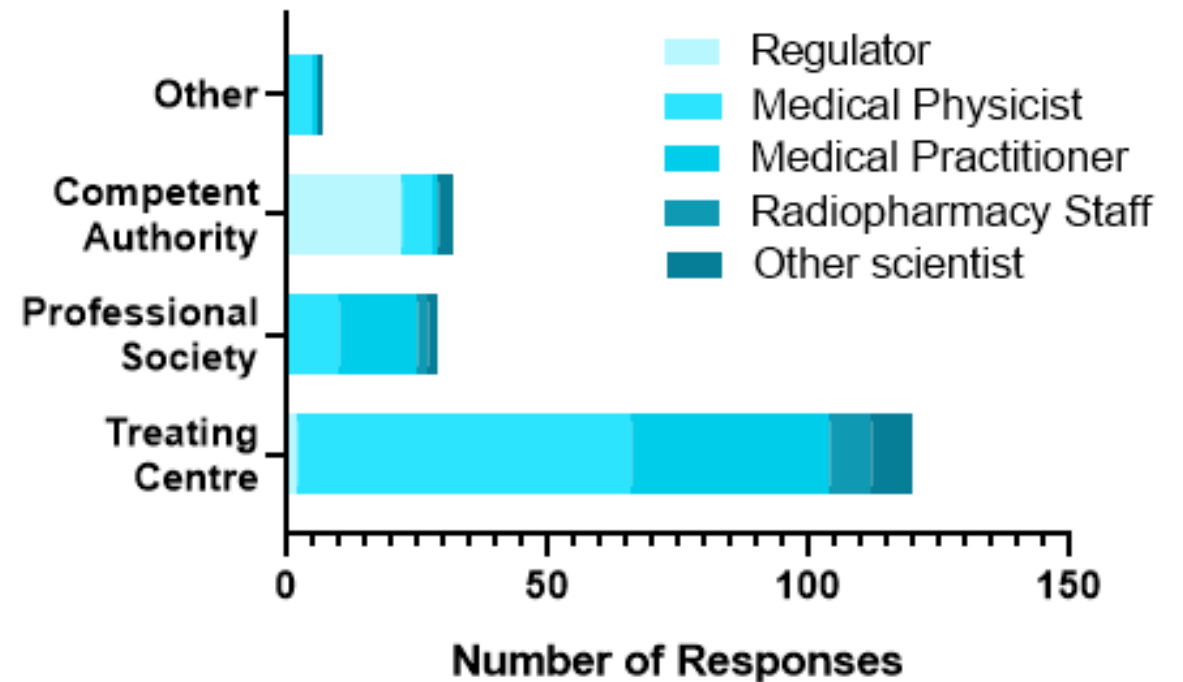
279 responses were received

After quality control: 193 responses were used in the analysis

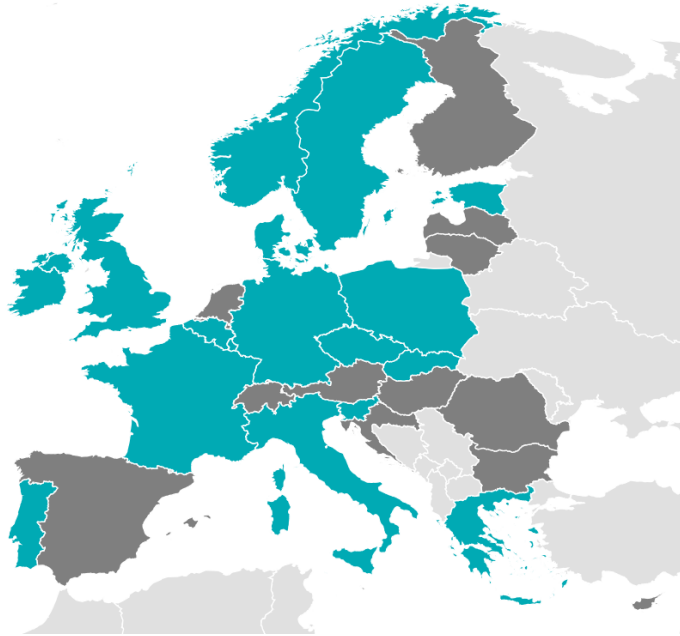
40 Countries

35 European countries

27 EU member states



Competent authorities



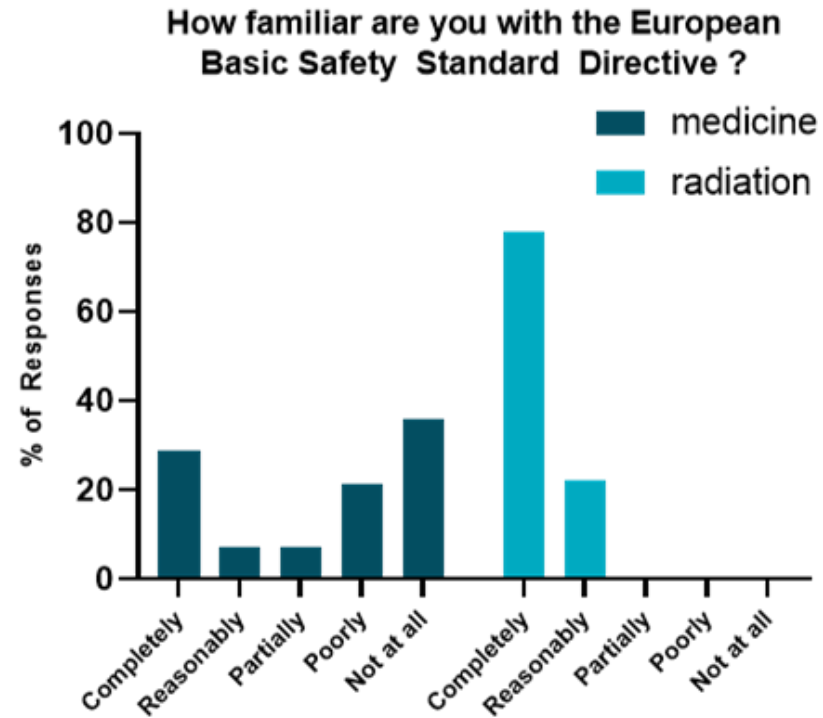
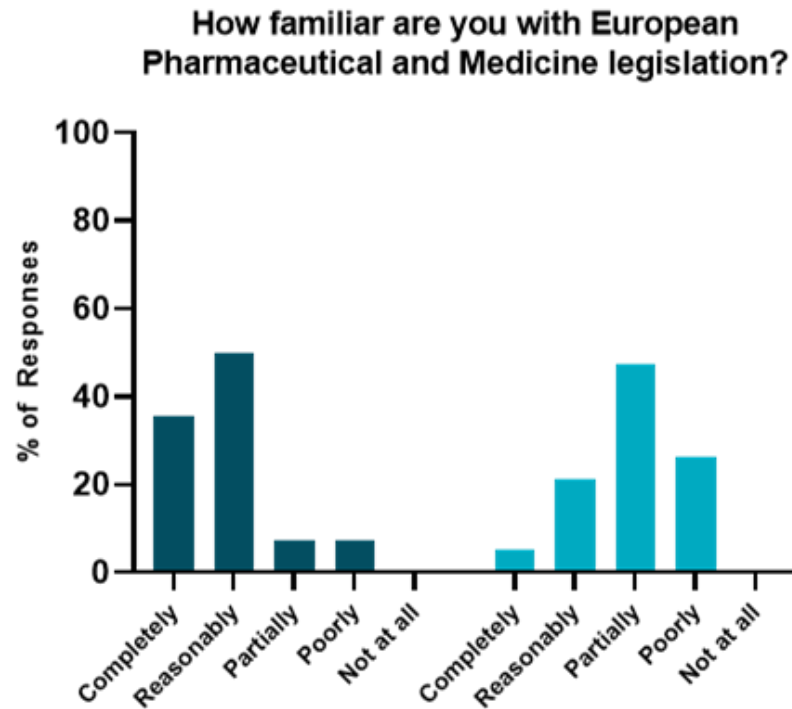
radiation and nuclear
authorities



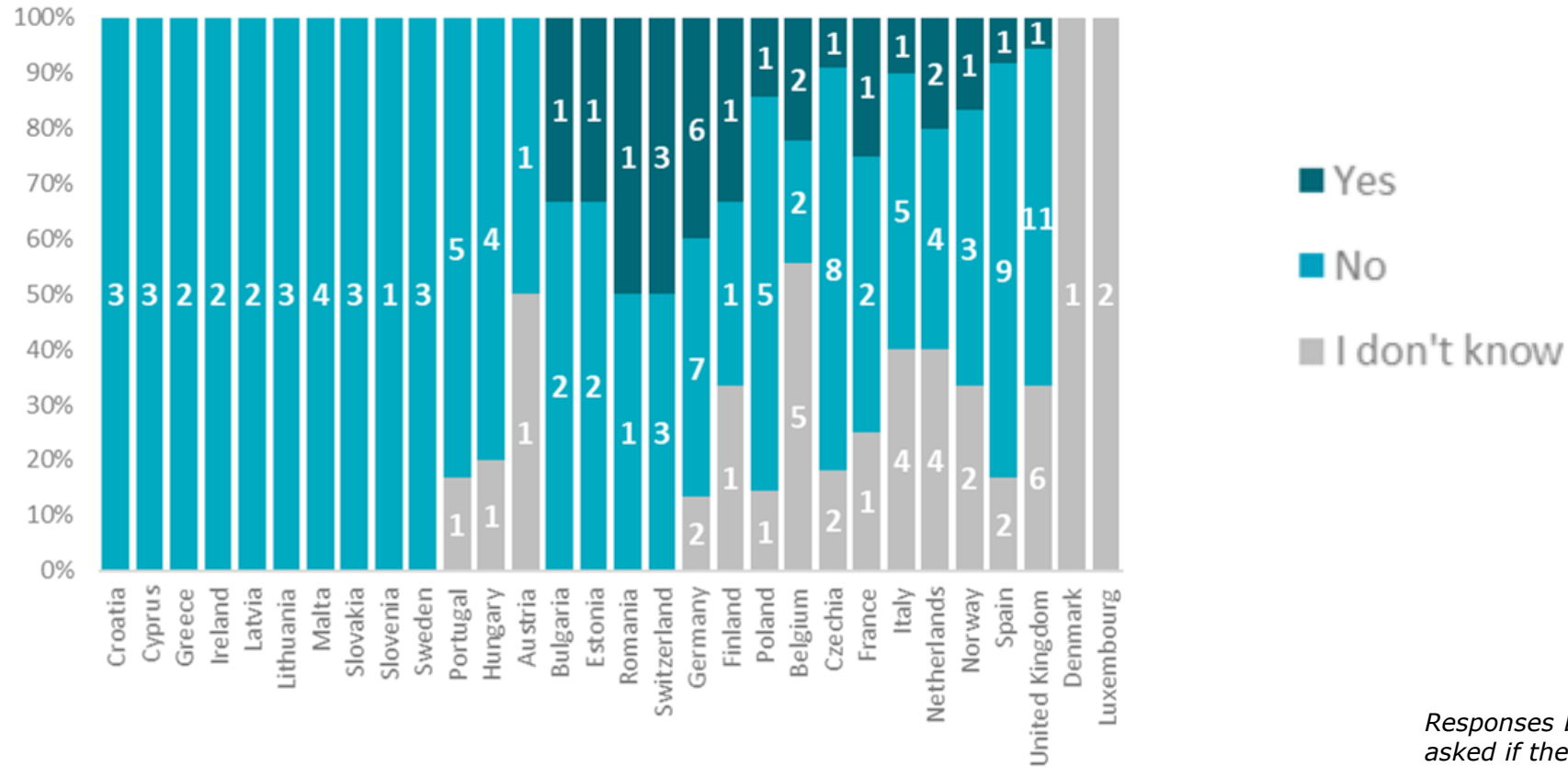
medicine & pharmaceutical
authorities

Fig. 4: Maps depicting countries in cyan where radiation and nuclear regulators completed the survey (a) and where pharmaceutical and medicine regulators completed the survey (b)

