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Healthcare Professionals' Knowledge, Attitudes, and Practices in Radiopharmaceuticals Pharmacovigilance: Contributions to the Development and Validation of a Questionnaire

Nathalia Maciel de Arruda

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Healthcare Professionals' Knowledge, Attitudes, and Practices in Radiopharmaceuticals Pharmacovigilance: Contributions to the Development and Validation of a Questionnaire

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Dissertação apresentada para cumprimento dos requisitos necessários à obtenção do grau de Mestre em **Farmácia – Farmacoterapia e Farmacoepidemiologia** pela Escola Superior de Saúde do Instituto Politécnico do Porto.

Acknowledgment

I would like to express my deepest gratitude to my family, who has always supported me unconditionally, to my friends, and to everyone who, directly or indirectly, contributed to the completion of this thesis and believed in me. Especially to my husband, who always encouraged me to push beyond my limits and accepted to cross the ocean so that I could pursue my long-dreamed master's degree. To each of you, my heartfelt thanks.

Resumo

Introdução: A farmacovigilância monitoriza a segurança de medicamentos, vacinas e substâncias biológicas, promovendo o seu uso racional e prevenindo reações adversas. A notificação espontânea de reações adversas a medicamentos (RAMs) é o principal método de farmacovigilância e gera alertas para minimizar os riscos. Apesar da sua importância, estes eventos são frequentemente subnotificados. No caso dos radiofármacos, esta monitorização é ainda mais complexa devido à possibilidade de reações tardias e à subnotificação. Este estudo pretende contribuir para o desenvolvimento de questionário destinado a avaliar as atitudes, conhecimentos e práticas de farmacovigilância de profissionais de saúde, relativamente a radiofármacos **Metodologia:** Foi realizada uma *scoping review* de questionários que avaliam conhecimento, atitudes e práticas de farmacovigilância entre profissionais de saúde, e o método Delphi foi aplicado para desenvolver um questionário em português para essa avaliação. **Resultados:** A *scoping review* recolheu 14 estudos que serviram de base para o desenvolvimento de um novo questionário. O questionário desenvolvido contém 41 perguntas, divididas em quatro seções: Dados Sociodemográficos, Conhecimento sobre Farmacovigilância, Atitudes e Práticas em Relação à Notificação de Reações Adversas a Radiofármacos, e Motivações e Barreiras à Notificação de Reações Adversas a Radiofármacos. **Conclusão:** Este estudo permitiu o desenvolvimento do questionário validado por consenso, destacou a necessidade de sistemas de notificação acessíveis e de educação contínua para os profissionais.

Palavras-chave: farmacovigilância, profissionais de saúde, radiofármaco, notificações espontâneas, medicina nuclear, questionário, reações adversas a medicamentos, Portugal, notificação de reações adversas.

Abstract

Background: Pharmacovigilance monitors the safety of medications, vaccines, and biological substances, promoting their rational use and preventing adverse reactions. Spontaneous reporting of ADRs is the primary method of pharmacovigilance, generating alerts to minimize risks. Despite its importance, these events are often underreported. In the case of radiopharmaceuticals, this monitoring is more complex due to the possibility of delayed reactions and underreporting. **Methodology:** A scoping review was conducted of questionnaires that assess knowledge, attitudes, and practices of pharmacovigilance among healthcare professionals, and the Delphi method was applied to develop a questionnaire in Portuguese for this evaluation. **Results:** The scoping study resulted in 14 studies that served as the foundation for the development of a new questionnaire, which aims to assess healthcare professionals' understanding and practices related to radiopharmaceutical pharmacovigilance. The developed questionnaire contains 42 questions, divided into four sections: Sociodemographic Data, Knowledge about Pharmacovigilance, Attitudes and Practices Regarding Reporting Adverse Reactions to Radiopharmaceuticals, and Motivations and Barriers to Reporting Adverse Reactions to Radiopharmaceuticals. **Conclusion:** A validated questionnaire developed through a Delphi study emphasized the need for accessible reporting systems and ongoing education for professionals. Establishing an efficient reporting culture is crucial for ensuring patient safety and optimizing the clinical use of radiopharmaceuticals.

Keywords: pharmacovigilance, healthcare professionals, radiopharmaceutical, spontaneous reports, nuclear medicine, questionnaire, adverse drug reactions, Portugal, and adverse reaction notification.

Index

LIST OF ACRONYMS

ADRs	Adverse Drug Reactions
CPLP	Community of Portuguese Language Countries
DGRM	Drug Risk Management Directorate
EANM	European Association of Nuclear Medicine
ESS	School of Health Sciences
INFARMED	National Authority of Medicines and Health Products
MA	Marketing Authorization
RCAAP	The Scientific Open Access Repository of Portugal
RPUs	Regional Pharmacovigilance Units
SNF	National Pharmacovigilance System
SPC	Summary of Product Characteristics
WHO	World Health Organization

Images's Index

Tables's Index

Appendix Index

1. Introduction

1.1. Definitions and Concepts

Pharmacovigilance is defined by the World Health Organization (WHO) as the science and activities related to the detection, evaluation, understanding, and prevention of adverse reactions or other medication-related problems. Its work involves the safety monitoring of all medications, vaccines, and biological substances that have received Marketing Authorization (MA), this makes it an essential activity for promoting the rational use of medicines. MA is granted for a medication following an analysis of its safety and efficacy profile, with this information included and available in the Summary of Product Characteristics (SPC); however, these details may change post-marketing. When a medication is marketed, there is an increased number of reported adverse reactions, as the number of individuals exposed to the medication during clinical trials is limited. Additionally, certain groups of individuals may be excluded from these trials (e.g., pregnant women, nursing mothers, the elderly, individuals with comorbidities, or those using concomitant medications). Furthermore, some reactions may manifest only in the long term. This complicates the identification of all real or potential risks at the time of MA application, with such risks often being discovered and characterized only after the medication is available on the market, where the entire population is exposed to it (Herdeiro et al., 2012).

Defined in 1972 by the WHO, Adverse Drug Reactions (ADRs) are any harmful and unintended responses following the administration of a medication, occurring at dosages typically used for prophylaxis, diagnosis, or treatment, and which can be attributed to a causal relationship between the adverse occurrence and the medication. However, in 2012, the definition of an adverse reaction was revised at the European level to encompass harmful and unintentional reactions to a medication, including the use of medications that have not yet been marketed as well as post-marketed medications due to misuse, occupational exposure, or improper use. Therapeutic decision-making must always consider the "risks" associated with a medication in relation to its anticipated "benefits" (Ferreira-da-Silva et al., 2021).

