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REVIEW

Ensuring safety in cytotoxic drug preparation: A systematic review of guidelines addressing education for pharmacy professionals

Fernando Moreira*, Ângelo Jesus, Cláudia Pinho, Marlene Santos, Mélanie Serdoura, Agostinho Cruz

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ABSTRACT

Background: Chemotherapy preparation involves the use of specific techniques and equipment, given the need to maintain preparation sterility and its strict prescribed composition, and avoid occupational exposure to cytotoxic agents.
Objective: This study aims to identify the most relevant contents for pharmacy professionals' education and training programs and to elucidate the evaluation procedure these professionals should follow when handling cytotoxics.
Methods: We adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines in conducting and reporting this systematic review. We conducted a literature search in PubMed, Cochrane, and Literatura Latino-Americana e do Caribe em Ciências da Saúde to identify guidelines on cytotoxic drug preparation published between 2004 and 2024. Inclusion criteria included guidelines written in English, Spanish, or Portuguese that addressed the education, training, and/or evaluation of pharmacy professionals involved in handling cytotoxic drugs. We excluded guidelines developed for other health professionals (e.g. nurses) and guidelines exclusively addressing the manipulation of oral dosage forms. Citation searching was also performed to avoid search biases. Three researchers independently selected 20 guidelines that met the inclusion criteria, out of 3781 unique references identified. Four appraisers assessed the guidelines using the Appraisal of Guidelines for Research and Evaluation-II tool.
Results: Recommendations for training in cytotoxic drug handling generally included pre-initiation and periodic assessment. Personal protective equipment and engineering controls use, spill management, and aseptic technique were the most frequently mentioned specific training contents. We have developed a training proposal based on the guidelines, with 4 training levels that address the specific identified content. Each level presents potential competency assessment strategies.
Conclusion: Included publications frequently recognized that conducting educational programs before and during the preparation of cytotoxic drugs was important and the combination of theoretical and practical learning seems of the utmost relevance. The development or update of guidelines in this area should prioritize their effective applicability to facilitate their implementation.

Background

In 2022, there were 20.0 million new cancer cases, and cancer was the leading cause of premature death in several countries, with 9.7 million fatalities.[1] As cancer cases rise, the recognition of the importance of efficient health services has also increased.[2] Accordingly, more health care workers trained in diagnosing and treating cancer will be necessary, including those dedicated to producing chemotherapy.[3,4] Even though

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* **Correspondence:** Fernando Moreira, PhD, LAQV/REQUIMTE, Escola Superior de Saúde, Instituto Politécnico do Porto, Rua Dr. António Bernardino de Almeida, 4200-072 Porto, Portugal.
E-mail address: ffm@ess.ipp.pt (F. Moreira).

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Key Points

Background:

- Chemotherapy preparation for antineoplastic treatments involves a high level of methodological rigor and the adoption of specific handling techniques to guarantee quality preparations and to prevent professionals from being exposed to cytotoxic agents.
- Administrative controls, which encompass policies, procedures, and training programs, act by changing people's behavior and are considered by major organizations as some of the most important measures of protection for employees handling cytotoxic drugs.
- There are several international guidelines that provide recommendations on the handling of cytotoxic drugs, but there are some inconsistencies and differences in the recommendations, particularly in terms of the training and assessment needs of pharmacy professionals.

Findings:

- Professionals should undergo training and a competency assessment before beginning to handle cytotoxic drugs, and they should do this regularly (at least once a year) after starting work to ensure compliance with guidelines.
- Some topics are frequently mentioned in guidelines and should therefore be incorporated in training programs: use of equipment limiting occupational exposure to cytotoxic drugs, management of accidental spills, and adoption of aseptic technique.
- There is a high degree of clarity in terms of the presentation of the guidelines. However, their applicability is low, compromising implementation. By providing guidance on how to implement the recommendations, new or updated versions could enhance their applicability.

chemotherapy's side effects have brought attention to new cancer treatment approaches and the critical role of surgery in treating various solid tumors, the most effective and widely used treatment for most cancers is still chemotherapy.[5,6] Thus, health care institutions need to adequately train and prepare professionals in the tasks associated with accurate, safe, and efficient chemotherapy preparation more than ever.[7,8] Pharmacy professionals (pharmacists and pharmacy technicians) involved in cytotoxic handling may repeatedly expose themselves to very small quantities, leading to cumulative toxicity.[9] Studies have shown that medical staff who come into contact with cytotoxic drugs experience major effects on their DNA, reproductive systems, and the development of new cancers.[10-15] Inadequate education of pharmacy professionals might cause these effects. In fact, the lack of investment in the skills and knowledge of health care professionals is one of the main barriers commonly identified for the safe handling of cytotoxic drugs. On the other hand, adequate training facilitates the safe handling of cytotoxic drugs by health professionals, enabling the adoption of exposure control measures.[16]

A guideline is a type of publication comprising a set of statements, directions, or principles presenting current or future rules or policy to assist health professionals. Government agencies at any level, institutions, organizations, or convening expert panels develop these documents, providing appropriate procedures for specific circumstances. Guidelines contribute to the consistency in the performance of specific procedures.[17,18] Despite the existence of guidelines on handling cytotoxic drugs, there appears to be no universally detailed plan, neither for training nor assessment of pharmacy professionals involved in the compounding of cytotoxic drugs.[19] According to Fazel et al.,[16] no standardized training requirements for handling cytotoxic drugs is a major safety gap. Furthermore, training is often inadequate and merely based on informal peer feedback.[20] Studies concluded that lack of training is one of the main direct causes of cytotoxic exposure, which increases incidents such as needlestick injuries and spills.[21]

Objectives

This study aims to (1) evidence the major strengths and limitations of guidelines on cytotoxic handling that mention specific education and training of pharmacy personnel; and (2) identify the most relevant specific content to be provided in training of professionals who perform or intend to perform the preparation of cytotoxic drugs, as well as the most critical moments for its performance.

Methods

Study design

Researchers conducted this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[22] and registered the protocol in PROSPERO (ID: CRD42024530917).

Search strategy

The researchers performed a search through the Cochrane Library, Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS) and PubMed (including Medline and Pubmed Central) databases. Supplementary File 1 depicts a detailed description of the search equations entered in the different databases. The search formula PEO (P for Problem; E for Exposure; and O for Outcome), used in other previously published reviews,[23,24] enabled the identification of key concepts. Accordingly, the following research query was used in Pubmed and Cochrane databases: "(Handl* OR Manipul*) AND ("Hazardous" OR Cytotox* OR Cytosta*) AND (Education OR Training OR Assessment OR Evaluation OR Administrative OR Guidelines OR Recommendation OR Guidance)". In LILACS database, the search queries "(Handl$ OR Manipul$) AND ("Hazardous" OR Cytotox$ OR Cytosta$) AND (Education OR Training OR Assessment OR Evaluation OR Administrative OR Guidelines OR Recommendation OR Guidance)"; "(Manusea$ OR Manipul$) AND (Perigoso OR Citotox$ OR Citosta$) AND (Educação OR Formação OR Avaliação OR Diretrizes OR

Recomendação OR Orientação)"; (Manej$ OR Manipul$) AND (Peligroso OR Citotox$ OR Citosta$) AND (Educación OR Formación OR Evaluación OR Directrices OR Recomendación OR Orientación)" were used.

Researchers included results between September 2004, the date of the first alert by the National Institute for Occupational Safety & Health that established the current internationally accepted definition of "Hazardous Substances",[25] and December 31, 2024. The researchers conducted a backward citation search through all unique references cited in the guidelines that met the inclusion criteria and all systematic reviews that they flagged during the assessment of eligibility, to avoid search bias (on January 28, 2025). Thus, by checking reference lists of any included guidelines and retrieved relevant systematic reviews, the researchers checked for any eligible studies that might have been missed by the database searches, maintaining the same screening method that was used in the initial search. Endnote software (version 21) identified duplicate references with the "Library > Find Duplicates" tool. Then, the software displayed duplicates sequentially, prompting the user to select the reference to keep and to move the duplicates to the trash folder. The manual review of all identified references strengthened duplicate detection. Three reviewers screened the title, abstract and full-text considering the inclusion and exclusion criteria to identify eligible guidelines to include in the systematic review.