Cross discipline knowledge

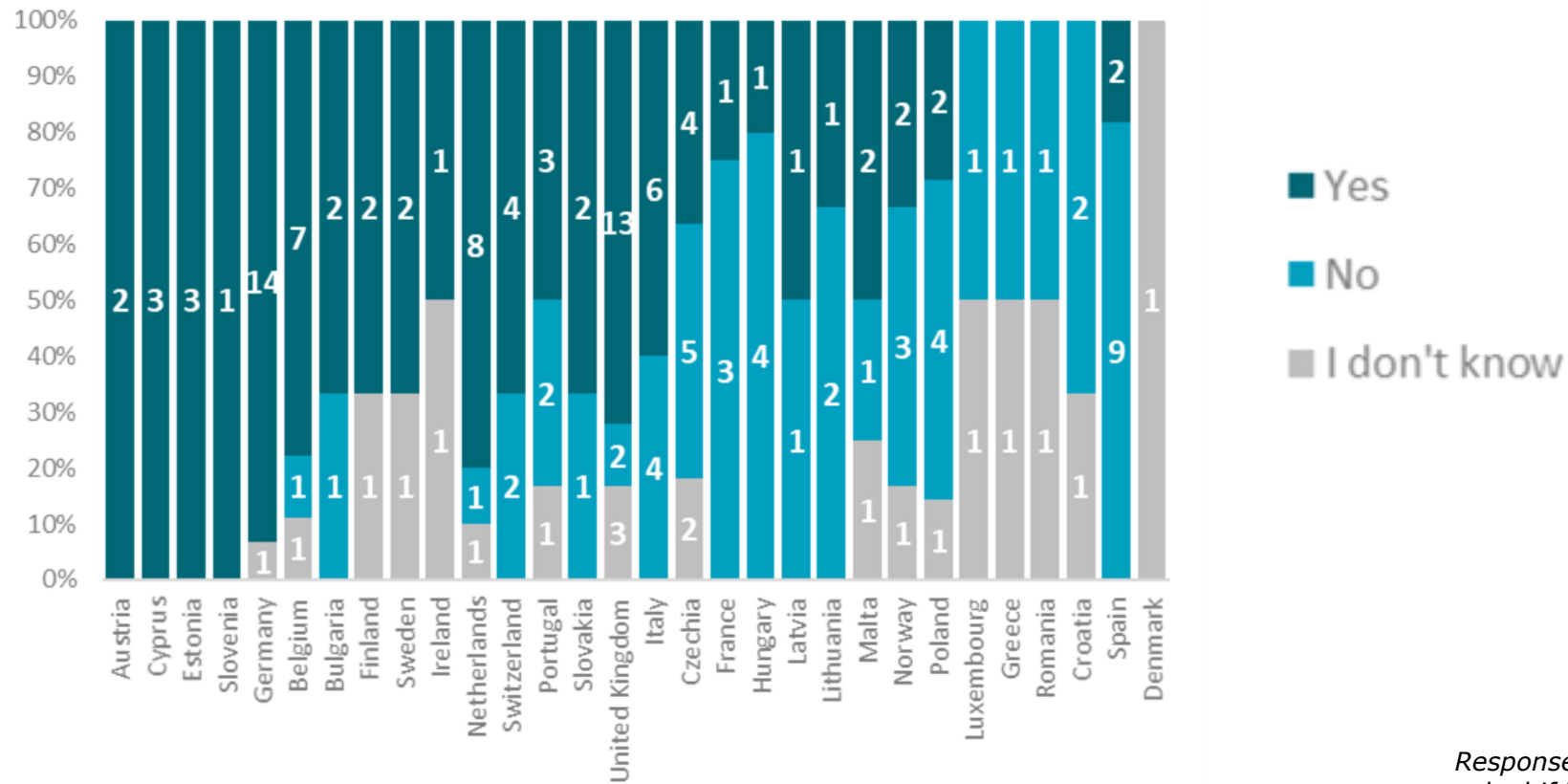


National pharmaceutical regulations specifically for therapeutic radiopharmaceuticals



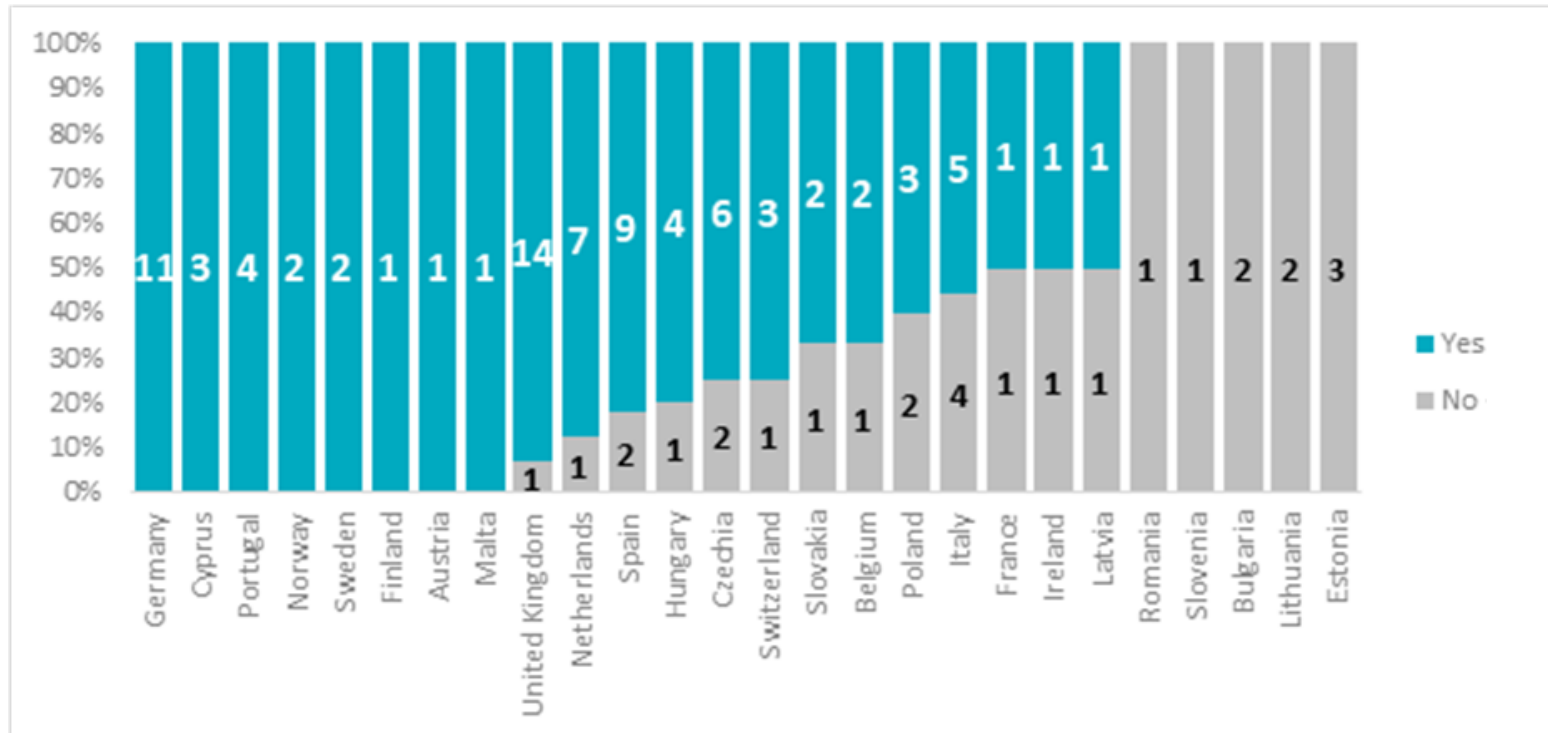
Responses by survey participants when asked if there were any national pharmaceutical regulations specifically for therapeutic radiopharmaceuticals

Therapeutic radiopharmaceuticals without marketing authorisation



Responses by survey participants when asked if it is permissible to prepare and administer therapeutic radiopharmaceuticals without marketing authorisation in their country

Administer outside of the posology indicated in the SmPC?



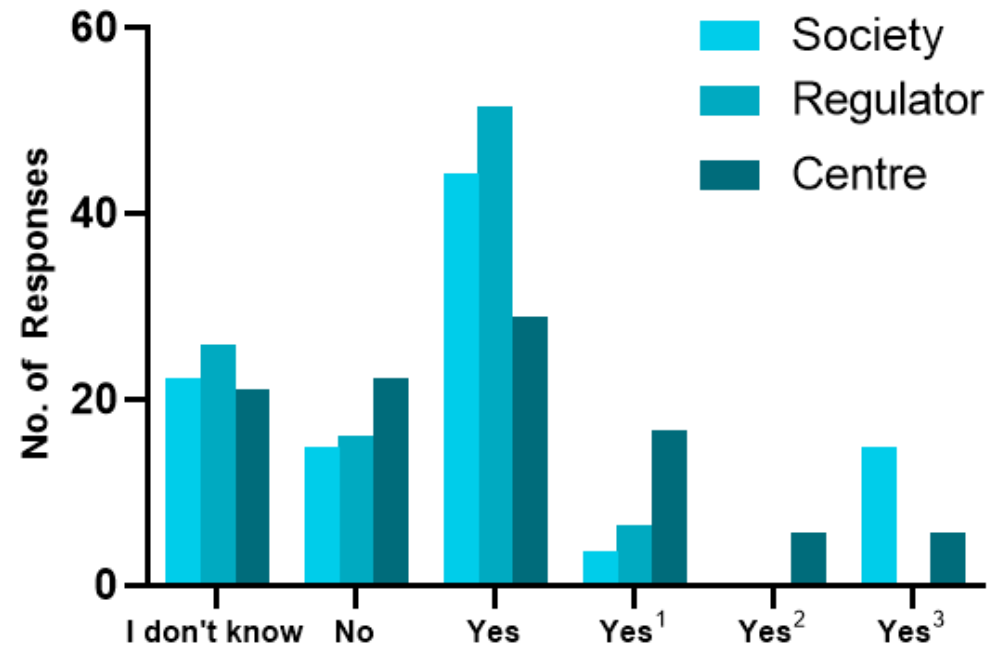
Responses by survey participants when asked whether in their country is it allowed to administer authorised therapeutic radionuclides outside of the posology indicated on the package insert

Administer outside of the posology indicated in the SmPC?