1.2. History of Pharmacovigilance

The establishment of the Global Pharmacovigilance System began in the 1960s, as a consequence of the disaster caused by the administration of thalidomide to pregnant women, which resulted in thousands of cases of phocomelia (a rare and severe congenital malformation) in children exposed to the drug during gestation. The thalidomide disaster prompted the creation of organized systems to monitor the safety of medications following their market introduction (Herdeiro et al., 2012). It was only after four years on the market that the teratogenicity associated with thalidomide was discovered, leading to its withdrawal (Kim & Scialli, 2011). In 1963, the WHO decided to implement monitoring of ADRs with the aim of detection, recording, and evaluation of these reactions, intending to minimize the risks associated with medication use (Herdeiro et al., 2012). In 1968, a pilot project coordinated by the WHO was developed to investigate and monitor issues related to medication use, with a view to establishing the International Pharmacovigilance System. However, it was not until 1970 that a permanent system for monitoring adverse reactions was established, marking the operational phase of International Pharmacovigilance, which now operates in over 124 countries as full members and 29 countries as associate members (Herdeiro et al., 2012; Pernas, 2009).

Currently, each country has its own medication monitoring system. The aim of the Pharmacovigilance system is to evaluate medications and ensure that their risks do not outweigh their benefits, while also maintaining a system for the detection, recording, and evaluation of potential ADRs, aiming to minimize occurrences and effects of such interactions (Ferreira-da-Silva et al., 2021). Since then, pharmacovigilance has become a public health priority, as ADRs present a high rate of morbidity and mortality in developed countries, resulting in substantial costs for healthcare services and representing a significant burden for patients. The incidence of ADR cases varies by age group, elderly individuals are more affected in hospital settings compared to other age groups due to polypharmacy (Kongkaew et al., 2008).

1.3. Pharmacovigilance System in Portugal

In Portugal, the *Sistema Nacional de Farmacovigilância* (SNF) was established only in 1992, initially set up in a centralized manner. However, since the 2000s, it has operated in a decentralized format, with the creation of Regional Pharmacovigilance Units (RPUs). The establishment of the RPUs has led to increased dissemination of pharmacovigilance, further involving healthcare professionals and fostering closer interaction between reporters and the Pharmacovigilance System. It also included universities to promote their technical and scientific competencies, resulting in an increase in the number of reported ADRs (Batel-Marques et al., 2015). Currently, the SNF comprises nine RPUs that cover the entire continental territory and also function as centers for scientific research and pharmacoepidemiological studies related to medication safety, ensuring proper collection and evaluation of ADRs, as well as continuous promotion of the spontaneous notification system for healthcare professionals (Herdeiro et al., 2012).

According to the SNF, in Portugal, the number of ADR notifications has progressed since the system's inception, reflecting a constant and sustained increase in recent years. Among healthcare professionals, physicians are the primary reporters, followed by hospital pharmacists, who have also shown significant increases in reporting over the past few years. Other healthcare professionals contribute to notifications, although in relatively low numbers (Ferreira-da-Silva et al., 2021). For a pharmacovigilance program to succeed, it is crucial to engage all healthcare professionals who have contact with patients and are involved in reporting adverse drug reactions (Khan et al., 2023).

An analysis conducted by INFARMED, National Authority of Medicines and Health Products, regarding ADR notifications received by the SNF, from its creation in 1992 until 2015, indicates a significant increase in the number of notifications over the years, particularly following the establishment of the RPUs. It was noted that the number of notifications in 2015 was approximately 14 times higher than in 2000, when the RPUs began to be established, demonstrating the improvement of the Pharmacovigilance System, as illustrated in Image 1. Furthermore, Image 2 shows that the primary reporters are pharmaceutical industries, followed by healthcare professionals, particularly physicians, pharmacists, and nurses. There has also been observed engagement from patients in spontaneous reporting. This highlights the importance of studies like this to further promote

the spontaneous notification system among healthcare professionals in other fields, such as medical imaging and radiotherapy.

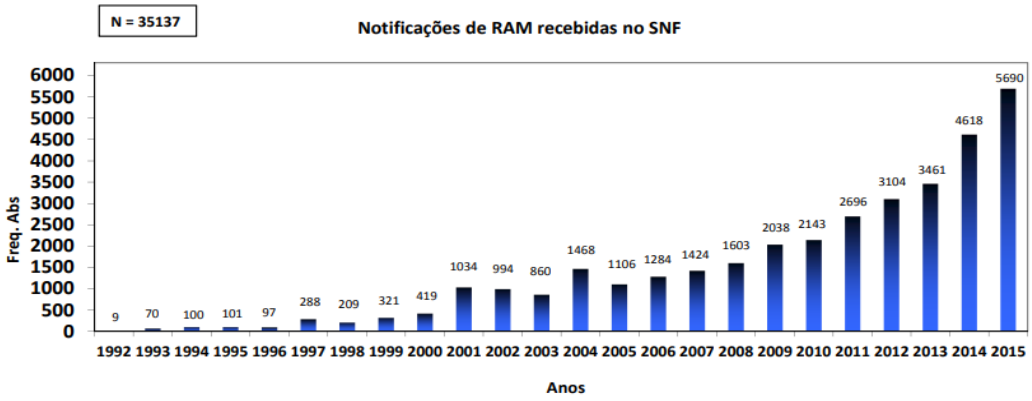

IMAGE 1: Notifications of ADR received in the SNF between 1992 and 2015, removed from: [https://www.infarmed.pt/documents/15786/17838/notificacoes_RAM_2015.pdf/53747787-7dd1-4f8b-a574-39e8b4c75594?version=1.0].

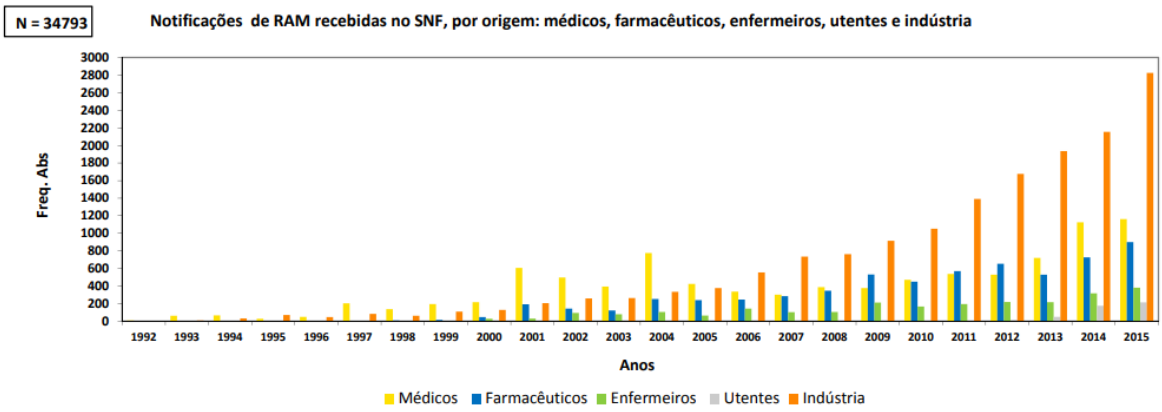

IMAGE 2: ADR notifications received in the SNF from doctors, pharmacists, nurses, and industry, removed from: [https://www.infarmed.pt/documents/15786/17838/notificacoes_RAM_por_origem_2015.pdf/62c831fe-1623-4e0b-8623-1efd89bc9597?version=1.0].