Study selection criteria and process

Researchers defined the inclusion criteria as (1) documents presented as organizational, governmental, or technical guidelines, standards of practice, or articles describing one specific guideline; (2) that depicted education, training, and/or assessment for compounding cytotoxic drugs by pharmacy personnel. Researchers excluded documents strictly related to the handling of oral dosage forms; guidelines exclusively produced for other health professionals (e.g. nurses); recommendations made for nonhospital/clinical settings (pharmaceutical industry; academic setting); and documents written in a different language from English, Portuguese, or Spanish. Researchers also excluded guidelines on cytotoxic drug preparation that presented relevant recommendations on several topics, but did not mention, at least, one specific content to be addressed in educational or training programs or one critical moment to perform training or assessment.[26] The mere mention of the need for training or education in handling cytotoxic drugs did not result in inclusion in this review. Indeed, only guidelines that were specific about the content or timing of training, education, or assessment for pharmacy professionals were considered. When different versions of the same guideline were available (as happened with the International Society of Oncology Pharmacy Practitioners [ISOPP] publications, particularly with the 2007[27] and 2022[28] versions), we considered only the most up-to-date version.

Data extraction

Three researchers reinforced the documents' analysis by searching the specific terms "education", "training", "assessment" and "evaluation" (and their equivalents in Spanish and Portuguese), using the "Find" toolbar and independently registered all sentences associated with the described terms, or others with the same meaning in Microsoft Excel (version 365). To overcome any missing data, the researchers compared the results and elaborated a final joint version of all mentions. The mentions that recommended training and assessment were tabulated and compared against the planned groups for each synthesis, enabling the identification of which studies were eligible for each synthesis. The grouping of data considered the following topics suggested phase for carrying out training and/or assessment; specific training or assessment to be carried out; and the type of training or assessment suggested (theoretical or practical). Other sought data included the mention of documentation for performed courses and assessments. A narrative, textual approach, through summarizing, analyzing, and assessing the body of evidence included in this review, enabled us to conduct the qualitative synthesis. Analysis of the specific contents of recommended educational/training programs revealed patterns and highlighted both homogeneity and heterogeneity. Following translation of expressions in languages other than English into English versions, and registration, mapping, and conversion to uniform expressions, the researchers synthesized the specific contents in different tables.

Statistical analysis

Researchers appraised selected guidelines using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument, which is considered one of the most widely used and prolifically cited tools to perform a comprehensive appraisal of guidelines.[29-31] The AGREE II instrument consists of 23 items, organized within 6 domains (scope and purpose; stakeholder involvement; rigor of development; clarity of presentation; applicability; editorial independence). As recommended, to increase reliability, 4 researchers independently assessed all included guidelines.[32] After collecting all the scores given by each researcher for each domain, the research team calculated the domain scores by summing the scores for each domain item. They then scaled these scores using the following formula: (obtained score − minimal possible score)/(maximal possible score − minimal possible score). Researchers also calculated the median and interquartile range for the domain scores and applied a cutoff system to each domain, also described in other reviews that assessed the quality of published guidelines.[33-35] The cutoff system was as follows: <30% = low quality; 30% to 60% = medium quality; >60%: high quality.

To formally assess the inter-rater reliability for AGREE-II scores, the researchers determined the intraclass correlation coefficient (ICC) using a two-way random model evaluating absolute agreement of single measures on the software IBM SPSS Statistics 29.0.1.0. ICC values below 0.5 denote poor reliability; 0.5–0.75 denote moderate reliability, 0.75–0.9 denote good reliability, and ICCs >0.9 denote excellent reliability.[36]

Results

Quality appraisal of the selected guidelines

The PRISMA[22] diagram illustrates the selection of guidelines (Figure 1).

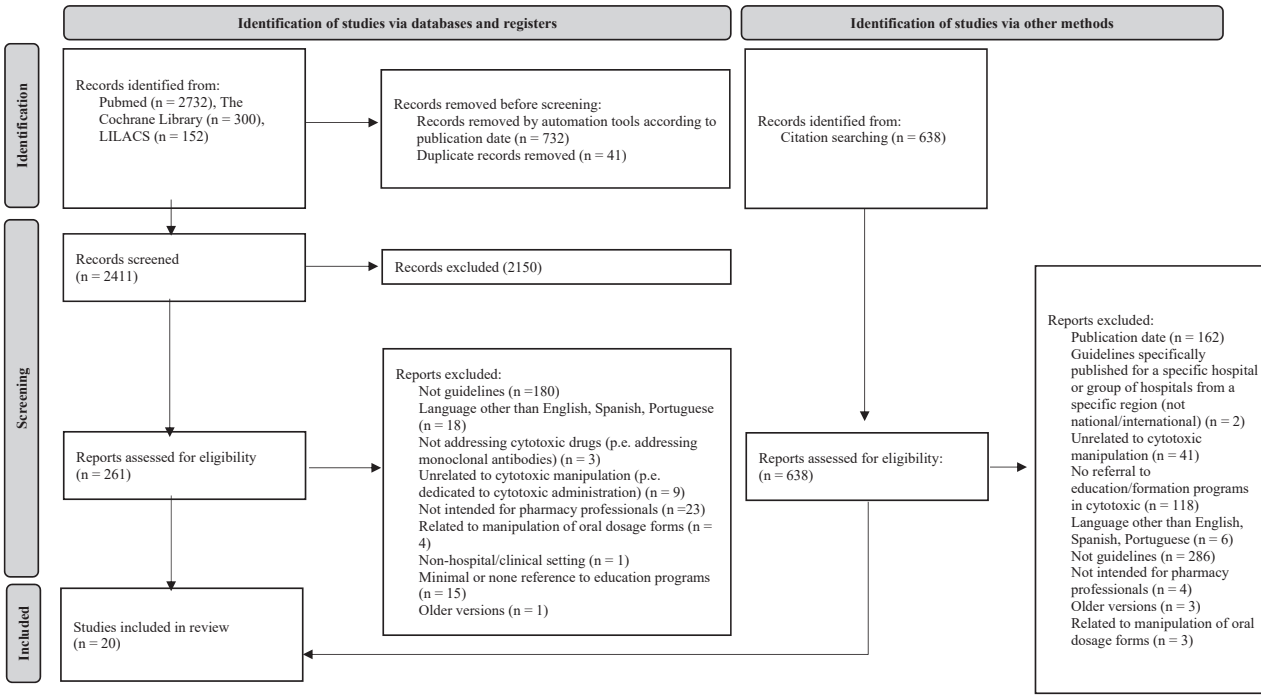

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of the methodological procedure to select the guidelines about education and training on cytotoxic drugs manipulation.

Globally, 4 (Scope and purpose, Stakeholder involvement, Rigor of Development, and Editorial Independence) of the 6 objective domains presented a medium quality (35%–57%) (Table 1). The "applicability" domain demonstrated low quality (20%) in most of the guidelines, while the "clarity of presentation" domain demonstrated high quality (70%). As to ICC, the reliability assessment varied from 0.76 to 0.99 and had a mean of 0.90 (standard deviation: 0.07). In the present study, the inter-rater reliability between the 4 appraisers was excellent for twelve guidelines and good for 8 guidelines.

Critical moments for performing training and assessment in handling cytotoxic drugs

Fifteen (75%) of the twenty guidelines analyzed in this study recommend training in cytotoxic handling before the professional formally and independently starts duties in task,[28,37,38,42-52,54] and recommend regular training after starting work[25,28,39-47,49,51,53,54]; and 7 guidelines (35%) recommend training whenever new drugs, equipment and/or procedures are to be implemented.[28,44,47,48,50-52] Eight guidelines (40%) express the need to assess competencies before starting in the new assignment.[25,28,37,46,47,50-52] Twelve guidelines (60%) expressly mention that periodic reassessment is necessary.[25,28,37,38,40,42,44,46-48,50,52] Ten of the twenty guidelines (50%) consider the importance of formal recording of training and/or assessment of professionals in cytotoxic handling.[28,40,42,45,47-50,52,54]

Use of resources to limit occupational exposure to cytotoxic drugs

Twelve guidelines[25,28,38,40,43,45,47-50,52,54] (60%) emphasize the importance of personal protective equipment (PPE) training for professionals involved in the handling of cytotoxic drugs (Table 2). Several guidelines give special attention to the need for adaptation training in the use of respiratory[38,40,47,50,52] protection.

