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Thèse préparée sous la direction des Prof. Antoine Geissbühler et Prof. Pascal Bonnabry

Handling of cytotoxic drugs and related waste in low and middle-income countries: A toolkit to promote safe handling practices

Thèse

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Intitulée :

"Handling of cytotoxic drugs and related waste in low and middle-income countries: A toolkit to promote safe handling practices"

La Faculté de médecine, sur préavis du Comité directeur du PhD, autorise l'impression de la présente thèse, sans prétendre par-là émettre d'opinion sur les propositions qui y sont énoncées.

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2. List of publications

2.1 Original articles

von Grünigen S, Geissbühler A, Bonnabry P. Cyto-SAT: A self-assessment tool for the safe handling of cytotoxic drugs adapted for use in low- and middle-income countries. J Oncol Pharm Pract. 2020 Sep 17:1078155220956687. doi: 10.1177/1078155220956687.

von Grünigen S, Geissbühler A, Bonnabry P. The safe handling of chemotherapy drugs in low- and middle-income countries: An overview of practices. J Oncol Pharm Pract. 2021 Feb 23:1078155221995539. doi: 10.1177/1078155221995539.

von Grünigen S, Falaschi L, Guichard N, Fleury-Souverain S, Geissbühler A, Bonnabry P. Development and Proof of Concept of an Audit Toolkit for the Safe Handling of Cytotoxic Drugs in Low- and Middle-Income Countries. JCO Glob Oncol. 2021 Sep;7:1480-1489. doi: 10.1200/GO.21.00205.

von Grünigen S, Dessane B, Le Pape P, Falaschi L, Geissbühler A, Bonnabry P. Development and Evaluation of an e-Learning Module for Low- and Middle-Income Countries on the Safe Handling of Chemotherapy Drugs. J Cancer Educ. 2021 Nov 17. doi: 10.1007/s13187-021-02113-z.

2.2 Oral communications:

von Grünigen S, Geissbühler A, Bonnabry P. Cyto-SAT: a self-assessment tool for safe handling of cytotoxic medicines in low and middle-income countries, XVIII International Symposium on Oncology Pharmacy Practice (ISOPP) 10-13 October 2019, London, UK

von Grünigen S, Geissbühler A, Bonnabry P. Safe handling of cytotoxic medicines in low and middle income countries - An overview of practices. 8th Geneva Health Forum, 24-26 March 2020, Geneva, Switzerland **(cancelled due to COVID-19)**

2.3 Poster Communication:

von Grünigen S, Geissbühler A, Bonnabry P. Cyto-SAT: a self-assessment tool for safe handling of cytotoxic medicines in low and middle-income countries, XVIII International Symposium on Oncology Pharmacy Practice (ISOPP) 10-13 October 2019, London, UK

von Grünigen S, Geissbühler A, Bonnabry P. Safe handling of cytotoxic medicines in low and middle income countries – An overview of practices, XVIII International Symposium on Oncology Pharmacy Practice (ISOPP) 10-13 October 2019, London, UK

von Grünigen S, Bonnabry P. Safe handling of cytotoxic medicines and related waste: Development of a self-assessment tool adapted to resource-constrained settings,7th Geneva Health Forum, 10-12 April 2018 Geneva, Switzerland

von Grünigen S, Bonnabry P. Safe handling of cytotoxic medicines and related waste: Development of a self-assessment tool adapted to resource-constrained settings, 21èmes Journées Franco-Suisses de Pharmacie Hospitalière, 8-9 mars 2018, Belfort, France (1st price of the written communications)

3. Abstract

Cancer is a global burden, including in low- and middle-income countries (LMICs). Cancer prevention and control have been part of the global agenda for some years. Many efforts were made to improve access to chemotherapies. Due to their intrinsic toxicity, cytotoxic drugs must be handled with great caution to ensure the safety of the patients and the personnel handling them. However, safe handling aspects still seem to be neglected in many LMIC cancer programs, where the increasing use of anti-cancer drugs is only recent.

This PhD focused on the safe handling of chemotherapy drugs in LMICs. The primary objective was to promote the improvement of handling practices, wherever cytotoxic drugs are transported, received, stored, prepared, administered, and disposed of, to ensure the quality of services and the patient and staff safety.