1.4. Spontaneous Reporting System

A spontaneous notification of an ADR consists of describing an adverse event that may have been caused by a medication, primarily aiming to promote the rational use of medicines based on safety and efficacy criteria. Following a suspected ADR, information is collected and analyzed regarding the reaction, identification of the ADR, assessment of the causal relationship between the adverse reaction and the medication, and evaluation of the medication's safety profile. This information is used to develop guidelines for the medication's

use and actions aimed at minimizing the risks associated with the drug in question (Pernas, 2009).

This method is the most important and forms the foundation of pharmacovigilance in most countries. It is extremely effective for enhancing post-marketing pharmacovigilance data, facilitating the generation of alert signals that promote further testing and studies to minimize risks. Such practices can prevent new cases by prompting the pharmaceutical industry to take possible actions, such as improving labeling or adding information to the patient leaflet. For a new medication to be considered safe, it must be on the market for several years; thus, the role of pharmacovigilance becomes indispensable for continuously evaluating the medication's safety profile (Khan et al., 2023; Ribeiro-Vaz et al., 2016).

All serious or unexpected ADRs must be reported by healthcare professionals or patients. The required data includes: details related to the adverse reaction (description, onset date, duration, severity, progression); identification related to the medication (batch number, route of administration, daily dosage, therapeutic indication); any concomitant medication use; patient information (initials, date of birth, weight, and height); and notifier information (name, specialty, workplace, contact details). This data generates alert signals that will be analyzed by the competent authorities. However, despite its importance, spontaneous reporting has disadvantages, such as limitations regarding the population exposed, difficulties in detecting ADRs, the quality of notifications, and especially underreporting. Reporting suspected ADRs by all healthcare professionals involved in patient contact is strongly supported by the WHO's Drug Monitoring Program (Passier et al., 2009).

In Portugal, the spontaneous notification system is implemented through the completion of a form (Adverse Drug Reaction Notification Form) developed by INFARMED, currently directed at all healthcare professionals. This form requests information regarding the ADR, the suspected medication, any concomitant medication, and patient details, including personal data and medical history (initials, age, sex, current medications, time to onset of the reaction, signs and symptoms, healthcare professional details, and additional data). Once completed, this form is forwarded to the Drug Risk Management Directorate (DGRM) of INFARMED for causality analysis.

The analysis is based on the collected information and the patient's evolution after suspension and reexposure. The profile of the adverse reaction is defined in terms of clinical and laboratory manifestations, severity and intensity, frequency for drugs within the same

class, possible mechanisms of action, causal relationship, predisposing factors, and reversibility or sequelae. Following the analysis, responses to specific questions provide the basis for classifying the reaction into categories. According to the degree of certainty regarding causal relationships between ADRs and the prescribed medication, the WHO distinguishes several causality categories: defined, probable, possible, unlikely, conditional, and unclassifiable. Once validated and coded, the data is transferred to a database for the Drug Risk Management Directorate (where the original database resides). Additionally, ADR notifications can be submitted via mail, fax, telephone, email, or an online form (Herdeiro et al., 2012).

1.5. Pharmacovigilance of Radiopharmaceuticals

A radiopharmaceutical is defined as any product containing a radioactive isotope associated with its composition, which can be used for specific purposes, both therapeutic, to cure or alleviate diseases, and diagnostic, typically in oncology, cardiology, and neurology to detect abnormal changes depending on the pathology. The use of radiopharmaceuticals must be monitored while the medication is in the patient's body. These medications often present various adverse reactions, such as pallor, fainting, sweating, hypotension, bronchospasms, pruritus, erythema, among others. It is crucial that these adverse reactions are reported, generating information for nuclear medicine to inform any future interventions when using the same drug again. They can also affect the gastrointestinal tract muscles, causing diarrhea and vomiting. However, adverse events resulting from radioactivity may take years to develop (Kumar et al., 2016; Pérez-Iruela et al., 2021). Radiopharmaceuticals are relatively safe medications, as they are usually administered in low doses or limited numbers. When used for diagnostic purposes, they are given in very low doses, thus lacking therapeutic effect; therefore, adverse events related to the use of radiopharmaceuticals for diagnostic purposes are considered rare (Schreuder et al., 2019). Moreover, adverse events associated with radiopharmaceuticals may be underreported or not easily detected, as the adverse event may occur after the patient has left the facility where the radiopharmaceutical was administered, and there is generally no follow-up for these patients.

Adverse reactions can occur in two forms: predictable reactions, which depend on the dosage and pharmacology of the medication, and unpredictable reactions, which are not dose-dependent and are often associated with immune responses. In addition to adverse

reactions, interactions between medications are also monitored. Regarding the reporting of ADRs in the case of radiopharmaceuticals, there is a challenge in establishing causal relationships between the administered radiopharmaceutical and the resulting effects, as ADRs frequently manifest after the patient has left the healthcare facility where the medication was given (Pérez-Iruela et al., 2021). Knowledge about the occurrence of adverse events associated with radiopharmaceuticals remains quite limited, underscoring the need to educate healthcare professionals to enable the detection of these events (Schreuder et al., 2019).

Despite the current challenges in pharmacovigilance for radiopharmaceuticals, various initiatives have been undertaken to address these issues (Martins et al., 2024). The European Medicines Agency has developed guidelines providing specific information on the submission of data related to radiopharmaceuticals, aiming to streamline the regulatory process (Schreuder et al., 2021). Studies have been conducted to determine the type, causality, and frequency of patient-reported adverse events associated with radiopharmaceuticals. These investigations aim to improve the understanding and management of these events from the patient's perspective, contributing to a more comprehensive pharmacovigilance approach. By focusing on patient-reported outcomes, researchers can gain valuable insights into the real-world impact of radiopharmaceuticals. The European Association of Nuclear Medicine (EANM) has established guidelines on good radiopharmacy practices to assist healthcare establishments in the preparation of radiopharmaceuticals, ensuring their safe administration (Gillings et al., 2021). These guidelines cover various aspects of radiopharmaceutical preparation, including quality control, documentation, and personnel requirements, providing a framework for consistent and safe practices across different institutions. Public access to pharmacovigilance data has been made available in several countries, promoting transparency and facilitating research. The Adverse Event Reporting System in the USA and EudraVigilance in Europe allow researchers, students, and the general public to access this information. This open access approach enables broader analysis of safety data and promotes collaborative efforts in improving radiopharmaceutical safety. These initiatives collectively represent crucial steps towards achieving a more harmonized approach to pharmacovigilance for radiopharmaceuticals globally. By addressing regulatory, clinical, and practical aspects of radiopharmaceutical use, these efforts aim to enhance patient safety and optimize the therapeutic potential of these unique medicinal products (Martins et al., 2024).

To the best of our knowledge there was no study conduct on knowledge, attitudes and practices of radiopharmaceutical´s pharmacovigilance among health care providers. Our study aims to conduct a scoping review on available pharmacovigilance questionnaires, aimed among health professionals, proposal of a questionnaire related to knowledge, attitudes and practices of radiopharmaceutical´s pharmacovigilance among health care providers, and finally proceed with a validation via Delphy Panel of the developed questionnaire.