Out of the considered guidelines, 9 (45%) mentioned the need for training in the use of engineering controls[25,28,38,40,43,47,48,50,52]: 6 (30%) referred to the importance of conducting specific training in the use of the containment primary engineering controls (C-PEC)[25,28,38,40,47,50]; 2 (10%) recognized the importance of training in cleanrooms (also referred to as containment secondary engineering controls)[28,50]; and 3 guidelines (15%) advocate for training in the use of puncturing devices such as the Closed System Drug-Transfer Devices (CSTD), as an alternative to needles[28,38,47] (Table 2).

Practice-oriented training

Thirteen guidelines (65%) state that training in accident and spill control, spill and/or accidental exposure kit use is necessary.[25,28,37-40,43,45,47-49,51,52] Eight (40%) of the guidelines recommend training in aseptic technique[28,37,40-42,47,50,51] and 3 (15%) mention the suitability of colored and/or fluorescent solutions for simulated preparation, either for training or assessment purposes.[28,40,47]

Table 1
Appraisal of Guidelines for Research and Evaluation II domain scores and overall Appraisal of Guidelines for Research and Evaluation II domain scoring of included guidelines and inter-rater reliability assessment

Identification		AGREE II domain						ICC
Organizational affiliation (reference)	Country	Scope and purpose (mS: 3; MS: 21)	Stakeholder involvement (mS: 3; MS: 21)	Rigor of development (mS: 8; MS: 56)	Clarity of presentation (mS: 3; MS: 21)	Applicability (mS: 4; MS: 28)	Editorial independence (mS: 2; MS: 14)	
National Institute for Occupational Safety and Health[25]	USA	High (79%) (IRS: 16-18)	High (67%) (IRS: 14-16)	Medium (42%) (IRS: 26-31)	High (90%) (IRS: 15-21)	Low (25%) (IRS: 8-13)	Medium (51%) (IRS: 8-9)	0.94
Society of Hospital Pharmacists of Australia[37]	Australia	Medium (60%) (IRS: 12-15)	Low (23%) (IRS: 5-9)	Medium (31%) (IRS: 22-25)	High (81%) (IRS: 15-19)	Low (27%) (IRS: 8-15)	Medium (34%) (IRS: 2-8)	0.89
Indian Health Services[38]	USA	Medium (42%) (IRS: 10-12)	Low (18%) (IRS: 6-7)	Low (14%) (IRS: 14-16)	High (71%) (IRS: 13-17)	Low (17%) (IRS: 4-12)	Medium (36%) (IRS: 2-8)	0.78
Instituto Nacional de Seguridad e Higiene en el Trabajo[39]	Spain	Medium (39%) (IRS: 8-12)	Low (19%) (IRS: 5-9)	Low (20%) (IRS: 12-20)	High (70%) (IRS: 14-18)	Low (15%) (IRS: 5-10)	Medium (38%) (IRS: 2-8)	0.77
Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales[40]	Canada	High (76%) (IRS: 15-19)	High (91%) (IRS: 19-20)	High (76%) (IRS: 40-47)	High (95%) (IRS: 19-21)	Medium (54%) (IRS: 18-20)	Medium (55%) (IRS: 8-9)	0.98
European Commission[41]	Belgium	Low (2%) (RS: 3-5)	Low (16%) (IRS: 5-9)	Low (17%) (IRS: 12-19)	Medium (54%) (IRS: 12-14)	Low (28%) (IRS: 9-15)	Medium (38%) (IRS: 2-8)	0.80
Canadian Association of Pharmacy in Oncology[42]	Canada	Medium (47%) (IRS: 10-14)	Medium (50%) (IRS: 11-13)	Medium (34%) (IRS: 22-27)	High (70%) (IRS: 15-16)	High (32%) (IRS: 9-15)	Medium (52%) (IRS: 7-9)	0.91
No organizational affiliation[43]	Canada	High (82%) (IRS: 16-19)	High (82%) (IRS: 17-18)	Medium (48%) (IRS: 29-36)	High (82%) (IRS: 16-19)	Low (21%) (IRS: 7-11)	Medium (60%) (IRS: 8-10)	0.95
Pan American health organization[44]	USA	Low (22%) (IRS: 5-10)	Medium (51%) (IRS: 12-13)	Medium (34%) (IRS: 20-28)	High (70%) (IRS: 15-16)	Medium (57%) (IRS: 19-21)	Medium (54%) (IRS: 8-9)	0.94
No organizational affiliation[45]	Canada	High (74%) (IRS: 15-18)	High (76%) (IRS: 16-17)	High (71%) (IRS: 40-44)	High (83%) (IRS: 17-19)	Low (21%) (IRS: 8-11)	High (94%) (IRS: 11-14)	0.99
American Society of Health-system pharmacists[46]	USA	High (63%) (IRS: 14-16)	High (72%) (IRS: 15-17)	Medium (39%) (IRS: 25-28)	Medium (48%) (IRS: 11-12)	Low (20%) (IRS: 7-11)	High (98%) (IRS: 13-14)	0.96
United States department of Labor[47]	USA	High (80%) (IRS: 16-18)	High (69%) (IRS: 15-16)	Medium (36%) (IRS: 24-28)	High (70%) (IRS: 14-17)	Low (20%) (IRS: 5-14)	Medium (36%) (IRS: 2-8)	0.88
Sociedad Española de Farmacia Hospitalaria[48]	Spain	High (62%) (IRS: 12-17)	Medium (57%) (IRS: 13-14)	Medium (55%) (IRS: 27-39)	Medium (37%) (IRS: 8-12)	Low (19%) (IRS: 6-12)	Medium (36%) (IRS: 2-8)	0.91
No organizational affiliation[49]	India	Medium (38%) (IRS: 9-11)	Medium (38%) (IRS: 9-10)	Low (27%) (IRS: 19-23)	Medium (47%) (IRS: 9-15)	ow (19%) (IRS: 9-10)	High (92%) (IRS: 12-14)	0.90
American Society of Health-System Pharmacists[50]	USA	High (73%) (IRS: 15-18)	High (78%) (IRS: 16-18)	High (63%) (IRS: 33-42)	High (65%) (IRS: 14-15)	Low (27%) (IRS: 7-15)	High (99%) (IRS: 14-14)	0.93
European Society of Oncology Pharmacy[51]	Belgium	Medium (42%) (IRS: 10-11)	Low (15%) (IRS: 3-7)	Low (24%) (IRS: 17-24)	High (67%) (IRS: 14-17)	Low (17%) (IRS: 6-13)	Medium (36%) (IRS: 2-8)	0.83
United States Pharmacopeial Convention[52]	USA	Low (28%) (IRS: 7-9)	Medium (57%) (IRS: 11-14)	Medium (43%) (IRS: 25-33)	High (69%) (IRS: 14-18)	Low (19%) (IRS: 7-11)	Medium (36%) (IRS: 2-8)	0.92
Instituto Nacional de Seguridad e Higiene en el Trabajo[53]	Spain	Low (24%) (IRS: 5-9)	Medium (35%) (IRS: 8-11)	Low (19%) (IRS: 14-19)	Medium (44%) (IRS: 9-12)	Low (13%) (IRS: 4-10)	Medium (38%) (IRS: 2-8)	0.76
International Society of Oncology Pharmacy Practitioners[28]	Canada	Medium (49%) (IRS: 9-13)	High (76%) (IRS: 16-18)	Medium (51%) (IRS: 31-34)	High (83%) (IRS: 18-18)	High (61%) (IRS: 18-24)	Medium (42%) (IRS: 2-9)	0.95
No organizational affiliation[54]	Canada	Medium (46%) (IRS: 11-13)	Medium (57%) (IRS: 12-14)	Medium (32%) (IRS: 23-25)	High (67%) (IRS: 14-16)	Low (17%) (IRS: 5-11)	High (92%) (IRS: 12-14)	0.93
Domain median score, (**interquartile range**)		**Medium 48%** (**38%-74%**)	**Medium 57%** (**26%-75%**)	**Medium 35%** (**25%-50%**)	**High 70%** (**57%-82%**)	**Low 20%** (**18%-28%**)	**Medium 46%** (**36%-84%**)	

Abbreviations used: AGREE, Appraisal of Guidelines for Research and Evaluation; ICC, intraclass correlation coefficient; IRS, Interval of Reviewer Scores; mS, minimum total score per reviewer; MS, maximum total score per reviewer.
Note: Red color shade indicates <30% = low quality; blue color shade indicates 30%-60% = medium quality and green color shade indicates >60%: high quality. Median and interquartile ranges for all included guidelines are written in bold.