The first study developed Cyto-SAT, a self-assessment tool designed to help staff at cancer centers in LMICs safely handle cytotoxic drugs. 134 items derived from international guidelines were validated by a strong consensus of international experts through a Delphi survey. The pilot-test of Cyto-SAT by 33 cancer centers from 26 LMICs confirmed its applicability in local settings, its usefulness and usability by healthcare facilities, and its acceptability as a quality improvement tool.

The second study provided an overview of the level of quality and safety of chemotherapy handling practices in LMICs. The results of the self-assessments with Cyto-SAT revealed wide disparities in practices among the 53 facilities in 34 countries. Many gaps were identified, particularly in the chemotherapy preparation step, especially in cancer centers from low-income countries. Major opportunities for improvement were also identified in key cross-cutting areas such as initial and continuous training of the staff as well as in effective incident management.

The third study allowed the development and proof of concept of a toolkit to facilitate a comprehensive assessment of chemotherapy handling practices in health facilities in LMICs. In addition to Cyto-SAT, three observation checklists for the prescribing, preparation, and administration of chemotherapy drugs were created. A surface-wipe sampling method was also part of the toolkit to measure cytotoxic contamination of the immediate environment. The toolkit was successfully applied in three African hospitals. It allowed an easy benchmarking of facilities and practices against international standards and the development of an action plan. The toolkit represented a valuable support to implement a continuous quality improvement process, promote best practices and ultimately ensure patient and staff safety.

In the fourth study, an online training module on safe handling of chemotherapy was developed based on Kern's six-step approach. Evaluation of the 11 asynchronous self-study lessons using a pretest/posttest system showed significant improvements in participants' theoretical knowledge in all but one lesson (which lacked statistical power) and a high degree of participant satisfaction with the content and courseware.

This PhD resulted in appropriate ready-to-use tools (assessment tools and e-learning) that can be easily used to assess and support the improvement of local practices. It also highlighted gaps and areas where improvements and corrective actions are needed to ensure patient and staff safety. This work represents a first step in the development of a comprehensive safe handling program. As a direct continuation of this thesis, there are three important objectives: (i) the large-scale deployment of these tools, (ii) the sustainability of their use, (iii) the optimization of the training program and its evaluation.

1. Résumé

La problématique du cancer est un fardeau mondial, y compris dans les pays à revenus faible et intermédiaire (PRFI). La prévention et le contrôle des cancers fait partie depuis plusieurs années de la stratégie de développement mondiale. De nombreux efforts ont notamment été réalisés afin d'améliorer l'accès aux traitements anticancéreux. En raison de leur toxicité intrinsèque, les médicaments cytotoxiques doivent être manipulés avec une grande prudence pour garantir la sécurité des patients et du personnel les manipulant. Pourtant, les aspects liés à la sécurité de manipulation semblent encore négligés dans de nombreux programmes de lutte contre le cancer des PRFI, où l'utilisation croissante des anticancéreux n'est que récente.

Ce travail de thèse s'est ainsi intéressé à la manipulation sécuritaire des médicaments anticancéreux dans les pays à revenus faible et intermédiaire. L'objectif principal était de promouvoir l'amélioration des pratiques afin de garantir la qualité des services et la sécurité des patients et du personnel.

La première étude a permis de développer Cyto-SAT, un outil d'auto-évaluation conçu pour aider le personnel des centres anticancéreux des PRFI à manipuler en toute sécurité les médicaments cytotoxiques. 134 items dérivés des recommandations internationales ont été validés par un fort consensus d'experts internationaux à travers une enquête Delphi. Le test de Cyto-SAT par 33 centres anticancéreux de 26 PRFI a confirmé son applicabilité dans les contextes locaux, son utilité et son utilisabilité par les établissements de santé et son acceptabilité comme outil d'amélioration de la qualité.

La deuxième étude fournit un état des lieux du niveau de qualité et de sécurité des pratiques de manipulation des chimiothérapies dans PRFI. Les résultats des auto-évaluations avec Cyto-SAT ont révélé de grandes disparités dans les pratiques parmi

les 53 établissements de 34 pays ayant participé. De nombreuses lacunes ont été mises en évidence notamment en ce qui concerne l'étape de préparation des chimiothérapies, en particulier dans les hôpitaux des pays à revenu faible. Des opportunités majeures d'amélioration ont également été identifiées dans des domaines transversaux essentiels tels que la formation initiale et continue du personnel ainsi que pour la gestion efficace des incidents.