2. Methodology (Materials and Methods)

The research was divided in two moments:

- A scoping review for questionannaires used to assess pharmacovigilance knowledge, attitudes, and practices among healthcare professionals
- A Delphi Study, to make a proposal for a Questionnaire in Portuguese , for assessing the knowledge, attitudes, and practices among healthcare professionals

2.1. Scoping Review

For the questionnaire development, a literature review of previous studies related to pharmacovigilance, healthcare professionals' knowledge, and attitudes towards adverse drug reaction reporting was conducted to identify relevant aspects, types of questions, and potential inquiries. The choice of conducting a scoping review is related with the need to map the available evidence on the topic under study and to identify existing knowledge gaps (Munn et al., 2018). This review was conducted following the methodology proposed by the Joanna Brigs Institute.

2.1.1. Research Question

The primary research question was: "What types of questionnaires have been used to assess pharmacovigilance knowledge, attitudes, and practices among healthcare professionals?

2.1.2. Eligibility Criteria

Studies were eligible if they:

1. Used a questionnaire or survey to assess pharmacovigilance knowledge, attitudes, or practices;
2. Focused on healthcare professionals (e.g. physicians, pharmacists, nurses);
3. Were published in English, Spanish and Portuguese;
4. No restrictions were placed on publication date or geographical location.

2.1.3. Search Strategy

A comprehensive search was conducted in the following electronic databases from inception to December 2023 on Pubmed/MEDLINE. The search strategy was developed with the following keywords: pharmacovigilance, healthcare professionals, questionnaire, adverse drug reactions, adverse reaction reporting. Reference lists of included studies were also screened for additional relevant articles. Grey literature was also searched in the Portuguese Open Access Scientific Repository (RCAAP).

2.1.4. Study selection

We utilized Rayyan, a web-based systematic review software, to facilitate the screening and selection process of studies. Rayyan was chosen for its ability to expedite the initial screening of abstracts and titles through semi-automation, while maintaining user-friendliness and compatibility with various skill levels. Two reviewers independently screened titles and abstracts of retrieved citations. Full texts of potentially relevant articles were then assessed independently by two reviewers against the eligibility criteria. Disagreements were resolved through discussion or consultation with a third reviewer (Mourad Ouzzani et al., 2016).

2.1.5. Data extraction

One reviewer extracted data, which was verified by a second reviewer. Information extracted included:

- Objectives;
- Target audience;
- Number of sections;
- Content within each section;
- Number of questions per section;
- Methods used for questionnaire development and validation

A synthesis was conducted to summarize the characteristics and content of pharmacovigilance questionnaires. Questionnaires were categorized based on the domains assessed and target healthcare professional group.

2.2. Delphi study

This Delphi study was built upon the scoping review findings to establish expert-driven guidelines for creating effective pharmacovigilance questionnaires, addressing current gaps in the literature and improving the quality of future research in this field.

2.2.1. Panel Composition

For the panel composition, experts of pharmacovigilance and nuclear medicine were contacted in Portugal. Contacts were made through Pharmacovigilance Regional Centers and Institutions of Higher education. Further contacts were made for Portuguese speaking experts working abroad. A total of 17 experts were contacted and 8 agreed to participate (3 from pharmacy and 5 from nuclear medicine).

2.2.2. Delphi Process

Round 1:

Initially, the first draft was reviewed by eight experts in pharmacy and nuclear medicine to ensure the clarity, relevance, and comprehensiveness of the questions. A pilot test was conducted with these professionals to identify any issues with the wording or structure of the questions. Based on the experts' feedback, the questionnaire was analyzed, revised, and edited, followed by a second round of review to finalize it, ensuring that it effectively captured the necessary information while being user-friendly and comprehensible.

Round 2:

A new version of the questionnaire was presented. Experts were asked to re-rate the items and provide feedback regarding the alterations.

Round 3:

The process was continued until consensus was reached or stability in responses was observed.

2.2.3 Ethical Considerations

This study is part of a larger research project that received approval from the Ethics Committee of the School of Health Sciences (ESS) (latest update: CE0090E). The expert panel members provided written consent, and their identities were kept anonymous.

3. Results and Discussions

3.1. Results from the Scoping Review

The scoping review identified 203 papers on the topic. After filtering for language and reviews, 189 papers were left. The reviewers assessed the papers in accordance with the PRISMA Diagram below.