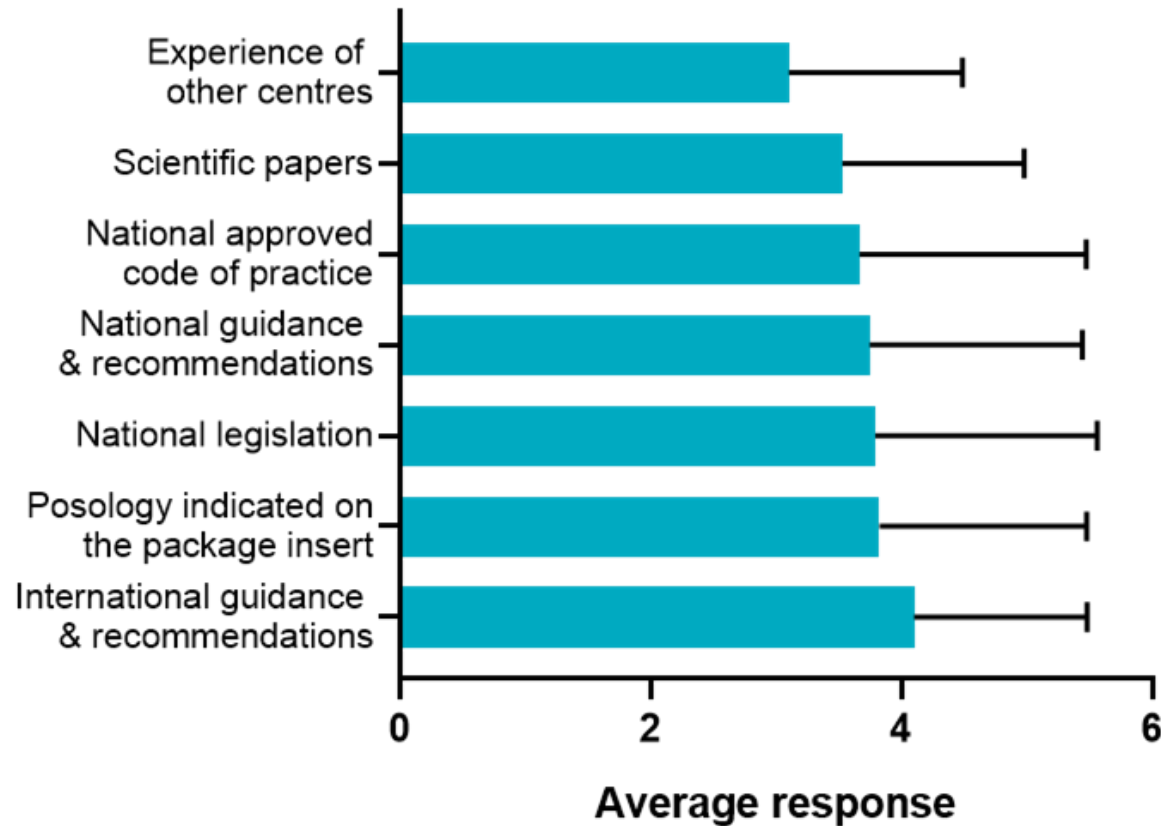
1 Yes, after approval by an ethics committee

2 Yes, but only after dosimetric planning

3 Yes, but only less than that indicated in the SmPC



What influences choice of treatment regimen?



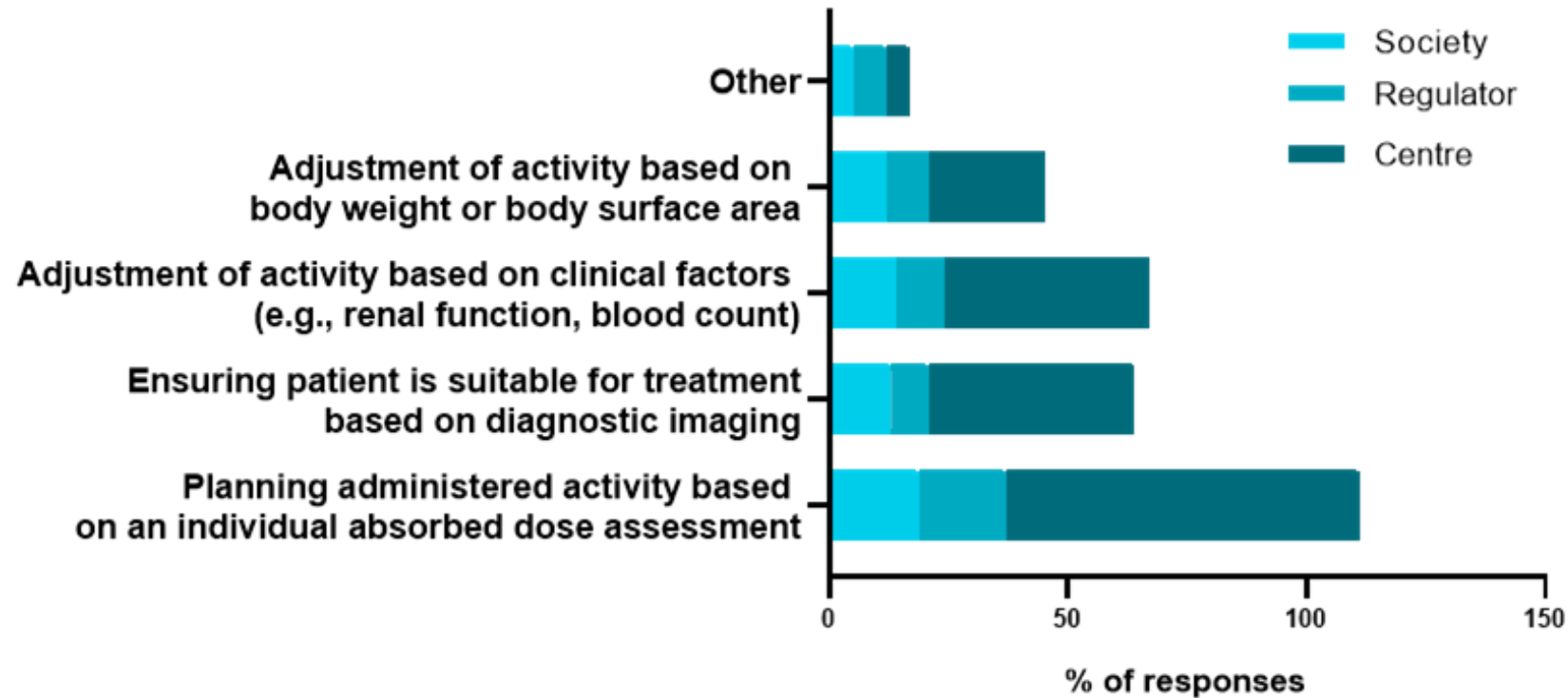
BSSD - Treatment optimisation and verification

6 regulators and/or societies stated it was not present in their national legislation

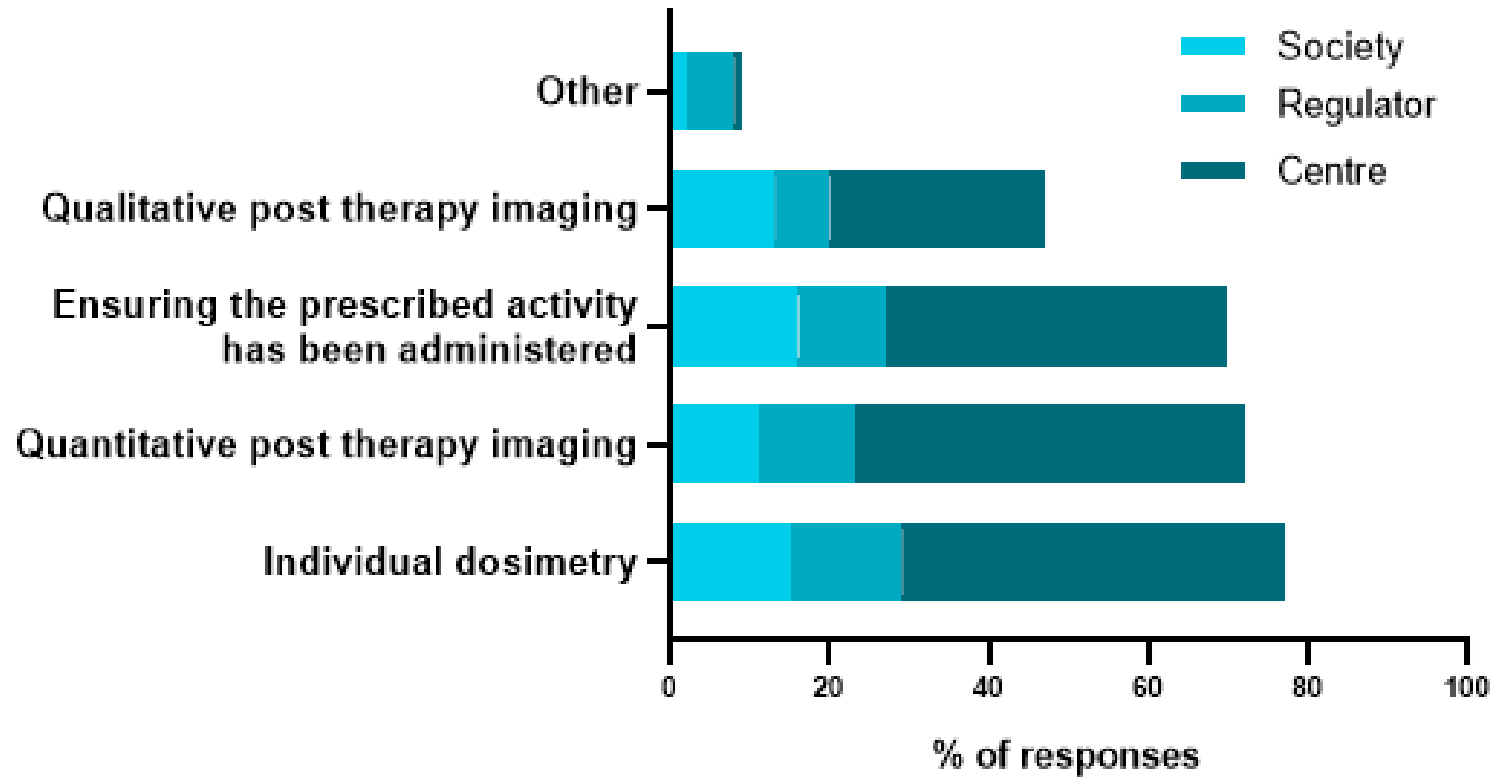
“In my opinion, this has been a translation mistake. For radionuclide therapy, the activity is obtained from clinical trials, as all drugs used for therapy”

“is a transcription of external radiotherapy not applicable in nuclear medicine”