La troisième étude a permis le développement et la preuve du concept d'une boîte à outils pour faciliter l'évaluation complète des pratiques de manipulation des chimiothérapies dans des établissements de santé de PRFI. En plus de Cyto-SAT, trois check-listes d'observation pour la prescription, la préparation et l'administration des chimiothérapies ont été créées. Une méthode d'échantillonnage par frottis de surface faisait également partie de la boîte à outils afin de mesurer la contamination cytotoxique de l'environnement immédiat. La boîte à outils a été appliquée avec succès dans trois hôpitaux africains. Elle a permis de comparer facilement et rapidement les pratiques aux normes internationales et de concevoir un plan d'action. Cette boîte à outils constitue un soutien précieux pour mettre en œuvre un processus d'amélioration continue de la qualité, promouvoir de meilleures pratiques pour au final assurer la sécurité des patients et du personnel.

Dans la quatrième étude, un module de formation en ligne sur la manipulation sécuritaire des chimiothérapies a été développé selon le modèle en six étapes de Kern. L'évaluation des 11 leçons d'auto-apprentissages asynchrones à l'aide d'un système de pré-test/post-test a montré une amélioration significative des connaissances théoriques des participants dans toutes les leçons sauf une (dont la puissance statistique était insuffisante) et un haut degré de satisfaction des participants par rapport au contenu et au didacticiel.

En conclusion, ce travail de thèse a permis de concevoir des outils appropriés prêts à l'emploi (outils d'évaluation et formation en ligne) pouvant facilement être utilisés pour évaluer et soutenir l'amélioration des pratiques locales. Elle a également mis en évidence des lacunes et des domaines pour lesquels des améliorations et des actions correctives sont nécessaires afin d’assurer la sécurité des patients et du personnel. Ce travail représente une première étape dans le développement d'un programme complet de sécurité des manipulations. Les perspectives envisageables dans le prolongement direct de cette thèse concernent trois objectifs importants : (i) Le déploiement à large échelle de ces outils, (ii) la pérennisation de leur utilisation, (iii) l'optimisation du programme de formation et son évaluation.

5. Outline

6. List of tables and figures

6.1 List of Tables

6.2 List of figures

7. List of Abbreviations

CMR	Carcinogenic, mutagenic, reprotoxic
DALYs	Disability-Adjusted Life Years
GMPs	Good Manufacturing Practices
HDI	Human Development Index
HUG	Hôpitaux Universitaires de Genève
IARC	International Agency for Research on Cancer
ISOPP	International Society of Oncology Pharmacy Practionners
LMICs	Low- and middle-income countries
LMS	Learning Management System
NIOSH	National Institute for Occupational Safety and Health
PPE	Personal Protective Equipment
SDGs	Sustainable Development Goals
UN	United Nations
WHA	World Health Assembly
WHO	World Health Organization

Introduction and “State of the Art”

8. Introduction and “State of the Art”

8.1 Cancer in low and middle-income countries

8.1.1 Global burden

Cancer is a leading cause of mortality and morbidity worldwide. In 2020, the GLOBOCAN statistics produced by the International Agency for Research on Cancer (IARC) estimated 19.3 million new cancer cases, 10 million cancer deaths and 41.6 million people living with cancer (within 5 years of diagnosis) worldwide.(1) This global burden represents 251 millions of Disability-Adjusted Life Years (DALYs) and is still growing.(2) By 2040, cancer is expected to be accountable for 28.4 million new cases and 13 million deaths.(3) Population growth and ageing are the major contributors to this rising burden. The distribution and burden of cancer varies between regions of the world and socio-economic groups, resulting in regional patterns of tumour types. Variations in the age structure of the population, genetics, and prevalence of risk factors, availability and use of diagnostic tests, and access to and quality of treatment all contribute to these geographical differences and inequalities. Understanding risk factors and their relationship to cancer characteristics is therefore of utmost importance in designing appropriate and effective cancer control strategies.(4–6) Indeed, acting on these key risks factors could prevent between 30 and 50% of cancers.(7) While cancer can affect anyone, the following lifestyle and environmental factors were linked to the development of certain types of tumours: tobacco and alcohol use, physical inactivity, overweight and obesity, unhealthy diet with low fruit and vegetable intake, chronic infections (e.g., hepatitis B and C, HIV/AIDS, human papillomavirus, helminth infections, Helicobacter pylori etc.), radiation, pollution of air, water and soil, and