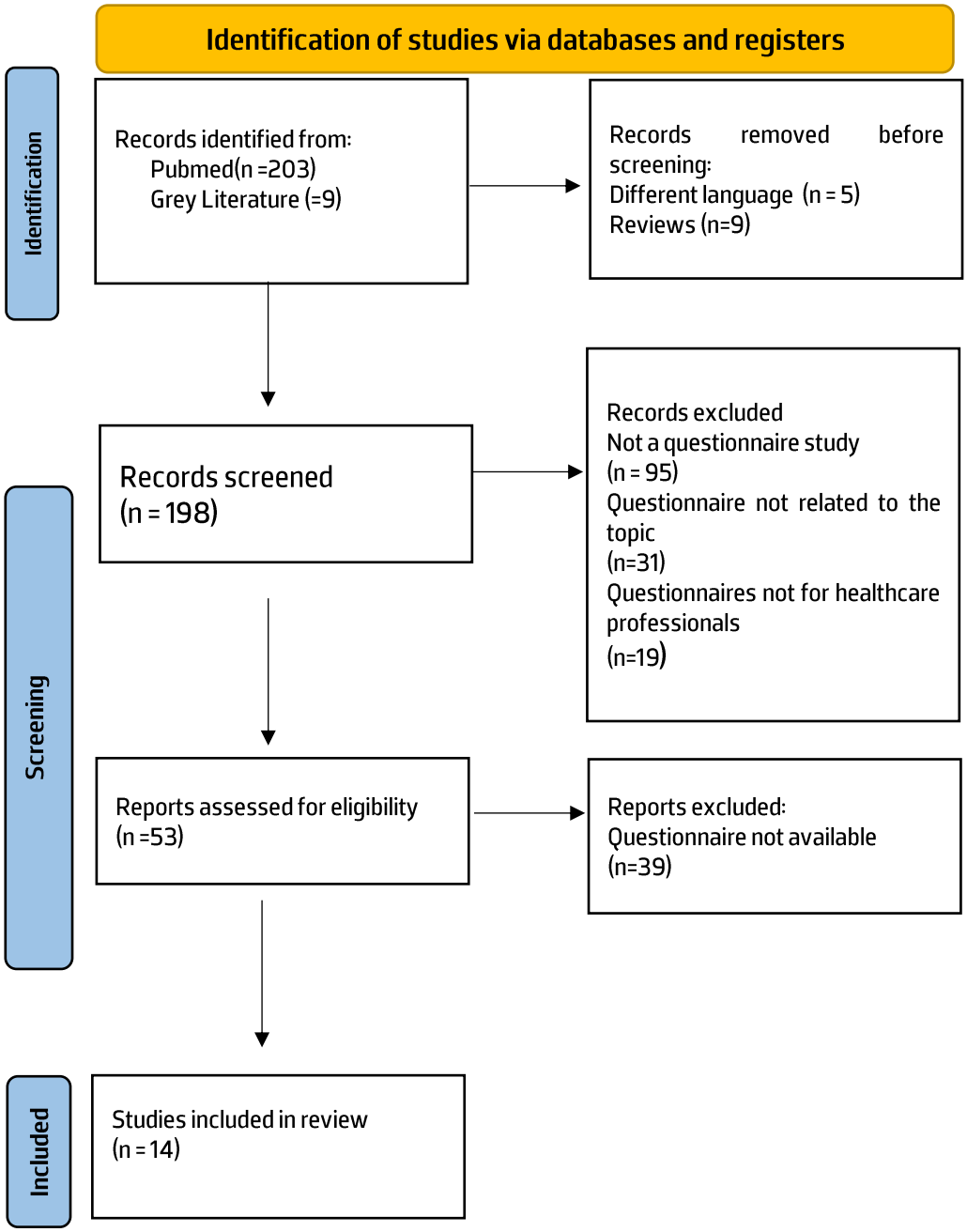

IMAGE 3: PRISMA diagram related to the research conducted.

3.1.1. Characterization of the reports retrieved

All 14 studies were assessed, and their characteristics were detailed in the table below.

Author	Title	Objectives	Dimensions	Population
(Passier et al., 2009)	Reporting of adverse drug reactions by general practitioners A questionnaire-based study in the netherlands	To reveal aspects of knowledge, attitudes, and behaviors that may encourage general practitioners to report (more) adr	Section 1: 6 questions – knowledge of pharmacovigilance Section 2: 5 questions – attitude and doubts Section 3: open question – suggestions for stimulating reporting	Doctors
(Pernas, 2009)	Farmacovigilância: As atitudes dos enfermeiros perante a notificação	To know and understand the attitudes and knowledge associated with underreporting of adrs by nurses in the region corresponding to the central portugal health administration	Section 1: instructions for correct filling Section 2: 16 questions – adr reporting Section 3: 3 questions – spontaneous adr reporting program Section 4: 6 questions – sociodemographic and professional data	Nurses
(Teixeira Rodrigues et al., 2015)	Physicians' attitudes and knowledge concerning antibiotic prescription and resistance: questionnaire development and reliability	To understand doctors' behavior in prescribing antibiotics to improve antibiotic use and combat rising antimicrobial resistance rates. To develop and validate content validity and reliability to assess attitudes and knowledge underlying physician prescribing of antibiotics	Section 1: instructions for filling out Section 2: 17 questions – attitudes and knowledge about prescribing Section 3: 9 questions – importance of knowledge sources Section 4: 4 questions – sociodemographic and professional data Section 5: open question – ideas about antibiotics and resistance	Doctors
(Mendes Marques et al., 2016)	Nurses' attitudes and spontaneous adverse drug reaction reporting: a case-control study in portugal	Identify attitudes and knowledge related to underreporting of adr by nurses	Section 1: instructions for filling out the questionnaire Section 2: 16 questions – attitudes and knowledge related to adrs Section 3: 3 questions – participation in the	Nurses

			pharmacovigilance system Section 4: 7 questions – personal and professional information	
(Almandil, 2016)	Healthcare professionals' awareness and knowledge of adverse drug reactions and pharmacovigilance	To document the knowledge and attitudes towards adr notification systems and pharmacovigilance among health professionals	Section 1: 5 questions – demographic information Section 2: 17 questions divided into knowledge and perception sections Section 3: adr reporting practices	Health professionals
(Matos, Joaquim, et al., 2017)	Attitudes and knowledge of community pharmacy professionals regarding the spontaneous reporting of adverse drug reactions: a preliminary study in Coimbra, Portugal	To describe the attitudes and knowledge of different community pharmacy professionals about spontaneous adr reporting and to identify factors that may influence adr reporting	Section 1: 4 questions – sociodemographic, personal, and professional characteristics Section 2: 21 questions – behavior, knowledge, and attitude towards spontaneous adr reporting	Community pharmacy professionals
(Matos, Rodrigues, et al., 2017)	Attitudes and opinions of Portuguese community pharmacy professionals towards patient reporting of adverse drug reactions and the pharmacovigilance system	To assess pharmacy professionals, improve consumer involvement in pharmacovigilance, and describe their attitudes toward the pharmacovigilance system and adr reporting by consumers	Section 1: 3 questions – personal information Section 2: 7 questions – factors that encourage reporting Section 3: 13 questions – knowledge about pharmacovigilance Section 4: 6 questions – relationship between professionals and consumers	Community pharmacy professionals
(Angelis et al., 2017)	Testing an explanatory model of nurses' intention to report adverse drug reactions in hospital settings	To test an explanatory model of nurses' intention to report adverse drug reactions in hospital settings, based on the theory of planned behavior	Section 1: 5 questions – sociodemographic Section 2: 8 questions – attitudes towards adr reporting	Nurses
(Laven et al., 2018)	Reporting adverse drug reactions: contribution, knowledge and perception of German pharmacy professionals	To assess the knowledge, contribution, and perception of german pharmacists regarding pharmacovigilance activities to identify their needs for better informing on the subject	Section 1: 4 questions – demographic data Section 2: 3 questions – behavior of pharmacy professionals Section 3: 8 questions – knowledge of pharmacovigilance Section 4: 4 questions – perception of pharmacovigilance Section 5: open question – future reporting	Pharmacists

(Li et al., 2018)	Community pharmacists' knowledge and perspectives of reporting adverse drug reactions in Australia: a cross-sectional survey	To measure the knowledge and perspectives of community pharmacists regarding adr reporting and their reporting practices	Section 1: 10 questions – knowledge of pharmacovigilance Section 2: 13 questions – perspectives on adr reporting Section 3: 4 questions – pharmacist practice	Pharmacists
(Hussain et al., 2021)	Exploring healthcare professionals' knowledge, attitude, and practices towards pharmacovigilance: a cross-sectional survey	To assess the knowledge, attitude, and practices of health professionals (hcps) regarding pharmacovigilance activities in pakistan	Part 1: 18 questions – knowledge about adr reporting Part 2: 7 questions – attitudes of health professionals Part 3: 10 questions – practices regarding adr reporting	Doctors, pharmacists, and nurses
(Adedeji et al., 2021)	Adverse drug reactions reporting practice and Associated factors among community health Extension workers in public health facilities, Southwest, nigeria	To evaluate the attitude, knowledge, practice, and determinants of adr reporting in public health institutions in nigeria.	Section 1: 7 questions – sociodemographic Section 2: 20 questions – knowledge about adr reporting Section 3: 15 questions – attitudes towards adr reporting Section 4: practices and suggestions for improvements	Community health workers
(Li et al., 2022)	Why hospitalbased healthcare professionals do not report adverse Drug reactions: a mixed methods study using the theoretical domains Framework	To identify factors associated with adr reporting and mapping them for a behavioral change framework to inform future interventions designed to improve adr underreporting	Section 1: 5 questions – knowledge about adr reporting system Section 2: 11 questions – greater likelihood of reporting adrs Section 3: 14 questions – lower likelihood of reporting adrs	Health professionals (doctors, nurses, pharmacists)
(Ferreira-da-Silva et al., 2023)	Motivation and knowledge of portuguese community pharmacists Towards the reporting of suspected adverse reactions to medicines: A cross sectional survey	To evaluate the motivation and knowledge of spontaneous adr reporting by community pharmacists in porto, portugal, and generate real evidence about	Section 1: 2 questions – eligibility criteria Section 2: 5 questions – sociodemographic data Section 3: 4 questions – prior habits in spontaneous reporting	Community pharmacists