Table 2
Mentions of need to perform training in using resources with potential to limit occupational exposure to cytotoxic drugs

References	Specific engineering controls and related mentions	Mentions to PPE use
The National Institute for Occupational Safety and Health[25]	C-PEC: "Train all staff who use ventilated cabinets to employ work practices established for their particular equipment."	"Establish procedures and provide training for handling hazardous drugs safely, cleaning up spills, and using all equipment and PPE properly."
Indian Health Service[38]	C-PEC, CSTD, and luer-lock connections: "Staff must be trained on work practices that reduce potential exposures including proper maintenance and use of BSCs (if available), use of closed system devices (if available), priming, and use of luer-lock connections. (…) all staff using BSCs shall be trained in its proper use."	"Staff must be trained on the proper donning and doffing of PPE. The circumstances under which it should be worn, how long it should be worn, and limitations of PPE. Respiratory protection PPE will require additional training and respirator fit testing."
Association Paritaire Pour la Santé et la Sécurité du Travail du Secteur Affaires Sociales[40]	C-PEC: "The training program should include an assessment tool for each sector: (…) an annual assessment of the quality of sterile handling in preparation cabinets (…)."	"The Continuing education and Orientation program should, at the very least, include the following: (…)use of personal protective equipment, including the proper respirators (…)."
Green, et al.[43]	Unspecified: "Training should cover (…) containment systems (…)."	"Training should cover (…) appropriate personal protective equipment (…)."
Occupational safety and health administration[47]	C-PEC and CSTD: "Training should include at least the following elements: (…) Proper use of safety equipment such as biological safety cabinets, compounding aseptic containment isolators, and closed system transfer devices."	"Whenever respirators are used, OSHA's respiratory protection standard (…) must be followed, which includes requirements for respirator selection, medical evaluation, fit testing and training. Protective equipment and environments should be accompanied by a stringent program of work practices, including operator training and demonstrated competence (…). Employees must be trained in proper methods to remove contaminated gloves and gowns (…)."
Sociedad Española de Farmacia Hospitalaria[48]	Unspecified: "The training programme must be adapted (…), and shall include at least the following: (…) Proper use of containment and barrier equipment and devices."	"The training programme must be adapted (…), and shall include at least the following: (…) correct use of PPE (…)."
Capoor and Bhowmik[49]		"It is the HCFs' responsibility to provide the necessary and adequate PPE and training on how to use the equipment."
American Society of Health-System Pharmacists[50]	C-PEC and C-SEC: "Use of a class II BSC must be accompanied by a stringent program of work practices, including training."; "all staff who will be compounding HDs must be trained in (…) primary, secondary, and supplementary engineering controls."	"As required by OSHA, a complete respiratory program, including proper training and fit-testing, must be completed by all staff require to use respirators. All personnel who work with or around HDs must be trained to appropriately perform their jobs using the established precautions and required PPE."
Eisenberg[52]	"General areas of education as required by USP <800>: (…) use of safety equipment (…)."	"General areas of education as required by USP <800>: (…)Proper use of PPE (…)."
International Society of Oncology Pharmacy Practitioners[28]	C-SEC, C-PEC and CSTD: "The following elements should be added for appropriate staff groups: (…) Theory of containment devices and barriers. (…). This program may contain the following elements: (…) Operational standards for C-SEC including airflow, pressures and safe operating parameters; use of a relevant C-PEC (…);use of institution-specific specialized equipment, including CSTD."	"The following elements should be added for appropriate staff groups: (…) PPE (including donning and doffing) (…)."
Easty, et al.[45]		"It is the employer's responsibility to provide the necessary ppe and training on how to use the equipment."
Kennedy, et al.[54]		"It is very important that health care workers are educated in the appropriate selection and use of Personal protective equipment for protection against exposure to cytotoxic drugs. (…) it is the employer's responsibility to provide the necessary protective equipment and training on how to use the equipment."

Abbreviations used: C-PEC, containment primary engineering controls; C-SEC, containment secondary engineering controls; CSTD, closed-system transfer devices; HCF, health-care facilities; HD, hazardous drugs; PPE, personal protective equipment.

Table 3
Specific relevant theoretical typology education and practice-oriented training considered in the included guidelines about cytotoxic drugs preparation

Reference	Theory-based education				Practice-orientated training			
	Waste management/ disposal	Guidelines, regulations and/or recommendations	Oncological diseases and/or identification, pharmacology and pharmacokinetics of drugs	Health risks inherent to handling practices	Simulated training with noncytotoxic solutions	Aseptic technique training	Training under negative pressure	Management of accidents, spills and/or use of spill and/or accidental exposure kits
The National Institute for Occupational Safety and Health[25]								x
Society of Hospital Pharmacists of Australia[37]	x			x		x		x
Instituto Nacional de Seguridad e Higiene en el Trabajo[39]				x				x
Indian Health Service[38]	x			x				x
Association Paritaire Pour la Santé et la Sécurité du Travail du Secteur Affaires Sociales[40]				x	x	x		x
EudraLex[41]						x		
Green et al.[43]		x		x				x
Occupational Safety and Health Administration[47]	x	x	x	x	x	x	x	x
Sociedad Española de Farmacia Hospitalaria[48]	x	x	x	x				x
Capoor and Bhowmik[49]								x
American Society of Health-System Pharmacists[50]				x		x	x	
European Society of Oncology Pharmacy[51]	x	x	x			x		x
Canadian Association of Pharmacy in Oncology[42]	x					x		
Eisenberg[52]	x	x	x	x				x
Easty, et al.[45]								x
International Society of Oncology Pharmacy Practitioners[28]	x		x	x	x	x		x

Theory-based education

In addition to the previously mentioned topics, whose practical training approach should be reinforced by previous theoretical training, several primarily theoretical topics are also mentioned. This includes the recognition of health risks inherent in handling practices, a topic that is found in half (50%) of the documents.[28,37-40,43,47,48,50,52] Other topics include (1) the identification of dangerous drugs, pharmaceutical forms, and their risks[28,47,51,52]; (2) the acknowledgment of national and international laws, rules, regulations, and good practices[28,43,47,48,51,52]; (3) the management of acute exposure[52]; (4) recognition of the stabilities and compatibilities of cytotoxic drugs[51]; (5) basic pharmacology of cytotoxic drugs[28,47,51]; and (6) cancer types and treatment options[51] (Table 3).