Treatment planning

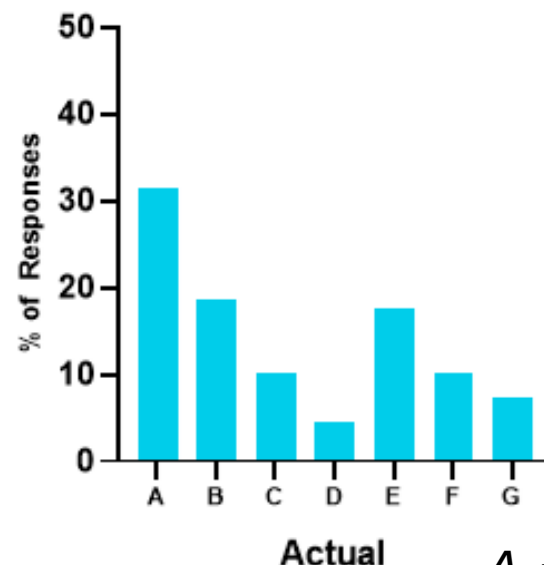
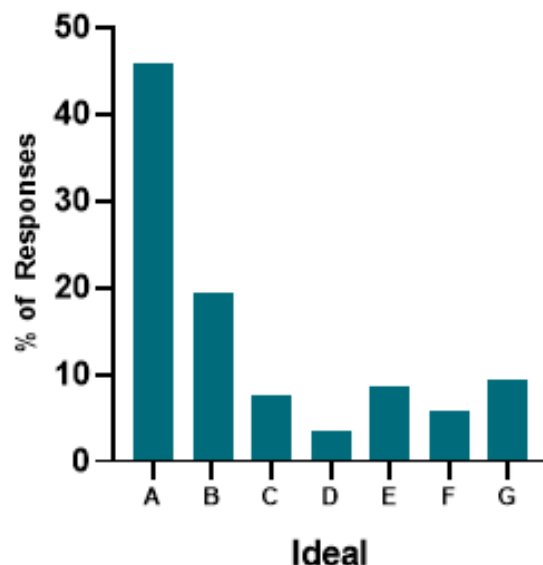
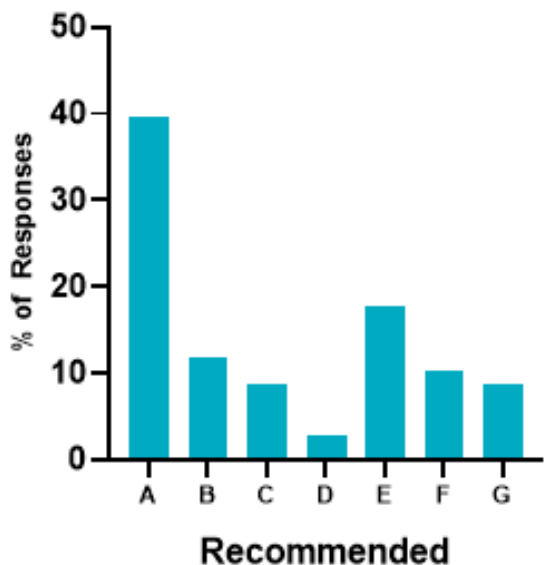


Treatment verification



Current practice / guidance

¹³¹I benign thyroid planning

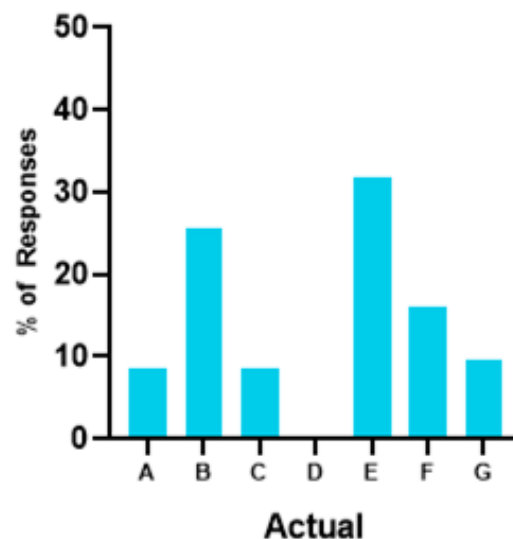
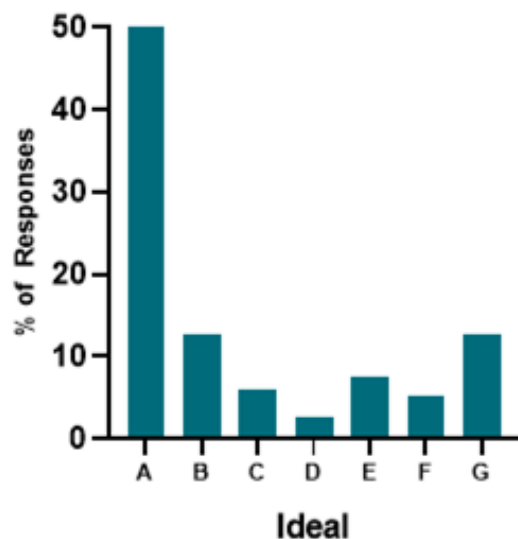
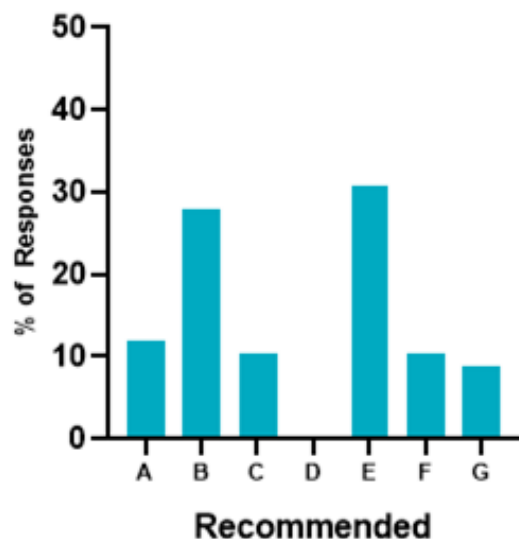


A = Dosimetry

- A = absorbed dose assessment*
- B = diagnostic imaging*
- C = clinical factors*
- D = body weight/surface area*
- E = Fixed activity*
- F = Other*
- G = I don't know*