		the main factors determining adr reporting and raise potential alternatives to the current reporting procedure in community pharmacy	Section 4: 35 questions – knowledge about the portuguese pharmacovigilance system	

Table 1 – Description of the analyzed studies

Questionnaires assessing knowledge, attitudes, and practices of pharmacovigilance among healthcare professionals are essential tools to understand and improve drug safety monitoring. These instruments play a crucial role in identifying gaps in understanding, finding barriers to effective reporting, and informing about interventions to enhance pharmacovigilance activities. For the purpose of this study, we analyzed 13 articles and 1 thesis. The target audience encompasses healthcare professionals such as doctors, nurses, and both hospital and community pharmacists, with a majority being applied to nurses. None of the questionnaires was specific for radiopharmaceuticals.

The structure of these questionnaires typically encompasses several key sections. They often begin with a demographic component, gathering information about respondents' professional backgrounds, including their specific roles, years of experience, and practice settings (Adedeji et al., 2021; Almandil, 2016; Angelis et al., 2017; Ferreira-da-Silva et al., 2023; Laven et al., 2018; Matos, Joaquim, et al., 2017; Matos, Rodrigues, et al., 2017; Pernas, 2009; Teixeira Rodrigues et al., 2015). This contextual information is vital for analyzing how different factors might influence pharmacovigilance knowledge and practices across various healthcare sectors.

The knowledge assessment section is also present in the majority of these questionnaires. It typically includes questions designed to evaluate healthcare professionals' understanding of pharmacovigilance concepts, such as the definition and scope of pharmacovigilance, the criteria for identifying adverse drug reactions, and the processes involved in reporting them. This section often also assesses awareness of national pharmacovigilance systems, regulatory requirements, and the roles of different stakeholders in the pharmacovigilance process (Almandil, 2016; Ferreira-da-Silva et al., 2023; Hussain et al., 2021; Laven et al., 2018; Li et al., 2018; Matos, Rodrigues, et al., 2017; Passier et al., 2009). Questions adapted for this study were included, such as: Are you aware of the existence of any Regional Pharmacovigilance Unit in the area where you work?; Are you familiar with the

different methods for reporting an Adverse Reaction (AR)?; Do you know the portal for reporting an AR? (Ferreira-da-Silva et al., 2023).

Attitude evaluation is another component of these questionnaires. This section explores healthcare professionals' perceptions, beliefs, and motivations related to ADR reporting and pharmacovigilance activities. Questions in this area might probe respondents' views on the importance of ADR reporting, their sense of professional responsibility in this regard, and their confidence in the pharmacovigilance system (Adedeji et al., 2021; Almandil, 2016; Angelis et al., 2017; Ferreira-da-Silva et al., 2023; Hussain et al., 2021; Laven et al., 2018; Li et al., 2018; Matos, Joaquim, et al., 2017; Matos, Rodrigues, et al., 2017; Mendes Marques et al., 2016; Passier et al., 2009). An example of a question from this section was: When was the last time you had contact with a patient who presented suspected adverse reactions ? (Adedeji et al., 2021)

The attitudes section focuses on the behaviors and experiences of healthcare professionals concerning pharmacovigilance. It typically includes questions about the frequency of encountering ADRs, actual reporting practices, and participation in pharmacovigilance-related activities or training. Some questions were adapted, such as: Reporting a suspected adverse reaction to a radiopharmaceutical is a simple and intuitive process; I believe that reporting a suspected adverse reaction to a radiopharmaceutical is a professional obligation; As a healthcare professional, I consider myself to have sufficient clinical knowledge to identify a suspected adverse reaction to a radiopharmaceutical; I consider it important to report reactions that have not yet been described in the RCM (Ferreira-da-Silva et al., 2023).

Developing these questionnaires is a meticulous process that often involves several stages. Researchers typically begin with a comprehensive literature review to identify existing instruments and key topics/dimensions. This is often followed by input from expert panels to ensure content validity and relevance to current pharmacovigilance practices and regulations (Angelis et al., 2017; Li et al., 2018; Matos, Rodrigues, et al., 2017; Pernas, 2009; Teixeira Rodrigues et al., 2015). Moreover some authors (Almandil, 2016; Angelis et al., 2017; Li et al., 2018, 2022; Matos, Joaquim, et al., 2017; Matos, Rodrigues, et al., 2017; Mendes Marques et al., 2016; Passier et al., 2009; Teixeira Rodrigues et al., 2015) highlighted limitations such as low response rates, very specific and/or statistically insignificant small samples. The analysis emphasized the need for a standardized questionnaire that could

comprehensively and accurately capture the attitudes and practices of healthcare professionals regarding pharmacovigilance.

The application of these questionnaires in research has yielded valuable insights across various healthcare settings globally. For instance, some studies have identified knowledge gaps regarding ADR reporting procedures and the scope of reportable events. Attitudinal assessments have revealed common barriers such as lack of time, uncertainty about reporting processes, and concerns about professional liability.

3.1.2. Development of the first draft of the questionnaire

Based on this research, a questionnaire consisting of 41 questions was developed. The questions were divided into short-answer, multiple-choice, and Likert scale questions, distributed across four sections: demographic and professional information, general knowledge of pharmacovigilance, attitudes towards reporting adverse reactions to radiopharmaceuticals, and motivations and barriers to reporting. This structure allowed for a comprehensive assessment of the participants' knowledge and attitudes. Additionally, the questionnaire included an introduction with information about the study's objectives, the estimated completion time, and assurance of response confidentiality. The questionnaire titled "Pharmacovigilance of Radiopharmaceuticals: Knowledge and Attitudes of Healthcare Professionals" is available in Appendix 1.

3.2. Delphy Study

Round 1:

The questionnaire was uploaded to a Microsoft Forms. Expert were asked to rate the importance and relevance of the questionnaire sections and questions. Experts were also asked to identify any issues with the wording, structure of the questions and missing items.