Discussion

Quality appraisal of the selected guidelines

According to Hoffmann-Eßer et al.,[55] a significant proportion of guideline reviews apply a cut-off point to distinguish between high- and low-quality guidelines with one third of them using a 3-step system. In the study by Hoffmann-Eßer et al.,[55] 10 of the 13 included reviews that used a 3-step system applied the same cut-off values adopted in the present review to assess each domain (<30% = low quality; 30%–60% = medium quality; >60%: high quality).[56-65] For example, in the evaluation of guidelines for androgenetic alopecia, the researchers conducted thirty evaluations (5 guidelines; 6 domains), finding that twenty scored above 60% and researchers categorized them as high quality, while 5 scored below 30% and researchers classified them as low quality.[58] In another study assessing fissure sealant guidelines, researchers made eighteen evaluations (across 3 guidelines and 6 domains), rating 8 as high quality (>60%) and another 8 as low quality (<30%).[60] In the present study, 3 of the included guidelines did not present any value considered to be of low quality for any of the domains assessed.[28,40,42] Another 2 guidelines obtained the maximum number of domains assessed as high quality (5 domains).[45,50] Guidelines from Association Paritaire Pour la Santé et la Sécurité du Travail du Secteur Affaires Sociales[40] scored highest in domain 3 (rigor of development). Researchers often consider

domain 3 a pivotal criterion in reviews comparing the quality of guidelines.[66-69] The low-quality ratings of most guidelines in the applicability domain suggest that future documents in this field should adopt an approach that advises and/or presents tools on how to put the recommendations into practice.

Critical moments for performing training and assessment in handling cytotoxic drugs

Hospital units must provide training and competency assessments in cytotoxic handling for pharmacy professionals before starting work and regularly thereafter in order to fulfil the recommendations of most guidelines. However, several publications indicate a lack of universal compliance with this requirement.[70,71] Professionals have already self-reported a direct link between the absence of education and training and the unsafe handling of cytotoxic agents reinforcing the importance of training and assessment in this area.[9]

Equipment that limits occupational exposure to cytotoxic drugs

Directive 2004/37/EC of the European Parliament and the Council, states that, besides eliminating or substituting the hazard, the administrative controls (in which education is included), and the use of engineering controls and PPE are the most important measures of protection for employees in the workplace.[72] Some self-reported data in observational studies with pharmacy professionals suggest that the training and assessment programs set up by hospital units should be rethought to promote an increase in knowledge and adherence to the correct use of available equipment, in topics such as PPE[20,70] and C-PEC.[73]

Pharmacy professionals have not yet generally adopted CSTD.[21,74] The main reasons for the low adherence to the use of CSTD are their cost and the lack of training in their use.[74] These findings reinforce the idea that CSTD training should be promoted, corroborating the recommendations of the Indian Health Service,[38] the Occupational Safety and Health Administration,[47] and the ISOPP.[28] Studies have associated CSTD use with a decrease in cytotoxic agent exposure, thereby promoting safer handling.[75-79] CSTD prevent the spread of aerosols inside the laminar flow chamber, as well as being less prone to accidental punctures compared to needles. The relevance of training in operating with other needleless transfer systems, like spikes, might also be considered given the fact that, although not possessing aerosol retention capacity, they are less expensive than CSTD and safer than needles.[80]

Importance of training in aseptic technique and spill management

Adopting adequate facilities, equipment, and working practices to ensure the sterility of intravenous solutions is crucial for protecting cancer patients.[81] While PPE use and manipulation in C-PEC are crucial foundations of aseptic technique in chemotherapy preparation, they represent only a portion of this broader technique. Personal hygiene rules, the type of movements made inside the C-PEC, cautious and skillful handling of syringes and needles, disinfecting vials and transfer of sterile devices into the C-PEC (e.g. gauze dressings, infusion systems) are other elements to consider.[82,83] Although half of the guidelines recommend training in aseptic technique, not all professionals adopt it when handling cytotoxic drugs. A publication reported that 55% of the interviewees (n = 27) produced cytotoxic drugs in a nonaseptic manner.[71]

Regarding accidental spills, pharmacy professionals should treat them immediately after they occur, which requires that the staff be trained to do so and that they have a spill kit readily available when dangerous drugs are prepared.[52,84] Studies that questioned various health care professionals who habitually worked with cytotoxic drugs revealed that from 38.1% to 41.7% of pharmacy professionals disagreed or completely disagreed about having the capacity to deal with accidental spills.[70] However, these incidents appear to be frequent. A retrospective observational study reported that 21% of pharmacy professionals said they had had spillages during cytotoxic drugs' handling in the week prior to taking part in the study (n = 179).[85]

Assessment programs

The assessment of professionals in handling cytotoxic drugs provides formal evidence of the professionals' ability for that task. Hospitals should make these assessments mandatory before the beginning of tasks and regularly thereafter. To assess the practical performance of professionals in the preparation of cytotoxic drugs, a commonly recommended alternative is the use of colored solutions (such as red dye) or fluorescent solutions under ultraviolet light (such as fluorescein and quinine). These innocuous solutions allow the safe preparation during simulations and might enable the identification of the practices that cause spillages.[28,47,86] Solutions that are not colored under normal light conditions have the advantage of not influencing the professionals during the simulation and resembling more closely most cytotoxic drug solutions, contributing to a greater immersibility during the simulation.[86]

Proposal for the standardization of training programs for the handling of cytotoxic drugs, in a professional context

Considering the recommendations, we elaborated a proposal of training and assessments for pharmacy professionals handling cytotoxic drugs (Figure 2). The presented proposal considered both theoretical and practical education, and targeted the domains of knowledge, judgment, professional and technical skills. Recent studies confirmed the importance and suitability of combining both theoretical and practical education in handling cytotoxic drugs.[87,88] Previous research has already described the relevance of starting the training with on-the-job theoretical learning for other health professional groups performing demanding specific technical tasks.[89] Given that starting from the general to the specific is appropriate, the first theoretical level has more broad information. The second level depicts a theoretical course on technical aspects directly related to manipulation. The third and fourth training levels would basically consist of the practical application of the theoretical concepts the trainees acquired in the previous training level. The main difference between levels 3 and 4 lies in the focus of the practical training - while level 3 would focus on preventing