Current practice / guidance

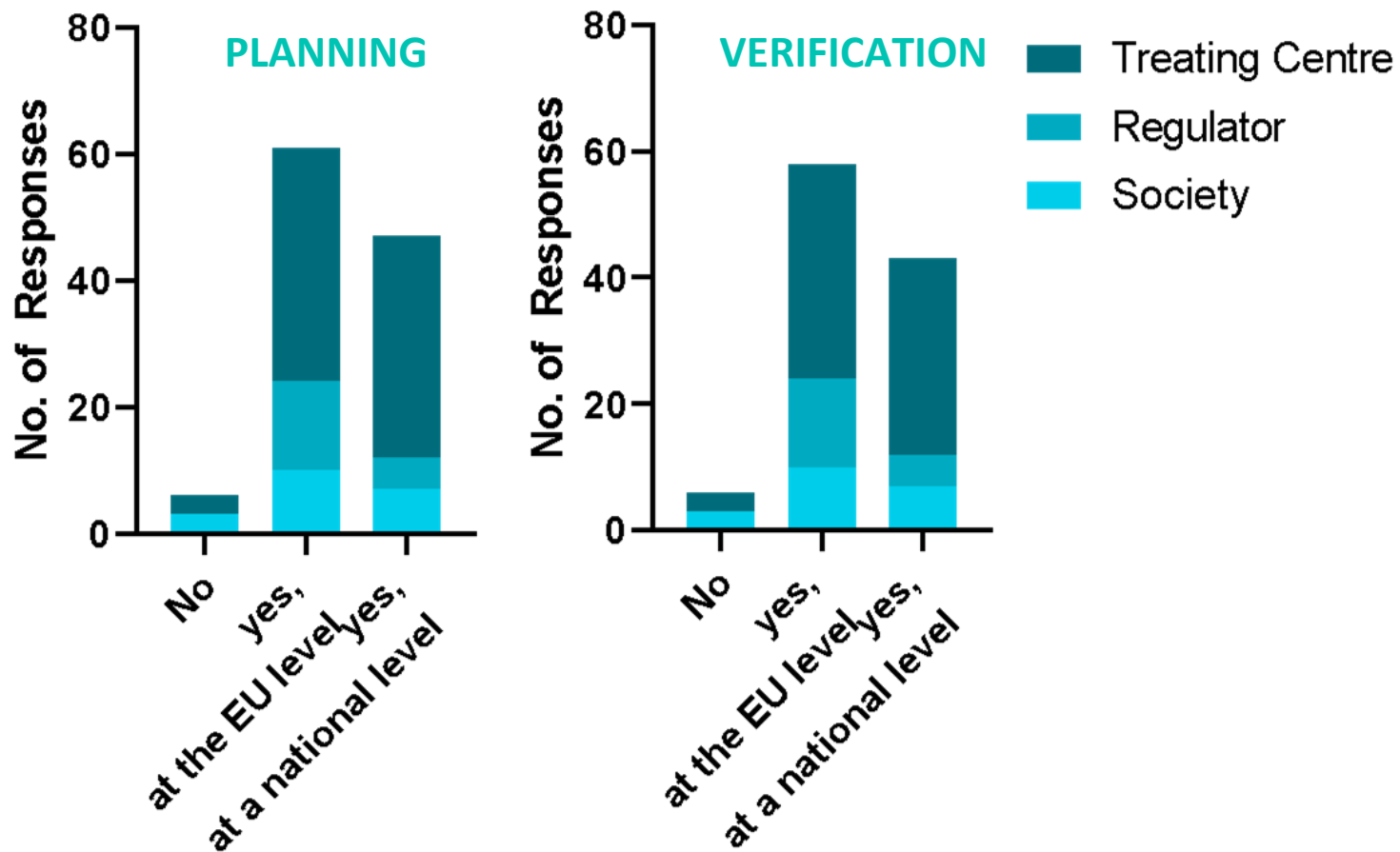
^{177}Lu DOTATATE planning



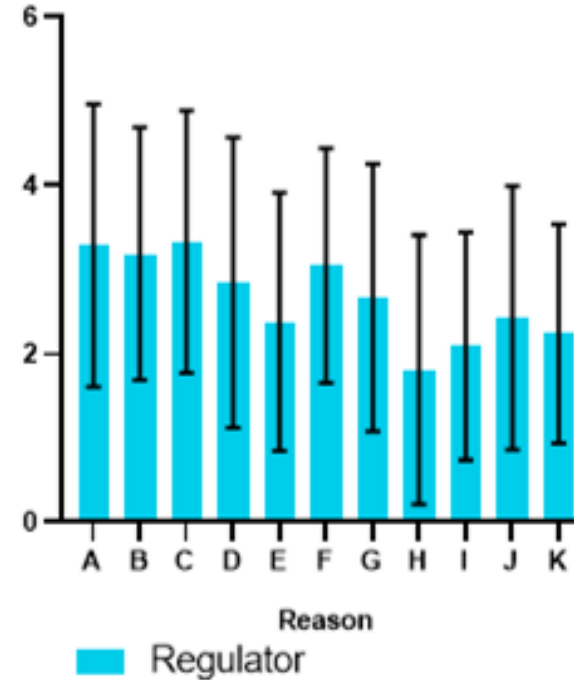
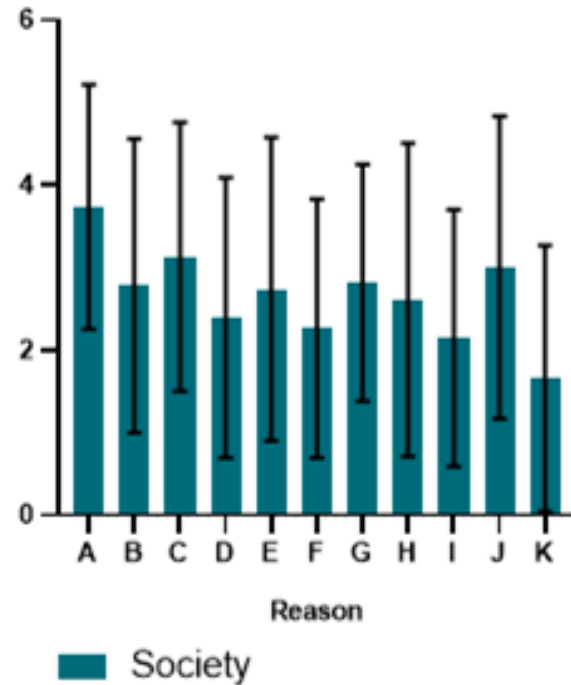
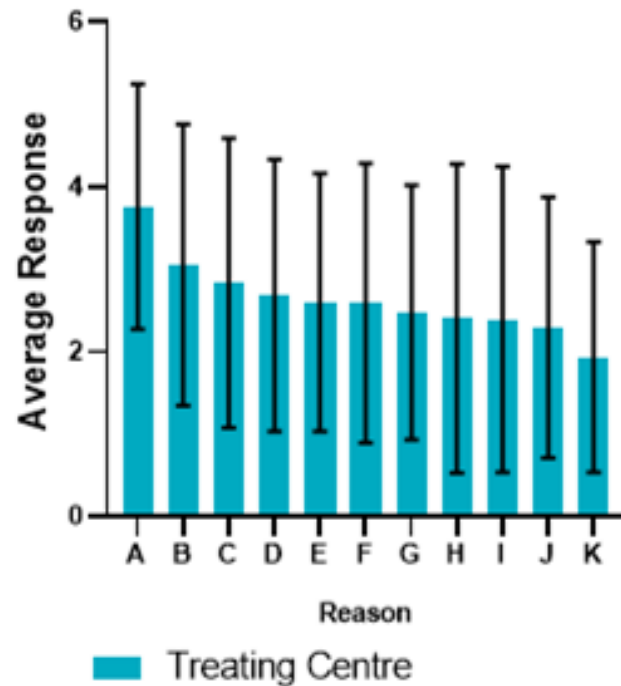
A = Dosimetry
E = Fixed activity

A = absorbed dose assessment
B = diagnostic imaging
C = clinical factors
D = body weight/surface area
E = Fixed activity
F = Other
G = I don't know

Is further guidance required?



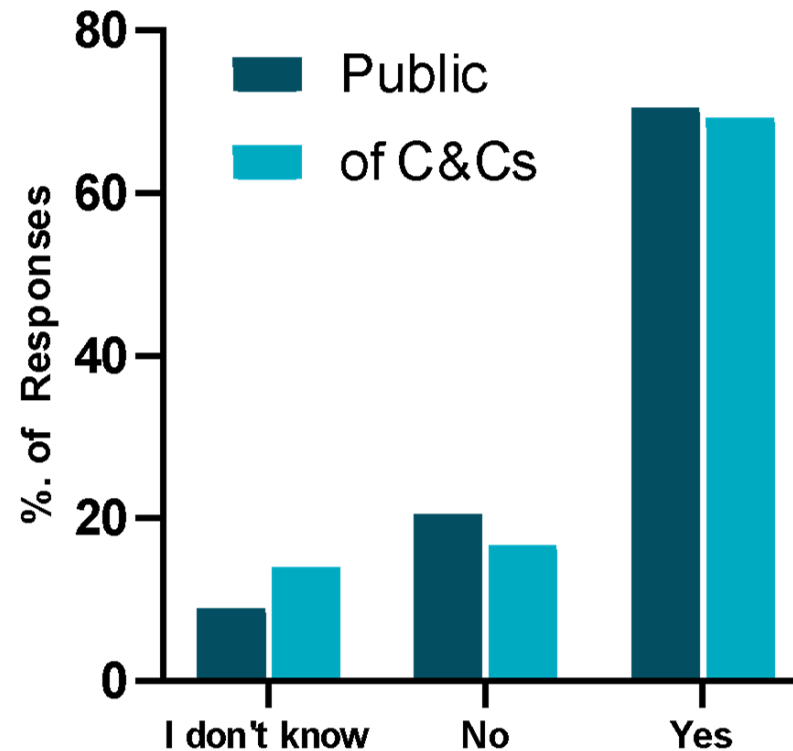
Barriers



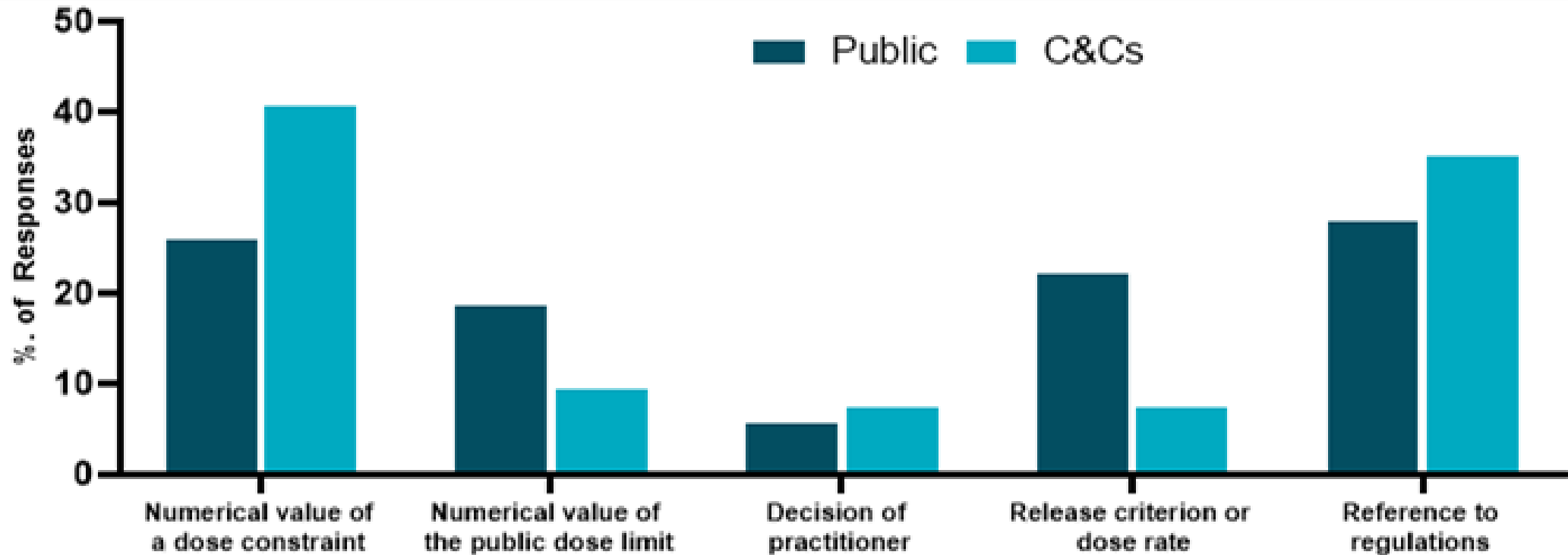
- A = Shortage of funding/reimbursement**
- B = Shortage of medical physicists working in nuclear medicine**
- C = Limited access to dedicated software**
- D = Lack of knowledge and know-how in performing individual treatment planning**
- E = Requirement to follow the posology**
- F = Limited access to scanners or other equipment needed**
- G = Shortage of other staff**
- H = No legislative requirement**
- I = Unnecessary burden to the patient**
- J = No scientific evidence for added value of dose planning**
- K = There is a clinical risk in prescribing outside the standard posology**

Dose constraints

Are there dose constraints for members of the public and comforters and carers established in your country?



Dose constraint



Typical constraints

Article 12

Dose limits for public exposure

2. Member States shall set the limit on the effective dose for public exposure at 1 mSv in a year.

Table 1: Examples of the use of dose constraints in some European countries

Country	General public	Comforters/Carers
A	No specific constraint	No specific constraint
B	0.25 mSv per treatment cycle	Children < 18 y: 1 mSv per treatment cycle Adults > 18 y and < 60 y: 3 mSv per treatment cycle Adults > 60 y: 15 mSv per treatment cycle
C	0.3 mSv/y	Pregnant women: 1 mSv/y Children < 2 y: 1 mSv/y Children between 3 and 10 y: 1 mSv per treatment cycle Children > 10 y and adults: 3 mSv per treatment cycle Adults > 60 y: 15 mSv per treatment cycle
D	0.3 mSv per procedure	5 mSv per procedure
E	0.3 mSv per treatment cycle	< 60y: 3 mSv per treatment cycle > 60y: 15 mSv per treatment cycle
F	No specific constraint	No specific constraints
G	No specific constraint	No specific constraints
H	0.1 mSv per treatment cycle	Children < 18 y: 1 mSv per treatment cycle Adults > 18 y and < 70 y: 3 mSv per treatment cycle Adults > 70 y: 15 mSv per treatment cycle

Typical constraints

NRC Regulations Title 10, Code of Federal Regulations

§ 35.75 Release of individuals containing unsealed byproduct material or implants containing byproduct material.

(a) A licensee may authorize the release from its control of any individual who has been administered unsealed byproduct material or implants containing byproduct material if the total effective dose equivalent to any other individual from exposure to the released individual is not likely to exceed 5 mSv (0.5 rem).¹

Table 1: Examples of the use of dose constraints in some European countries

Country	General public	Comforters/Carers
A	No specific constraint	No specific constraint
B	0.25 mSv per treatment cycle	Children < 18 y: 1 mSv per treatment cycle Adults > 18 y and < 60 y: 3 mSv per treatment cycle Adults > 60 y: 15 mSv per treatment cycle
	3 mSv/y	Pregnant women: 1 mSv/y Children < 2 y: 1 mSv/y Children between 3 and 10 y: 1 mSv per treatment cycle Children > 10 y and adults: 3 mSv per treatment cycle Adults > 60 y: 15 mSv per treatment cycle
	3 mSv per procedure	5 mSv per procedure
	3 mSv per treatment cycle	< 60y: 3 mSv per treatment cycle > 60y: 15 mSv per treatment cycle
F	No specific constraint	No specific constraints
G	No specific constraint	No specific constraints
H	0.1 mSv per treatment cycle	Children < 18 y: 1 mSv per treatment cycle Adults > 18 y and < 70 y: 3 mSv per treatment cycle Adults > 70 y: 15 mSv per treatment cycle