After validation by specialist experts, the following changes were made:

In section 1, titled "Sociodemographic and Professional Data," for question one, the term "gender" was changed to "sex." For question two, concerning age, and question six, concerning the length of time practicing the profession, the format was changed from open-ended questions to age and time brackets. For question three, concerning profession, more options were added, including pharmacist, nurse, and nuclear medicine resident, along with an open field "other" to cover all professionals who might have contact with

radiopharmaceuticals. Additionally, the term "nuclear medicine technician" was changed to "diagnostic and therapeutic technician - nuclear medicine." A new question was added regarding the area of practice, with the following options: conventional nuclear medicine, PET nuclear medicine, outpatient therapy, inpatient therapy, and an open field "other." For question seven, regarding the sector where the professional works, a subtitle was added specifying "in the last 5 years" if the professional had changed their sector of practice. It was proposed to split the question about specific training into two separate questions, resulting in question eight, which addresses specific training in pharmacovigilance and adverse drug reaction (ADR) reporting, and question nine, which focuses specifically on ADR reporting related to radiopharmaceuticals. For question ten, the meaning of the acronym CPLP (Community of Portuguese Language Countries) was added.

In section 2, titled Knowledge about Pharmacovigilance, for question eleven, which was about the professional's knowledge of the existence of a Pharmacovigilance center in their geographical area, the term "centers of Pharmacovigilance" was changed to the correct term "Regional Pharmacovigilance Unit," and "geographical area" was changed to "region where you perform your duties." The order of questions twelve and thirteen was altered, so now it first asks about familiarity with the different ways to report an ADR, and then whether the respondent knows the portal for reporting an ADR.

In section 3, titled Attitudes and Practices Regarding the Reporting of ADRs of Radiopharmaceuticals, in question eighteen, the definition of a serious reaction was added to ensure that professionals who might not know the difference between serious and non-serious reactions respond correctly, and the option "never witnessed an ADR" was added. Question twenty was reformulated, as it was deemed more important to know the process for reporting an ADR than the means by which the ADR was reported. Question twenty-two was reformulated to find out from healthcare professionals who should report adverse reactions to radiopharmaceuticals: only the doctor, other healthcare professionals, the patient, and an open option "other" for the professional to provide their opinion if it differs from the options provided.

In section 4, titled Motivations and Barriers to Spontaneous Reporting of Adverse Reactions to Radiopharmaceuticals, the response options for all questions were modified to include the option "NS/NR" (No Response/No Opinion), in case the professional does not know how to respond, to avoid influencing the analysis of the results. In question twenty-

four, the term "dose of radiopharmaceutical" was changed to "activity of the radiopharmaceutical," since for these drugs what is measured is the activity, not the dose. In question thirty-two, the term "Pharmacovigilance System" was corrected to "National Pharmacovigilance System."

Additionally, throughout the questionnaire, modifications were made related to spelling errors and corrections of misspelled words. Some terms were modified, such as "complaints" to "suspicions," "report" to "notify," and "I believe" to "I consider." Some questions were eliminated due to redundancy.

Round 2:

After the first round a new revised questionnaire was deployed to the experts. They were asked to repeat the protocol. Consensus was found for all questions except one: definition of age of the participants. Three experts considered that we should use age intervals, and 6 experts considered we should use the real age.

Round 3:

In the third round, consensus was reached on all questions, with all experts agreeing that age should be requested as an absolute value, as this would allow for more accurate statistical analysis. This phase is still ongoing, which may affect the robustness of the preliminary results. The lack of complete validation may limit the interpretation and applicability of the conclusions until the process is finalized. The main limitation found in relation to the study was the absence of questionnaires for 39 studies, and due to time constraints, there was no contact with the authors of the articles. Another limitation was the limited availability of studies focusing on medical imaging and radiotherapy professionals, highlighting the importance of continuing this research.

4. Conclusion

The conclusion of this study highlights significant knowledge gaps among healthcare professionals regarding the identification and reporting of ADRs, which may contribute to the underreporting of these reactions. The lack of clarity regarding reporting processes, combined with barriers such as insufficient time and a lack of understanding of pharmacovigilance practices, has a significant impact on reporting rates.

This study resulted in the development of a robust and comprehensive questionnaire on the subject, which can be utilized in future studies related to this area. The development and validation of a specific questionnaire through a Delphi study contributed to identifying and assessing healthcare professionals' attitudes, perceptions, and practices, emphasizing the importance of clear communication and accessible reporting systems. Additionally, the study reinforces the need for continuous training for these professionals to improve ADR detection and reporting, particularly in the field of radiopharmaceuticals, where delayed or rare reactions make monitoring more challenging.

In summary, the study underscores that to advance in the field of radiopharmaceutical pharmacovigilance, it is essential to promote greater engagement and education among healthcare professionals, enhancing their ability to correctly identify and report ADRs. The implementation of more accessible systems and the establishment of an efficient reporting culture are crucial to ensuring patient safety and optimizing the use of radiopharmaceuticals in clinical practice.

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6. Appendix

FARMACOVIGILÂNCIA DE RADIOFÁRMACOS: CONHECIMENTO E ATITUDES DOS PROFISSIONAIS DE SAÚDE

DADOS SOCIODEMOGRÁFICOS

Sexo: ☐ Masculino ☐ Feminino
Idade:_____

Profissão:

☐ Médico Especialista em Medicina Nuclear ☐ Médico Interno em Medicina Nuclear ☐ Enfermeiro
☐ Técnico Superior de Diagnóstico e Terapêutica – Medicina Nuclear ☐ Farmacêutico ☐ Outra

Área de actuação:

☐ Medicina Nuclear Convencional ☐ Medicina Nuclear PET ☐ Terapêutica de Ambulatório
☐ Terapêutica de internamento ☐ Radiofarmácia ☐ Outra

Formação Académica: ☐ Licenciatura ☐ Mestrado ☐ Doutoramento

Há quanto tempo exerce a sua profissão? ☐ 0–2 anos ☐ 3–5 anos ☐ 6–10 anos ☐ Mais de 10 anos

Em que sector exerce a sua profissão? ☐ Sector Público ☐ Sector Privado
Caso tenha mudado o sector de actuação, considere aquele em que exerceu durante mais tempo nos últimos 5 anos.

Recebeu formação específica em farmacovigilância e notificação de RAM?

☐ Sim, durante a formação académica ☐ Sim, em formação extracurricular ☐ Não ☐ Outra

Recebeu formação específica sobre o reconhecimento e notificação de RAM relacionadas especificamente com radiofármacos?

☐ Sim, durante a formação académica ☐ Sim, em formação extracurricular ☐ Não

Qual país onde exerce sua profissão?

Caso tenha mudado o país de actuação, considere aquele em que exerceu durante mais tempo nos últimos 5 anos.