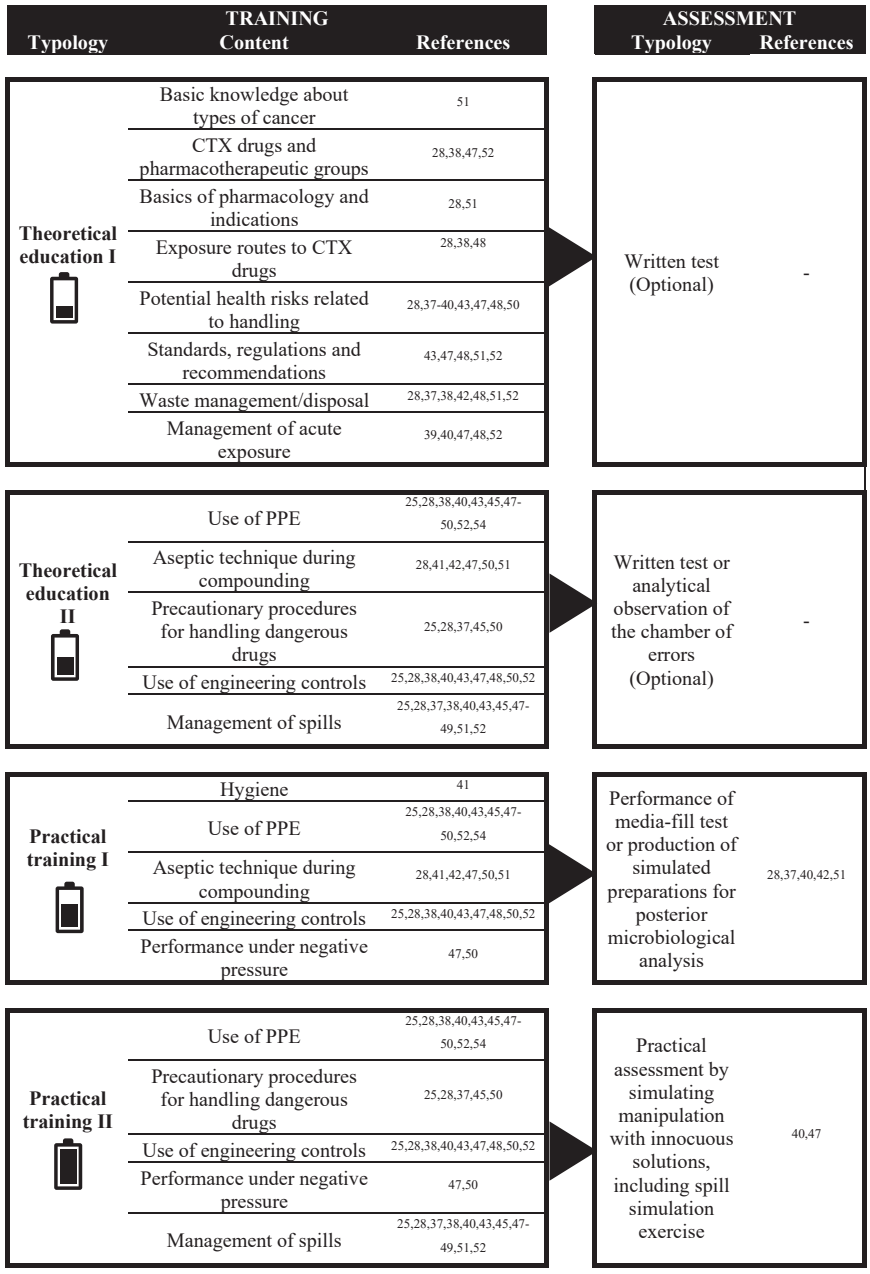

Figure 2. Proposal for standardization of training and assessment elements to be provided to pharmacy professionals aiming to handle cytotoxic drugs. Abbreviations used: CTX, cytotoxic; PPE, personal protective equipment.

contamination of preparations, level 4 would target specific technical skills that minimize exposure to cytotoxic drugs. Given the benefits of communities of practice and situated learning,[89] we recommend that the trainee participates in the teams responsible for handling cytotoxic drugs, during the 4 proposed training levels. At this stage, despite not carrying out handling activities, the trainee will have the opportunity to accompany and interact with experienced professionals in real handling activities, observing them closely.

The guidelines do not outline a specific, more theoretical test that would enable the assessment of professionals at levels one and two; therefore, we consider the assessment of these levels as optional. Still, if institutions consider it relevant, they can apply written tests or, in the case of the second level, assess the ability of trainees to detect bad practices deliberately committed by trainers in a "Chamber of Errors", during which the preparation of cytotoxic drugs is simulated.[90]

Recalling that most guidelines recommend repeating assessment on an annual basis, at minimum all professionals that are already handling cytotoxic drugs on a routine basis, should undergo yearly practical assessments linked to levels 3 and 4.

Documented records of training and assessment of pharmacy professionals in the handling of cytotoxic drugs should always be retained indefinitely in the professional's file.[28,45]

Conclusion

Guidelines on the handling of cytotoxic drugs often emphasize the importance of training and assessing professionals, both before they take up their tasks and periodically afterward. A hospital wishing to demonstrate a formal commitment to complying with international guidelines should include specific training about PPE, engineering controls, spillage management, practical training in aseptic technique, and education on the health risks inherent to occupational exposure to cytotoxic drugs. This review highlights the need for future guidelines to pay special attention to applicability, as the lack of clear strategic recommendations compromises their effective implementation. By presenting a proposal for minimum training that includes all specific contents identified in the different guidelines, in a sequential, rational manner, and divided into theoretical and practical bases, this study can contribute to the standardization of training for professionals in this area, increasing their safety and the effectiveness of the processes.

Disclosure

The authors declare no relevant conflicts of interest or financial relationships.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.japh.2025.102352.

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229–263.
2. Ferrara L, Otto M, Aapro M, et al. How to improve efficiency in cancer care: dimensions, methods, and areas of evaluation. *J Cancer Policy*. 2022;34:100355.
3. Seguin M, Morris M, McKee M, Nolte E. "There's not Enough Bodies to do the Demand": an exploration of key stakeholder views on the role of health service capacity in shaping cancer outcomes in 7 international cancer benchmarking partnership countries. *Int J Health Policy Manag*. 2022;11(7):1024–1034.
4. Trinh LD, Wong JT, Sullivan PA, Nguyen LH, Pham YT. Impact of a chemotherapy workload and productivity dashboard on pharmacy technician turnover. *Am J Health Syst Pharm*. 2019;76(13):992–997.
5. Zaigham A, Sakina R. An overview of cancer treatment modalities. In: Hafiz Naveed S, ed. *Neoplasm*. Ch. 6. London, UK: IntechOpen; 2018.
6. Deo SVS, Sharma J, Kumar S. GLOBOCAN 2020 report on global cancer burden: challenges and opportunities for surgical oncologists. *Ann Surg Oncol*. 2022;29(11):6497–6500.
7. Drapeau F, Claustre G, Gaimard S, Rossard C. [Preparation of injectable anticancer drugs within chemotherapy preparation unit: what levers are available to optimize and secure production?]. *Bull Cancer*. 2023;110(3):301–307. Préparation des traitements anticancéreux injectables au sein d'une unité de pharmacotechnie: quels leviers disponibles pour optimiser et sécuriser la production?
8. Van der Linden L, Van Aelst L. Pharmacists in oncology: evidence still needed, but teaching comes first. *Curr Pharm Teach Learn*. 2024;16(8):102114.
9. Topçu S, Beşer A. Oncology nurses' perspectives on safe handling precautions: a qualitative study. *Contemp Nurse*. 2017;53(3):271–283.
10. Ratner PA, Spinelli JJ, Beking K, et al. Cancer incidence and adverse pregnancy outcome in registered nurses potentially exposed to antineoplastic drugs. *BMC Nurs*. 2010;9:15.
11. Gianfredi V, Salvatori T, Nucci D, Villarini M, Moretti M. [Genotoxic risk in nurses handling antiblastic drugs: systematic review of literature and meta-analysis]. *Recenti Prog Med*. 2017;108(12):511–520. Rischio genotossico da manipolazione di farmaci chemioterapici antiblastici negli operatori sanitari professionalmente esposti: revisione sistematica della letteratura e meta-analisi.
12. Simons A, Toland S. Perceived adverse effects from handling systemic anti-cancer therapy agents. *Br J Nurs*. 2017;26(16):S38–S44.
13. McDiarmid MA, Rogers B, Oliver MS. Chromosomal effects of non-alkylating drug exposure in oncology personnel. *Environ Mol Mutagen*. 2014;55(4):369–374.
14. Moretti M, Grollino MG, Pavanello S, et al. Micronuclei and chromosome aberrations in subjects occupationally exposed to antineoplastic drugs: a multicentric approach. *Int Arch Occup Environ Health*. 2015;88(6):683–695.
15. Mahmoodi M, Soleyman-Jahi S, Zendehdel K, et al. Chromosomal aberrations, sister chromatid exchanges, and micronuclei in lymphocytes of oncology department personnel handling anti-neoplastic drugs. *Drug Chem Toxicol*. 2017;40(2):235–240.
16. Fazel SS, Keefe A, Shareef A, et al. Barriers and facilitators for the safe handling of antineoplastic drugs. *J Oncol Pharm Pract*. 2022;28(8):1709–1721.
17. Franco JVA, Arancibia M, Meza N, Madrid E, Kopitowski K. Clinical practice guidelines: concepts, limitations and challenges. *Medwave*. 2020;20(3):e7887. Guías de práctica clínica: conceptos, limitaciones y desafíos.
18. Joshi GP, Benzon HT, Gan TJ, Vetter TR. Consistent definitions of clinical practice guidelines, consensus statements, position statements, and practice alerts. *Anesth Analg*. 2019;129(6):1767–1770.
19. Bernabeu-Martínez MA, Ramos Merino M, Santos Gago JM, Álvarez Sabucedo LM, Wanden-Berghe C, Sanz-Valero J. Guidelines for safe handling of hazardous drugs: a systematic review. *PLoS One*. 2018;13(5):e0197172.
20. Constantinidis TC, Vagka E, Dallidou P, et al. Occupational health and safety of personnel handling chemotherapeutic agents in Greek hospitals. *Eur J Cancer Care*. 2011;20(1):123–131.
21. Hon CY, Abusitta D. Causes of health care workers' exposure to antineoplastic drugs: an exploratory study. *Can J Hosp Pharm*. 2016;69(3):216–223.
22. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
23. Kelly R, Brown D, McCance T, Boomer C. The experience of person-centred practice in a 100% single-room environment in acute care settings-A narrative literature review. *J Clin Nurs*. 2019;28(13-14):2369–2385.
24. Alemu AY, Derseh L, Kaba M, Gadisa E, Alemu K. Treatment outcomes of cutaneous leishmaniasis due to Leishmania aethiopica: a systematic review and meta-analysis. *PLoS One*. 2023;18(11):e0293529.
25. The National Institute for Occupational Safety and Health N. *Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings*. Atlanta, US: CDC - Centers for Disease Control and Prevention; 2004.
26. Celano P, Kennedy EB, Zon RT. Safe handling of hazardous drugs: ASCO standards summary. *J Oncol Pract*. 2019;15(2):112–114.
27. ISOPP Standards of Practice. Safe handling of cytotoxics. *J Oncol Pharm Pract*. 2007;13 Suppl:1–81.
28. International Society of Oncology Pharmacy Practitioners I. ISOPP standards for the safe handling of cytotoxics. *J Oncol Pharm Pract*. 2022;28(3_suppl):S1–S126.
29. Johnston A, Kelly SE, Hsieh SC, Skidmore B, Wells GA. Systematic reviews of clinical practice guidelines: a methodological guide. *J Clin Epidemiol*. 2019;108:64–76.
30. Hoffmann-Eßer W, Siering U, Neugebauer EA, Brockhaus AC, Lampert U, Eikermann M. Guideline appraisal with AGREE II: systematic review of the current evidence on how users handle the 2 overall assessments. *PLoS One*. 2017;12(3):e0174831.
31. Andrade R, Pereira R, van Cingel R, Staal JB, Espregueira-Mendes J. How should clinicians rehabilitate patients after ACL reconstruction? A systematic review of clinical practice guidelines (CPGs) with a focus on quality appraisal (AGREE II). *Br J Sports Med*. 2020;54(9):512–519.
32. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ*. 2010;182(18):E839–E842.
33. Sanclemente G, Acosta JL, Tamayo ME, Bonfill X, Alonso-Coello P. Clinical practice guidelines for treatment of acne vulgaris: a critical appraisal using the AGREE II instrument. *Arch Dermatol Res*. 2014;306(3):269–277.
34. Ye ZK, Li C, Zhai SD. Guidelines for therapeutic drug monitoring of vancomycin: a systematic review. *PLoS One*. 2014;9(6):e99044.