Typical constraints

CHAPTER II DEFINITIONS Article 4 Definitions

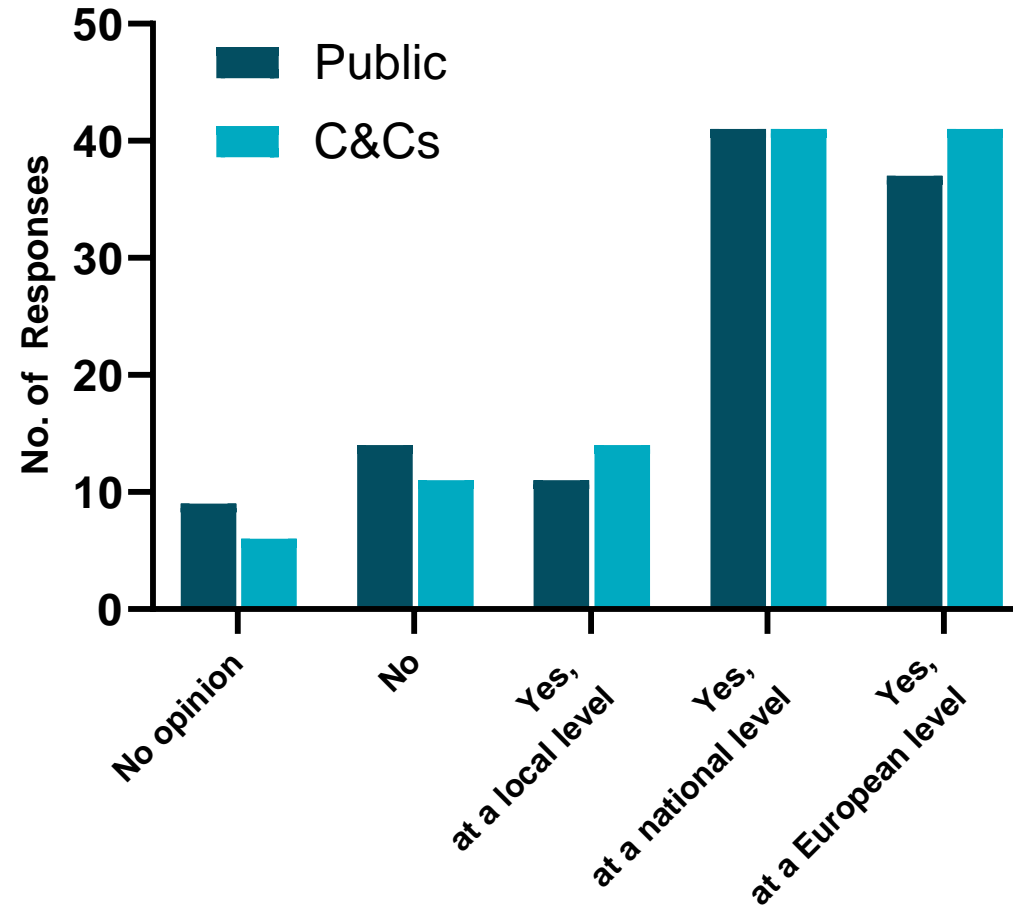
(10) “carers and comforters” means individuals **knowingly** and **willingly** incurring an exposure to ionising radiation by helping, other than as part of their occupation, in the support and comfort of individuals undergoing or having undergone medical exposure;

Table 1: Examples of the use of dose constraints in some European countries

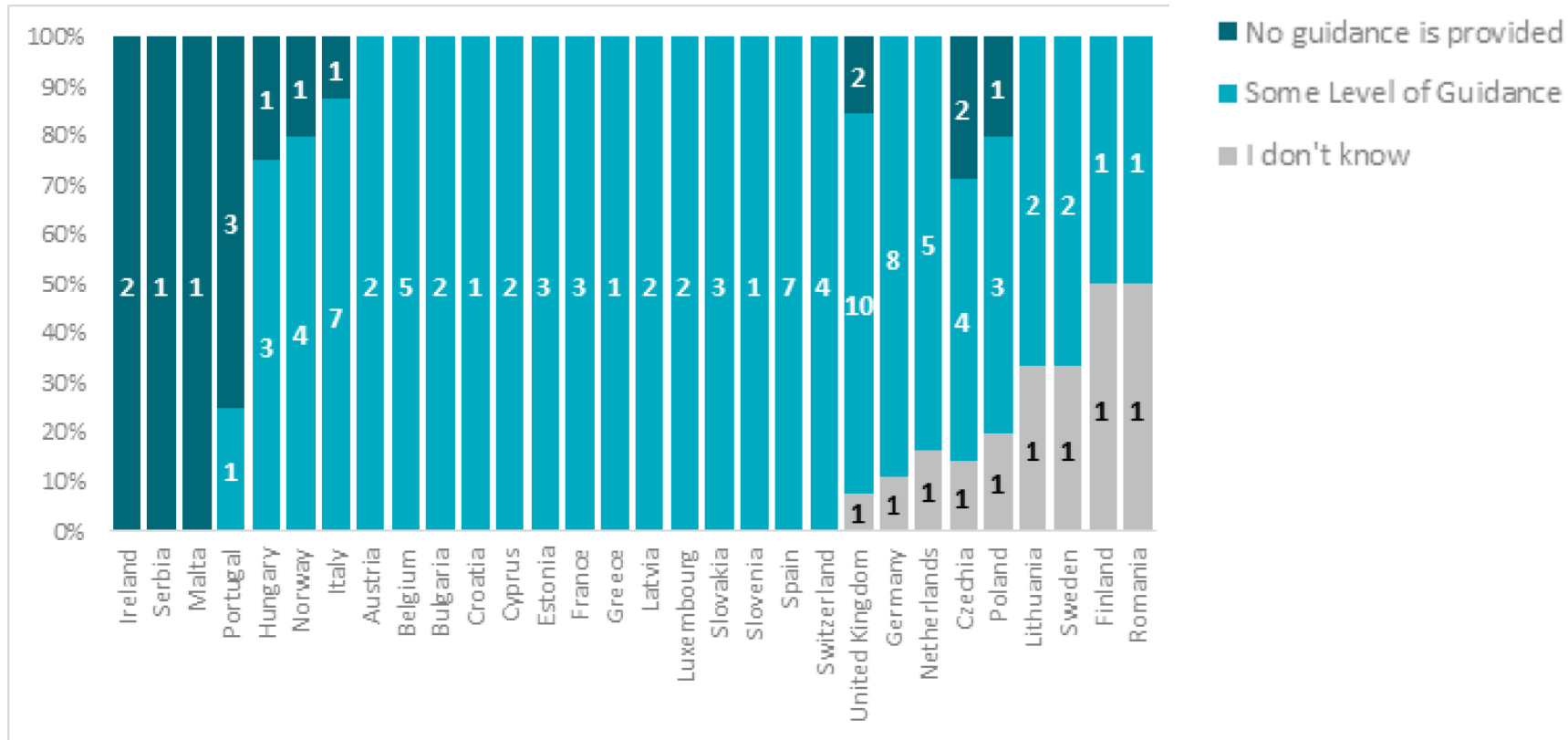
Country	General public	Comforters/Carers
A	No specific constraint	No specific constraint
B	0.25 mSv per treatment cycle	Children < 18 y: 1 mSv per treatment cycle Adults > 18 y and < 60 y: 3 mSv per treatment cycle Adults > 60 y: 15 mSv per treatment cycle
C	0.3 mSv/y	Pregnant women: 1 mSv/y Children < 2 y: 1 mSv/y Children between 3 and 10 y: 1 mSv per treatment cycle Children > 10 y and adults: 3 mSv per treatment cycle Adults > 60 y: 15 mSv per treatment cycle
D	0.3 mSv per procedure	5 mSv per procedure
E	0.3 mSv per treatment cycle	< 60y: 3 mSv per treatment cycle > 60y: 15 mSv per treatment cycle
F	No specific constraint	No specific constraints
G	No specific constraint	No specific constraints
H	0.1 mSv per treatment cycle	Children < 18 y: 1 mSv per treatment cycle Adults > 18 y and < 70 y: 3 mSv per treatment cycle Adults > 70 y: 15 mSv per treatment cycle

Harmonised dose constraints

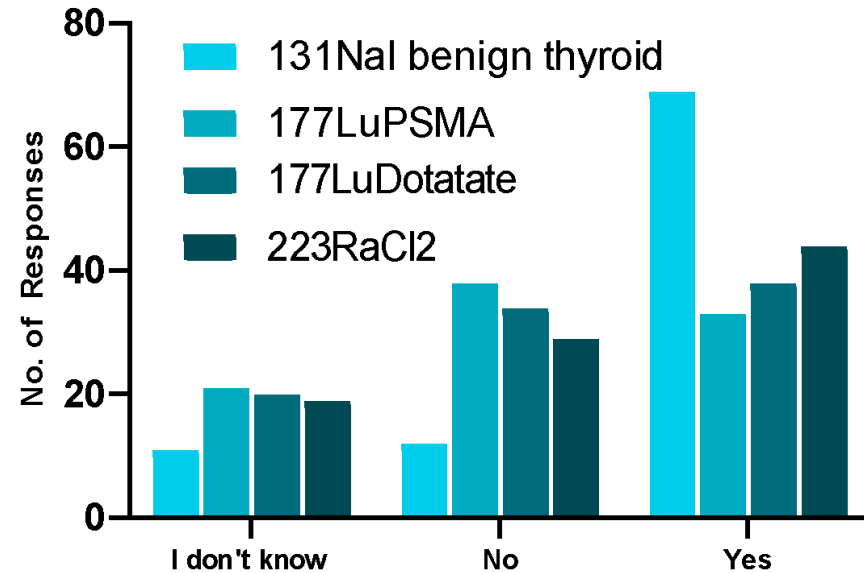
Fig. 31: Responses by survey participants when asked if it is appropriate to establish a specific dose constraint for the public and comforters and carers



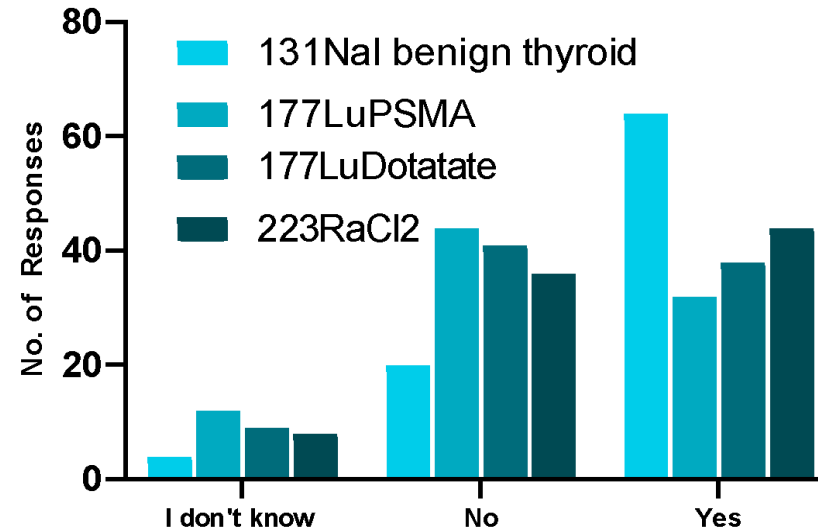
Patient release & instructions



Patient release & instructions



Instructions



Criteria for release

Examples

Release criteria and instructions [¹³¹I]NaI

Most commonly outpatient (but not exclusive)

Release criteria with dose rate or activity

Release criteria and instructions [¹⁷⁷Lu]DOTATATE

Dose rate such as 20 μSv/h or 25 uSv/h @1 m

Isolation for a defined period of time (6 to 48 hours)

Release criteria and instructions [²²³Ra]RaCl₂

Always outpatient

Instructions based on that provided in package insert

Effluent and waste

Journal of Radiological Protection

PAPER

Radiation safety of current European practices of therapeutic nuclear medicine: survey results from 20 HERCA countries

Ritva Bly^{1,2} 

Radiation and Nuclear Safety Authority (STUK), Helsinki, Finland

¹ Heads of the European Radiological Protection Competent Authorities (HERCA), Working Group on Medical Applications.