occupational exposure (e.g., asbestos, heavy metals, silica, polycyclic aromatic hydrocarbons). (4,7,8)

For a long time overshadowed by HIV/AIDS, tuberculosis and malaria, cancer is now widely recognized as global public health issue in low-and middle-income countries (LMICs) and not only a concern of wealthy and developed countries anymore. Importantly, according to IARC, the largest increase of cancer cases in the next years would occur in countries with low and medium Human Development Index (HDI) (64% to 95% increase) in comparison to countries with high and very high HDI (32% to 56%).(9,10) Cancer in LMICs represents a threat to economic and human development and a hurdle to Universal Health Coverage. Although, LMICs bears the major share of DALYs due to cancer, less than 5% of the global cancer budget is spent in these countries, resulting in evident inequity. The long-term disabilities and premature deaths caused by cancer induce a high financial and social burden on families and health system. (4,11–13) To address these challenges, the World Health Organization (WHO) in collaboration with other United Nations (UN) agencies and partners endorsed a “Global Action Plan for the Prevention and Control of Non-communicable Diseases 2013–2020.”(14) Reducing premature deaths from cancers and implementing cancer prevention initiatives were two objectives set out in both the WHO’s plan and the UN Sustainable Development Goals (SDGs). (14,15) In May 2017, 194 governments agreed on the need to strengthen political commitment, increase investments and prioritize actions to achieve the 2030 targets by passing the Agenda item 15.6 of the World Health Assembly resolution (WHA 70.12) entitled "Cancer Prevention and Control through an Integrated Approach". (7,16)

8.1.2 Cancer prevention and control strategies

Addressing the burden of cancer is however challenging. Cancer is not a single disease, but rather a multitude of diseases. Many cancers have heterogeneous characteristics, with many histological and biological subtypes. Specific diagnostic and therapeutic strategies and a skilled workforce are needed to implement them, not to mention the imperative of coordinated multidisciplinary patient management.(4,17)

Comprehensive and effective cancer management requires actions on many aspects. Adequate cancer surveillance and establishment of national cancer registries recording relevant data to assess and monitor cancer burden (e.g., incidence, prevalence, mortality, etc.) are critical steps in order to plan effective and sustainable control programs.(18,19) To support and reinforce the implementation of effective cancer programs in countries, WHO developed a practical guide for comprehensive cancer control describing four essential components: (1) prevention, (2) early detection, (3) diagnosis and treatment and (4) palliative care. (20) Besides, training and research in oncology are transversal and fundamental aspects of implementing cancer control program, and should not be underestimated. Lack of trained and competent staff in any component of a comprehensive program represents a major barrier to its effectiveness.(21,22) Research on the cost-effectiveness of cancer intervention in LMICs is necessary to define sustainable and resource-level-appropriate cancer control.(23,24)

Cancer treatment encompasses a variety of interventions, including surgery, radiotherapy, hormonotherapy and chemotherapy. Importantly, treatment programs need to be adapted to the context and the priority of LMICs. Human resources,

infrastructures and finances should be considered to ensure feasibility and sustainability.(20,22,23,25) These past years, substantial efforts have been made to improve access to affordable, high-quality chemotherapy treatments in resource-poor settings. By including essential medicines for cancer in its Model List, WHO aims to guide countries in prioritizing and selecting cost-effective anticancer medicines for their National Essential Medicines list. In 2015, after a comprehensive review of essential medicines for cancer conducted by the relevant WHO expert committee, 21 cytotoxic medicines were added in the WHO Model Lists of Essential Medicines for Adults and Children.(26) (27) Unfortunately, despite these efforts, availability and affordability of anticancer medicines are still very challenging, especially in lower-middle-income and low-income countries. Indeed, a WHO technical report showed that 32.0% and 57.7% of cancer medicines on the essential medicine list were available in lower middle-income countries and low-income countries, respectively, only if patients were willing to pay their full costs. (28) Moreover, poor insurance schemes, high out-of-pocket patient expenditure makes cancer medicines less affordable in LMICs.(29)