35. Acuña-Izcaray A, Sánchez-Angarita E, Plaza V, et al. Quality assessment of asthma clinical practice guidelines: a systematic appraisal. *Chest*. 2013;144(2):390–397.
36. Chee E, Huang K, Haggie S, Britton PN. Systematic review of clinical practice guidelines on the management of community acquired pneumonia in children. *Paediatr Respir Rev*. 2022;42:59–68.
37. Society of Hospital Pharmacists of Australia SCoSPiO. SHPA standards of practice for the safe handling of cytotoxic drugs in pharmacy departments. *J Pharm Pract Res*. 2005;35(1):44–52.
38. Indian Health Service I. *Indian Health Manual Chapter 27 - Controlling Occupational Exposure to Hazardous Drugs*. Maryland, US: Indian Health Service; 2006.
39. Instituto Nacional De Seguridad e Higiene en el Trabajo I. *Nota Técnica de Prevención 740 Exposición laboral a citostáticos en el ámbito sanitario*. Madrid, Spain: Instituto Nacional De Seguridad e Higiene en el Trabajo; 2006.
40. *Association Paritaire Pour la Santé et la Sécurité du Travail du Secteur Affaires Sociales A. Prevention Guide - Safe Handling of Hazardous Drugs*. Montreal, Canada: Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales; 2007.
41. EudraLex. *Medicinal Products for Human and Veterinary Use: Good Manufacturing Practice. Annex 1 Manufacture of Sterile Medicinal Products*. Brussels, Belgium: European Commission; 2008.
42. Canadian Association of Pharmacy in Oncology C. *Standards of Practice for Oncology Pharmacy in Canada*. Vancouver, Canada: Canadian Association of Pharmacy in Oncology; 2009.
43. Green E, Johnston M, Trudeau M, et al. Safe handling of parenteral cytotoxics: recommendations for Ontario. *J Oncol Pract*. 2009;5(5):245–249.
44. Pan American Health Organization P. *Safe Handling of Hazardous Chemotherapy Drugs in Limited-Resource Settings*. Washington D.C., US: World Health Organization; 2013.
45. Easty AC, Coakley N, Cheng R, et al. Safe handling of cytotoxics: guideline recommendations. *Curr Oncol*. 2015;22(1):e27–e37.
46. Goldspiel B, Hoffman JM, Griffith NL, et al. ASHP guidelines on preventing medication errors with chemotherapy and biotherapy. *Am J Health Syst Pharm*. 2015;72(8):e6–e35.
47. Occupational Safety and Health Administration O. *Controlling Occupational Exposure to Hazardous Drugs*. Washington D.C., US: United States Department of Labor - Occupational Safety and Health Administration; 2016.
48. Sociedad Española de Farmacia Hospitalaria S. *Monografías de Farmacia Hospitalaria y de Atención Primaria: Medicamentos Peligrosos*. Madrid, Spain: Bayer Hispania SL; 2016.
49. Capoor MR, Bhowmik KT. Cytotoxic drug dispersal, cytotoxic safety, and cytotoxic waste management: practices and proposed India-specific guidelines. *Indian J Med Paediatr Oncol*. 2017;38(2):190–197.
50. American Society of Health-System Pharmacists A. ASHP guidelines on handling hazardous drugs. *Am J Health Syst Pharm*. 2018;75:1996–2031.
51. European Society of Oncology Pharmacy E. *Quapos 6 - Quality Standard for the Oncology Pharmacy Service*. Hamburg, Germany: European Society of Oncology Pharmacy; 2018.
52. Eisenberg S. USP <800> and strategies to promote hazardous drug safety. *J Infus Nurs*. 2018;41(1):12–23.
53. Instituto Nacional de Seguridad y Salud en el Trabajo I. *Nota Técnica de Prevención 1.134 - Exposición laboral a medicamentos peligrosos: sistemas seguros para su preparación*. Madrid, Spain: Instituto Nacional de Seguridad y Salud en el Trabajo; 2018.
54. Kennedy K, Vu K, Coakley N, et al. Safe handling of hazardous drugs. *J Oncol Pharm Pract*. 2023;29(2):401–412.
55. Hoffmann-Eßer W, Siering U, Neugebauer EAM, Lampert U, Eikermann M. Systematic review of current guideline appraisals performed with the Appraisal of Guidelines for Research & Evaluation II instrument—a third of AGREE II users apply a cut-off for guideline quality. *J Clin Epidemiol*. 2018;95:120–127.
56. Chen Y, Hu S, Wu L, Fang X, Xu W, Shen G. Clinical practice guidelines for hypertension in China: a systematic review of the methodological quality. *BMJ Open*. 2015;5(7):e008099.
57. Gutarra-Vilchez RB, Barajas-Nava L, Aleman A, et al. Systematic evaluation of the quality of clinical practice guidelines on the use of assisted reproductive techniques. *Hum Fertil*. 2014;17(1):28–36.
58. Huang M, Zhou X. Appraisal of guidelines for androgenetic alopecia using the appraisal of guidelines for research and evaluation II instrument. *J Eval Clin Pract*. 2015;21(6):1089–1094.
59. Li CC, Wang YQ, Li YP, Li XL. Critical appraisal of clinical practice guidelines for treating pancreatic cancer based on the global disease burden. *J Evid Based Med*. 2015;8(1):11–21.
60. San Martin-Galindo L, Rodríguez-Lozano FJ, Abalos-Labruzzi C, Niederman R. European fissure sealant guidelines: assessment using AGREE II. *Int J Dent Hyg*. 2017;15(1):37–45.
61. Santos F, Sola I, Rigau D, et al. Quality assessment of clinical practice guidelines for the prescription of antidepressant drugs during pregnancy. *Curr Clin Pharmacol*. 2012;7(1):7–14.
62. Schildmann EK, Schildmann J, Kiesewetter I. Medication and monitoring in palliative sedation therapy: a systematic review and quality assessment of published guidelines. *J Pain Symptom Manage*. 2015;49(4):734–746.
63. Shen J, Sun M, Zhou B, Yan J. Nonconformity in the clinical practice guidelines for subclinical Cushing's syndrome: which guidelines are trustworthy? *Eur J Endocrinol*. 2014;171(4):421–431.
64. Wang Y, Luo Q, Li Y, et al. Quality assessment of clinical practice guidelines on the treatment of hepatocellular carcinoma or metastatic liver cancer. *PLoS One*. 2014;9(8):e103939.
65. Yan J, Min J, Zhou B. Diagnosis of pheochromocytoma: a clinical practice guideline appraisal using AGREE II instrument. *J Eval Clin Pract*. 2013;19(4):626–632.
66. Arevalo-Rodriguez I, Pedraza OL, Rodríguez A, et al. Alzheimer's disease dementia guidelines for diagnostic testing: a systematic review. *Am J Alzheimers Dis Other Demen*. 2013;28(2):111–119.
67. Bekkering GE, Aertgeerts B, Asueta-Lorente JF, et al. Practitioner review: evidence-based practice guidelines on alcohol and drug misuse among adolescents: a systematic review. *J Child Psychol Psychiatry*. 2014;55(1):3–21.
68. Smith CA, Toupin-April K, Jutai JW, et al. A systematic critical appraisal of clinical practice guidelines in juvenile idiopathic arthritis using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument. *PLoS One*. 2015;10(9):e0137180.
69. Kim SG, Jung HK, Lee HL, et al. Guidelines for the diagnosis and treatment of helicobacter pylori infection in Korea, 2013 revised edition. *J Gastroenterol Hepatol*. 2014;29(7):1371–1386.
70. Hon CY, Teschke K, Shen H. Health care workers' knowledge, perceptions, and behaviors regarding antineoplastic drugs: survey from British Columbia, Canada. *J Occup Environ Hyg*. 2015;12(10):669–677.
71. Santos Junior A, Souza D, Garrido J, Tannus C, Saba H, Magalhães H. *Biossegurança em oncologia e o profissional farmacêutico: análise de prescrição e manipulação de medicamentos antineoplásicos*. 40. Bahia, Brazil: Revista Baiana de Saúde Pública; 2017.
72. Council EPat, ed. *Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work*. Brussels, Belgium: Official Journal of the European Communities; 2004.
73. Campos D, Silva I, Rego M, Correia P, Moreira F. Characterization of education, technical practices and attitudes of Portuguese pharmacy technicians towards manipulation of cytotoxic drugs. *J Oncol Pharm Pract*. 2024;30(5):893–901.
74. Boiano JM, Steege AL, Sweeney MH. Adherence to safe handling guidelines by health care workers who administer antineoplastic drugs. *J Occup Environ Hyg*. 2014;11(11):728–740.
75. Vyas N, Turner A, Clark JM, Sewell GJ. Evaluation of a closed-system cytotoxic transfer device in a pharmaceutical isolator. *J Oncol Pharm Pract*. 2016;22(1):10–19.
76. Soefje S, Rickabaugh K, Rajkumar R, Wall KP. Evaluation of closed-system transfer devices in reducing potential risk for surface contamination following simulated hazardous-drug preparation and compounding. *Int J Pharm Compd*. 2021;25(6):515–522.
77. Piccardo MT, Forlani A, Izzotti A. Effectiveness of closed system drug transfer devices in reducing leakage during antineoplastic drugs compounding. *Int J Environ Res Public Health*. 2021;18(15):7957.
78. Simon N, Vasseur M, Pinturaud M, et al. Effectiveness of a closed-system transfer device in reducing surface contamination in a new antineoplastic drug-compounding unit: a Prospective, controlled, Parallel study. *PLoS One*. 2016;11(7):e0159052.
79. Gurusamy KS, Best LM, Tanguay C, Lennan E, Korva M, Bussières JF. Closed-system drug-transfer devices plus safe handling of hazardous drugs versus safe handling alone for reducing exposure to infusional hazardous drugs in healthcare staff. *Cochrane Database Syst Rev*. 2018;3(3):Cd012860.
80. Ali N, Carmo H, Robalo R, Rocha L, Fernandes C, Moreira F. A simple and inexpensive method to monitor and minimize exposure from manipulation of cytotoxic drugs. *J Oncol Pharm Pract*. 2024;30(2):257–262.
81. Power LA, Coyne JW. ASHP guidelines on handling hazardous drugs. *Am J Health Syst Pharm*. 2018;75(24):1996–2031.
82. USP TUSPC. *<797> Pharmaceutical Compounding—Sterile Preparations*. Maryland, US: U.S. Pharmacopeia (USP); 2019.
83. Ocha PV, Jose. *Concepts in Sterile Preparations and Aseptic Technique*. 1st ed. Massachusetts, US: Jones & Bartlett Learning; 2014.
84. Meade E. Avoiding accidental exposure to intravenous cytotoxic drugs. *Br J Nurs*. 2014;23(16):S34. S36-9.