☐ Portugal ☐ Países da União Europeia ☐ Países Pertencente à Comunidade Portuguesa de Língua Portuguesa (CPLP) ☐ Outra

CONHECIMENTO SOBRE FARMACOVIGILÂNCIA

Tem conhecimento da existência de alguma Unidade Regional de Farmacovigilância na região onde desempenha as suas funções? ☐ Sim ☐ Não

Está familiarizado com os diferentes meios de notificar uma RAM? ☐ Sim ☐ Não

Conhece o portal para notificar uma RAM? ☐ Sim ☐ Não

ATITUDES E PRÁTICAS EM RELAÇÃO À NOTIFICAÇÃO DE REACÇÃO ADVERSA A RADIOFÁRMACOS

Está ciente das potencias reacções adversas associadas aos radiofármacos comumente utilizados na sua prática profissional? ☐ Sim ☐ Não

Considera que reacções adversas relacionadas com radiofármacos são subnotificadas? ☐ Sim ☐ Não

Considera que há necessidade de directrizes de farmacovigilância dedicadas especificamente para radiofármacos? ☐ Sim ☐Não

Qual foi a última vez que teve contacto com um utente que apresentou suspeitas de reacções adversas à radiofármacos?

☐ No último mês ☐ No último ano ☐ Entre 1 e 2 anos ☐ Mais de 2 anos ☐ Nunca

A última reacção adversa a um radiofármaco que presenciou, consistia numa:

☐ Reacção grave (consiste em qualquer reacção adversa que conduza à morte, ponha a vida em perigo, requeira a hospitalização ou o prolongamento da hospitalização, conduza a incapacidade persistente ou significativa ou envolva uma anomalia congénita)

☐ Reacção não grave ☐ Nunca presenciei uma RAM

Já notificou uma suspeita de RA à radiofármacos? ☐ Sim ☐ Não

Em caso de ter respondido de modo afirmativo à pergunta anterior, qual o processo utilizado para a notificação da RAM?

☐ Reportando ao laboratório responsável pelo medicamento ☐ Reportando ao Sistema Nacional de Farmacovigilância
☐ Reportando ao meu superior hierárquico ☐ Outra

No seu local de trabalho há uma cultura de aceitação e encorajamento de práticas de Farmacovigilância?

☐ Sim ☐ Não

Quem considera que deverá notificar as reacções adversas à radiofármacos?

☐Apenas o médico ☐ Qualquer profissional de Saúde ☐ O utente ☐ Outro

Está disposto(a) a participar em programs educacionais ou iniciativas destinadas a melhoras o conhecimento acerca da Farmacovigilância de radiofármacos? ☐ Sim ☐ Não

MOTIVAÇÕES E BARREIRAS À NOTIFICAÇÃO ESPONTÂNEA DE REACÇÕES ADVERSAS À RADIOFÁRMACOS

Classifique as afirmações abaixo de 1 – 5, onde 1 corresponde a "discordo totalmente"; 2 "discordo"; 3 "não concordo, nem discordo"; 4 "concordo"; 5 "concordo totalmente". Em caso de não saber responder, marque a opção "NS/NR – não sei/não responde"

A actividade do radiofármaco administrada é tão baixa que o risco de reacção adversa é negligenciável.

1 Discordo totalmente	2 Discordo	3 Não Concordo, Nem discordo	4 Concordo	5 Concordo totalmente

A maioria das reacções reportadas pelos utentes advém de estados de ansiedade dos mesmos, perante o procedimento.

1 Discordo totalmente	2 Discordo	3 Não Concordo, Nem discordo	4 Concordo	5 Concordo totalmente

Mesmo quando usamos outros medicamentos em simultâneo, não há risco de interação com os radiofármacos.

1 Discordo totalmente	2 Discordo	3 Não Concordo, Nem discordo	4 Concordo	5 Concordo totalmente

Receio que o anonimato ou a confidencialidade podem ser quebradas durante o processo de notificação.

1 Discordo totalmente	2 Discordo	3 Não Concordo, Nem discordo	4 Concordo	5 Concordo totalmente

Considero que notificar uma suspeit de reacção adversa a um radiofármaco seja uma obrigação profissional.

Discordo totalmente	2 Discordo	3 Não Concordo, Nem discordo	4 Concordo	5 Concordo totalmente

Notificar uma suspeita de reacção adversa a um radiofármaco é um processo simples e intuitivo.

1 Discordo totalmente	2 Discordo	3 Não Concordo, Nem discordo	4 Concordo	5 Concordo totalmente

Como profissional de saúde, considero ter conhecimento clínico suficiente para identificar uma suspeita de reacção adversa a um radiofármaco.

1 Discordo totalmente	2 Discordo	3 Não Concordo, Nem discordo	4 Concordo	5 Concordo totalmente

Na minha prática profissional diária, conigo detetar facilmente uma suspeita de reacção adversa a um radiofármaco.

1 Discordo totalmente	2 Discordo	3 Não Concordo, Nem discordo	4 Concordo	5 Concordo totalmente

Considero que a comunicação de uma suspeita de reacção adversa a um radiofármaco ao Sistema Nacional de Farmacovigilância poderá impactar na qualidade de vida do paciente ao nível pessoal, social e/ou económico.

1 Discordo totalmente	2 Discordo	3 Não Concordo, Nem discordo	4 Concordo	5 Concordo totalmente

Tenho uma actividade profissional muito intensa e não me sobra tempo para reportar reacções adversas a radiofármacos.

1 Discordo totalmente	2 Discordo	3 Não Concordo, Nem discordo	4 Concordo	5 Concordo totalmente

Não sei quando devo notificar uma reacção adversa a um radiofármaco.

1 Discordo totalmente	2 Discordo	3 Não Concordo, Nem discordo	4 Concordo	5 Concordo totalmente

Notifico uma reacção adversa a um radiofármaco apenas se não tiver certeza da relação causal.				
1 Discordo totalmente	2 Discordo	3 Não Concordo, Nem discordo	4 Concordo	5 Concordo totalmente
É quase impossível determinar se o radiofármaco é responsável pela reacção adversa apresentada.				
1 Discordo totalmente	2 Discordo	3 Não Concordo, Nem discordo	4 Concordo	5 Concordo totalmente
Estaria mais propenso a notificar uma suspeita de reacção adversa a um radiofármaco se o processo fosse mais prático e rápido.				
1 Discordo totalmente	2 Discordo	3 Não Concordo, Nem discordo	4 Concordo	5 Concordo totalmente
Só tenho obrigação de notificar reacções graves ou inesperadas.				
1 Discordo totalmente	2 Discordo	3 Não Concordo, Nem discordo	4 Concordo	5 Concordo totalmente
Só tenho obrigação de notificar reacções que já foram descritas no resumo de características do medicamento (RCM).				
1 Discordo totalmente	2 Discordo	3 Não Concordo, Nem discordo	4 Concordo	5 Concordo totalmente
Considero importante notificar reacções que ainda não foram descritas na RCM.				
1 Discordo totalmente	2 Discordo	3 Não Concordo, Nem discordo	4 Concordo	5 Concordo totalmente
Receio receber repercussões legais ou profissionais se notificar uma reacção adversa a um radiofármaco.				
1 Discordo totalmente	2 Discordo	3 Não Concordo, Nem discordo	4 Concordo	5 Concordo totalmente

Appendix 1: The developed questionnaire "Pharmacovigilance of Radiopharmaceuticals: Knowledge and Attitudes of Healthcare Professionals".