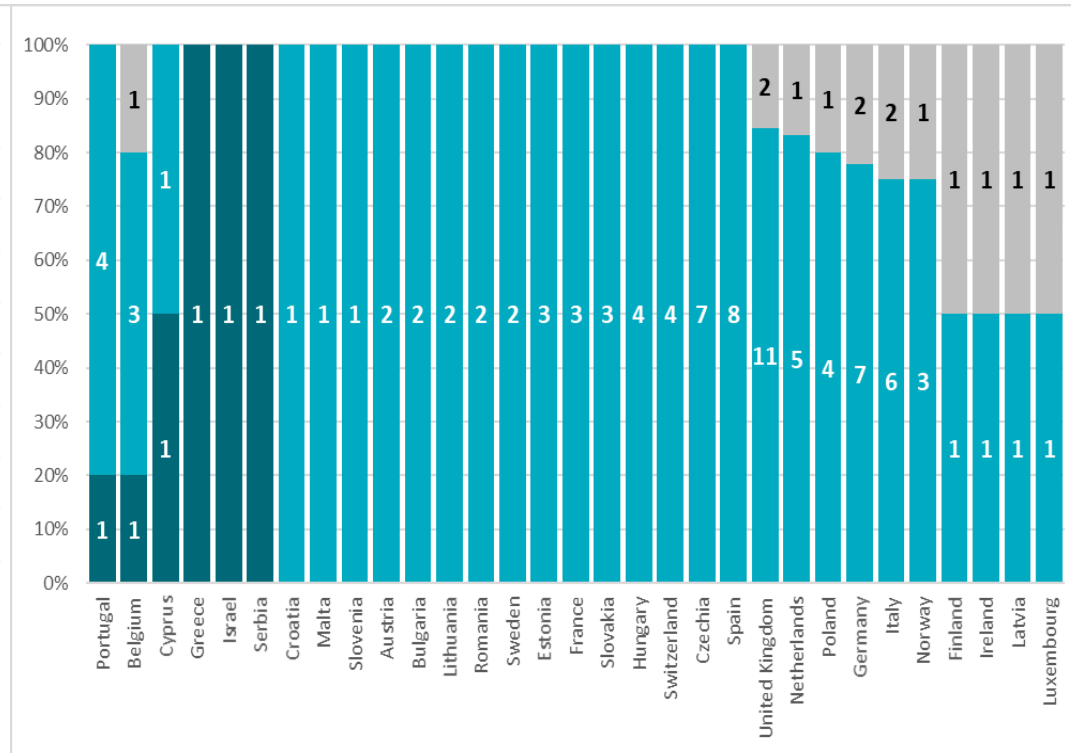
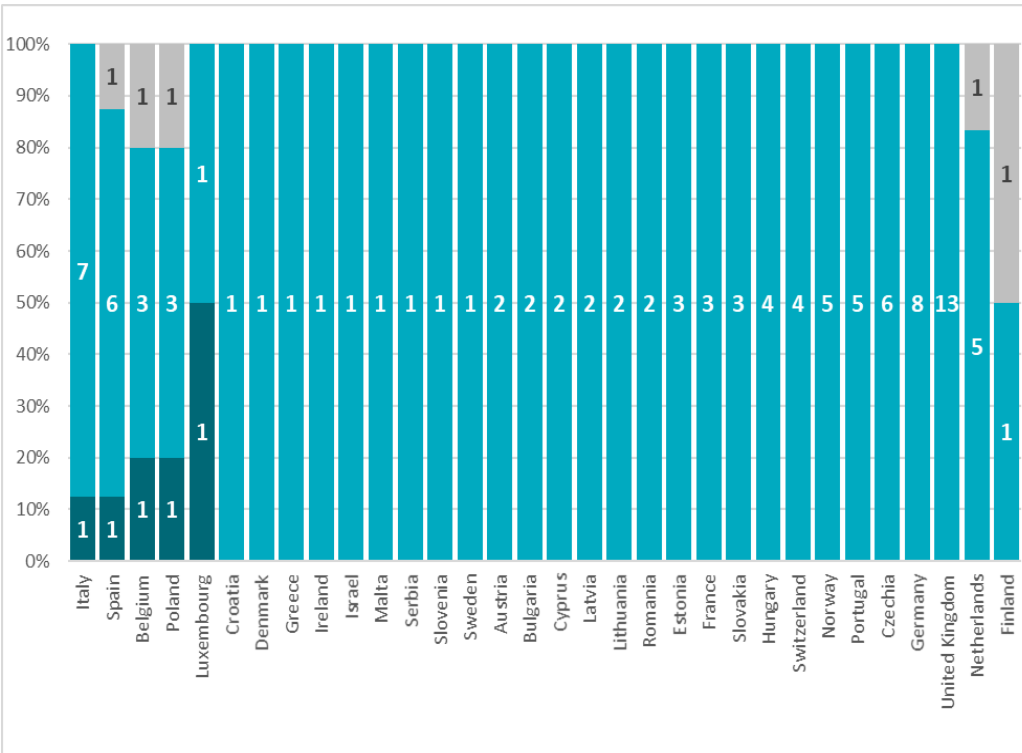
² HERCA is a voluntary association of the radiation protection authorities.

E-mail: ritva.bly@stuk.fi and secretariat@herca.org

Keywords: radionuclide therapy, molecular radiotherapy, therapeutic use of nuclear medicine, radiopharmaceutical therapy, European survey on nuclear medicine, dosimetry, medical physics expert

January 2023

Effluent and waste



Storage of solid waste

Release of effluent

Effluent and waste

Country	¹³¹ I	¹⁷⁷ Lu	²²³ Ra
Country A	5 Bq/L leaving hospital sewage	100 Bq/L when entering the public sewage system	
Country B (centre i)	350 GBq/year	3000 GBq/year	0.1 GBq/year
Country C (centre ii)	5 GBq/year	500 GBq/year	0.15 GBq/year
Country D	decay store for a few months		
Country E (centre i)	900 GBq/year	1800 GBq/year	1.4 GBq/year
Country E (centre ii)	900 GBq/year	480 GBq/year	1.2 GBq/year
Country F	The condition for effluent is “no radiological relevance,” which means that no population member should absorb more than 10 uSv per year.		
Country G	45 Bq/L leaving hospital sewage	1.9 kBq/L leaving hospital sewage	10 Bq/L leaving hospital sewage
Country H	18 reign (radiotoxicity equivalent, which is the activity that leads to an effective life dose of 1 Sv)		

Medical physics experts

Original paper

Education, training and registration of Medical Physics Experts across Europe

Ad J.J. Maas^{a, *}, Adriaan A. Lammertsma^b, Sam Agius^c, Christoph Bert^d, Brenda Byrne^e, Carmel J. Caruana^f, Paddy Gilligan^g, Efi Koutsouveli^h, Eric Paceⁱ, Marco Brambilla^j

^a Past Chairperson EFOMP Professional Matters Committee, Member MREC Brabant, Tilburg, Netherlands

^b Past Chairperson EFOMP Education & Training Committee, Full Professor Radiology & Nuclear Medicine, Amsterdam UMC, Netherlands

^c General Secretary EFOMP Professional Matters Committee, MPE Nuclear Medicine, Mater Dei Hospital, Msida, Malta

^d Chairperson EFOMP Education & Training Committee, Department of Radiation Oncology, Universitätsklinikum Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany

^e Chairperson EFOMP Professional Matters Committee, Principal Physicist Mater Misericordiae University Hospital, Dublin 7, Ireland

^f Member EFOMP Professional Matters and Education & Training Committees, Full Professor of Medical Physics, Faculty of Health Sciences, University of Malta, Msida, Malta

^g President EFOMP, Chief Physicist Mater Private Hospital, Dublin, Ireland

^h Secretary General EFOMP, Medical Physics Expert, Department of Medical Physics, Hygeia Hospital, Athens, Greece

ⁱ Secretary EFOMP Education & Training Committee, Medical Physics Expert Medical Imaging Department, Mater Dei Hospital, Msida, Malta

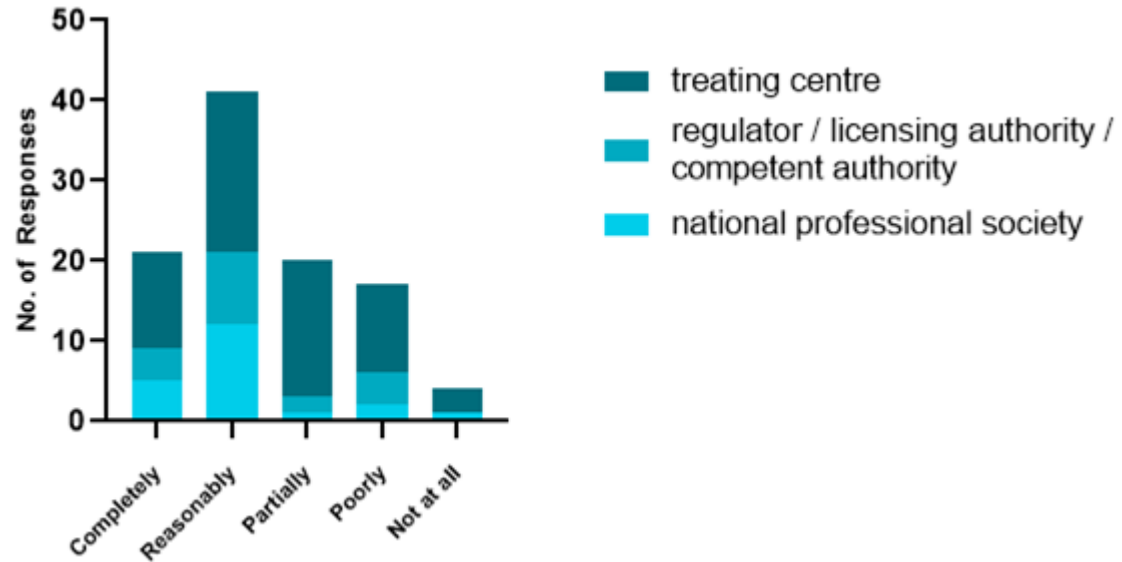
^j Past President EFOMP, Director of Health Physics Department, University Hospital, Novara, Italy