85. Boiano JM, Steege AL, Sweeney MH. Adherence to precautionary guidelines for compounding antineoplastic drugs: a survey of nurses and pharmacy practitioners. *J Occup Environ Hyg*. 2015;12(9):588–602.
86. Sadeghipour F, Lorenzini KI, Ziewitz C, Dobrinas M, Fleury M, Bonnabry P. Chemical contamination during the preparation of cytotoxics: validation protocol for operators in hospital pharmacies. *J Oncol Pharm Pract*. 2013;19(1):57–64.
87. Ozakin GY, Ciftci AH, Sanci K. Evaluation of a safe handling and cytotoxic drug preparation training program for oncology pharmacy practitioners. *J Oncol Pharm Pract*. 2019;25(8):1979–1986.
88. Aebersold ML, Kraft S, Farris KB, et al. Evaluation of an interprofessional training program to improve cancer drug therapy safety. *JCO Oncol Pract*. 2021;17(10):e1551–e1558.
89. Sadideen H, Plonczak A, Saadeddin M, Kneebone R. How educational theory can inform the training and practice of plastic surgeons. *Plast Reconstr Surg Glob Open*. 2018;6(12):e2042.
90. Loboda C, Vigneron J, Mulot C, May I, Demore B. A "chamber of errors" adaptation to assess pharmaceutical assistants' knowledge in chemotherapy preparation. *J Oncol Pharm Pract*. 2019;25(2):454–459.

Fernando Moreira, PhD, Assistant Professor,LAQV/REQUIMTE, Escola Superior de Saúde, Instituto Politécnico do Porto, Porto, Portugal

Ângelo Jesus, PhD, Associate Professor, LAQV/REQUIMTE, Escola Superior de Saúde, Instituto Politécnico do Porto, Porto, Portugal

Cláudia Pinho, PhD, Assistant Professor, LAQV/REQUIMTE, Escola Superior de Saúde, Instituto Politécnico do Porto, Porto, Portugal

Marlene Santos, PhD, Associate Professor, LAQV/REQUIMTE, Escola Superior de Saúde, Instituto Politécnico do Porto, Porto, Portugal; and Associate Professor, Molecular Oncology & Viral Pathology, IPO-Porto Research Center (CI-IPOP), Portuguese Institute of Oncology, Porto, Portugal

Mélanie Serdoura, BPharm, Hospital Pharmacy Technician, Centro Hospitalar Universitário de São João, Porto, Portugal

Agostinho Cruz, PhD, Senior Professor, LAQV/REQUIMTE, Escola Superior de Saúde, Instituto Politécnico do Porto, Porto, Portugal