May 2021



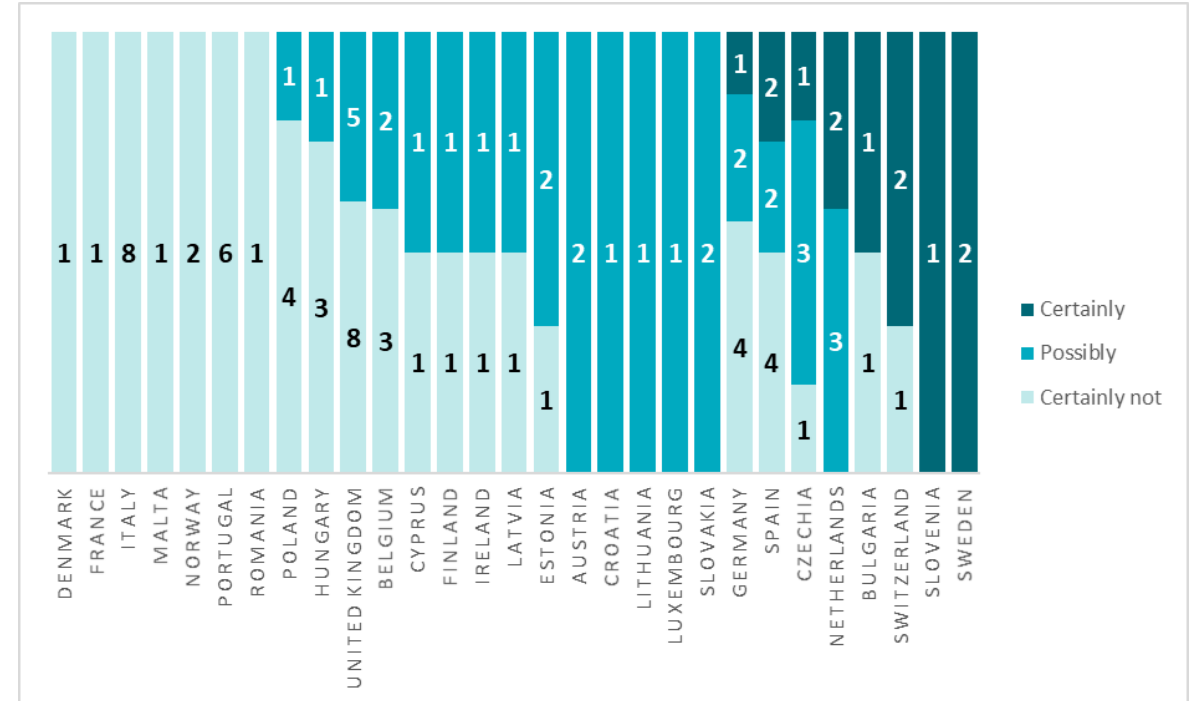
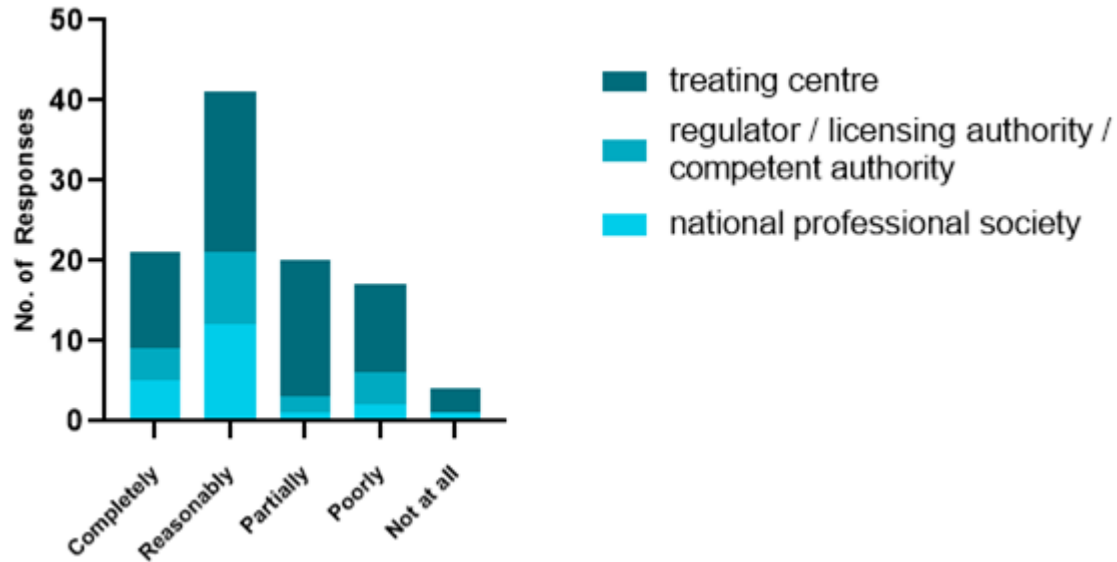
- Of the 25 EU states that participated in the EFOMP survey, 19 had national registration schemes for MPEs and 3 were considering implementing one
- Different European countries follow different paths to educate and train MPEs
- only in 50% of the centres distinguished between medical physicist and MPE
- MPE qualifications granted after BSc or MSc or up to 6.5 years post graduate clinical training in a specialist subject area

Medical physics expert



Role of the MPE

Medical physics expert



Medical physics expert

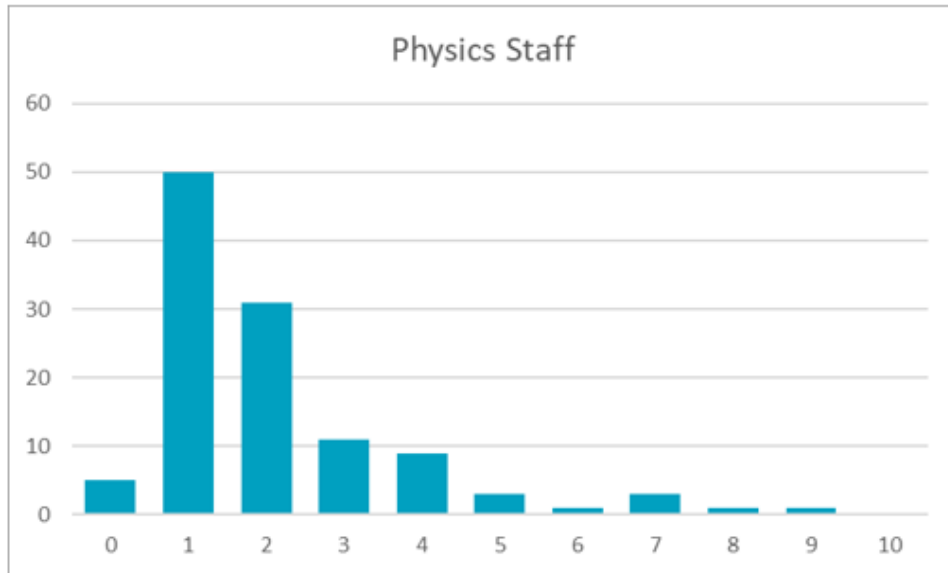
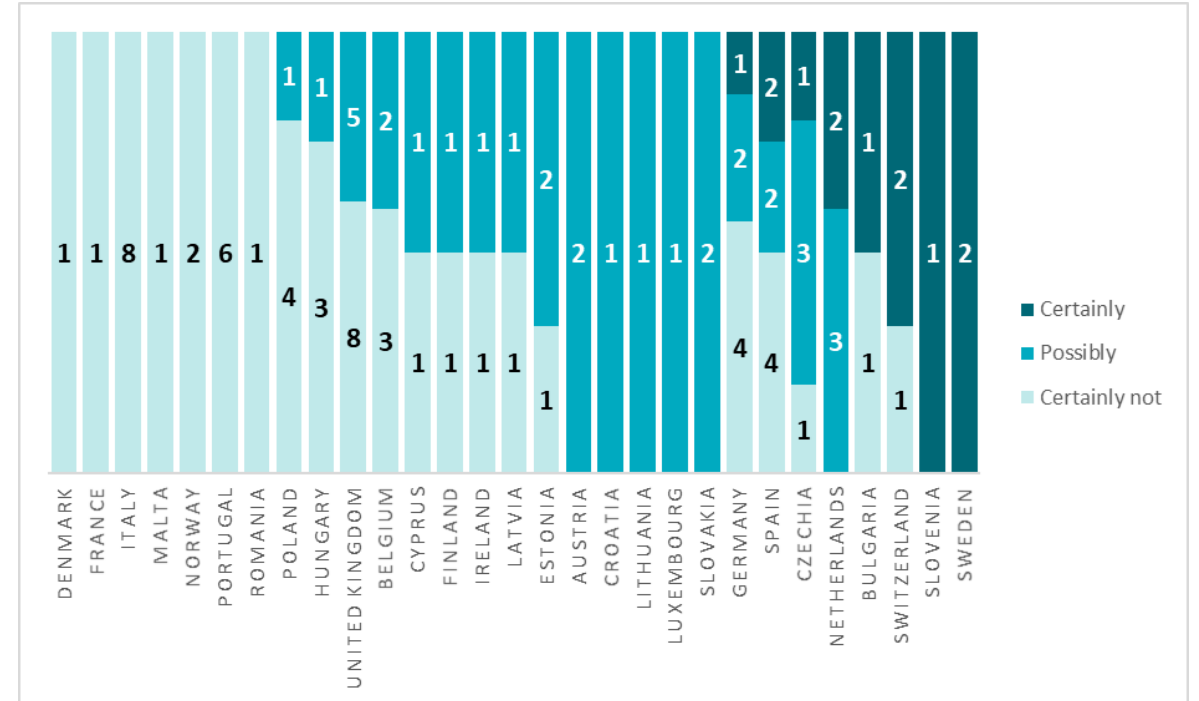


Fig. 39: Number of medical physicists per centre that completed the survey



Sufficient MPE support

Findings - Radiopharmaceutical legislation

- Lack of specificity concerning radioactive therapeutic compounds in the legislation at both a national and European level
- Heterogeneous implementation across Europe in particular impacting preparation, administration and distribution of radiopharmaceuticals without a marketing authorisation
- Different legislative processes across Europe potentially delaying and stifling development of, and patient access to, novel radiotherapeutic compounds
- Closer collaboration and disciplinary expertise across the regulatory frameworks and specialist regulator knowledge concerning NMT was identified as a potential means to tackling some of these concerns

Findings - Posology vs dosimetry

- Confusion within the community concerning the requirement for optimisation as stipulated in the BSSD and the need to follow the posology presented in the marketing authorisation
- Lack of specific instruction and therefore a perceived risk in treating off-label may be hindering optimisation at the clinical level
- Identified a need for dosimetry data from clinical trials to support such regimens and a need for regulatory guidance in how to conduct such studies

Findings - Planning and verification

- For most therapies there was a recognised desire for dosimetry guided optimisation and verification
- In most countries this was not sufficiently detailed in legislation or national guidance to become common practice
- Lack of resources in terms of reimbursement, know-how and sufficiently trained staff was identified as the predominant barrier
- Further recommendations would be beneficial, concerning both the requirements for planning and verification

Findings - Dose constraints and patient release

- Heterogeneity in the implementation of dose constraints and patient release criteria was apparent across member states
- Participants indicated a clear desire to see the development of unified dose constraint either at the national or European level
- Interpretation and translation, of “comforter and carer” appeared to vary across Europe. This could lead to significant differences in the potential exposure to household members following a patient's treatment with radionuclides
- Standardised national instructions provided to patients on release from hospital was generally missing for all but the more established therapies
- The social and economic implications of the hospital stay and restrictions on contact will therefore vary depending on the practise of the treating centres

Findings - Waste

- Conditions for management of radioactive waste and effluent were in place across Europe
- The underlying radiological assessments from which conditions are based was not clear
- Either based on an activity concentration limit or a maximum discharge limit per month or year
- Patient access to treatment may be hampered with either a need to travel to a large centre with sufficient waste facilities or potentially long waiting lists as centres are confined in the number of patients they can treat
- The social and economic implications of the hospital stay and restrictions on contact will therefore vary depending on the practise of the treating centres

Findings - Medical physics expert

- Medical physics support was considered insufficient in most countries and also raised as a barrier to implementing treatment planning and verification
- The level of training and accreditation of MPEs across Europe appears to vary, an issue currently being tackled within EFOMP
- There were observed differences in the number of MPEs per centre and this may be somewhat explained by size in addition to the different competencies and responsibilities at the national level