8.2 Risks associated with cytotoxic drugs

8.2.1 Cytotoxic drugs and classification of their risk

Cytotoxic drugs are named on their ability to kill tumor cells by interfering with cell's division. They are mainly used, but not only, for anticancer chemotherapy treatments.(30) Although the effectiveness and the benefit of chemotherapy treatment are acknowledged in numerous cancer types, cytotoxic drugs are also recognized as hazardous substances due to their potential mutagenic, carcinogenic and reproductive toxicity properties.(31)

Intrinsic toxic properties differ according to the substances. Several carcinogenic risk classifications of substances exist, the best known of which are the International Agency for Research on Cancer (IARC) and the European Union classifications.(32,33) The IARC classification of substances is based on "*the strength of the evidence of carcinogenicity"*(32) (table 1).

Table 1: IARC carcinogenic risks classification(32)

GROUP 1	Carcinogenic to humans
GROUP 2A	Probably carcinogenic to humans
GROUP 2B	Possibly carcinogenic to humans
GROUP 3	Not classifiable as to its carcinogenicity to humans
GROUP 4	Probably not carcinogenic to humans

The European Union uses the classification CMR (carcinogenic, mutagenic, reprotoxic) that is included in a regulation known as the CLP regulation (Classification, Labelling, Packaging). The classification considers the level of evidence for the observed CMR effect as shown in table 2.

Table 2: CMR classification of the European Union CLP regulation (34)

Carcinogens	Category 1A	Substances known to have carcinogenic potential for humans.
	Category 1B	Substances presumed to have carcinogenic potential for humans.
	Category 2	Substances suspected of having carcinogenic potential for humans.
Mutagens	Category 1A	Substances known to induce hereditary mutations in the germ cells of humans.
	Category 1B	Substances presumed to induce hereditary mutations in the germ cells of humans.
	Category 2	Substances of concern because they could induce hereditary mutations in the germ cells of humans.
Reprotoxins	Category 1A	Substances known to be toxic for human reproduction.
	Category 1B	Substances presumed to be toxic for human reproduction.
	Category 2	Substances suspected of being toxic for human reproduction.

Since 2004, The National Institute for Occupational Safety and Health (NIOSH), a U.S Federal Agency, publishes and regularly updates a list of medicines to be considered as hazardous. This list does not only include anticancer agents but also other types of drugs such as antiviral drugs, hormones, some bioengineered drugs, etc. NIOSH definition of “hazardous drugs” is based on the definition provided in 1990 by the American Society of Hospital Pharmacists and considered six features in humans and animals: (i) carcinogenicity, (ii) teratogenicity or other developmental toxicity, (iii) reproductive toxicity, (iv) organ toxicity at low doses, (v) genotoxicity, (vi) structure and toxicity profiles of new drugs that mimic existing drugs determined hazardous by the previous criteria.(31)

Currently more than 30 cytotoxic medicines are included in the latest versions of the WHO Model lists of essential medicines.(34,35) Table 3 presents the cytotoxic medicines included in the WHO model lists of Essential Medicines and their category of risk according to the various classification methods.

Table 3: Cytotoxic and adjuvant medicines in 22nd WHO Model List of Essential Medicines (LEM) and 8th Model list of Essential Medicines for Children (2021)

LEM	Cytotoxic medicines	presentation	NIOSH list(31)	IARC class.(32)	CMR class.(36)
A+C	Arsenic trioxide	Concentrate for for solution for infusion 1mg/mL	yes		-
A +C	Asparaginase	Powder for injection 10 000 UI in vial		n.a	CMR
A	Bendamustine	Injection 45mg/0.5 mL; 180mg/2mL	yes	n.a	CMR
A+C	Bleomycin	Powder for injection: 15 mg in vial	yes	2B	CMR
A+C	Calcium folinate	Injection 3mg/mL in 10 mL ampoule tablets :15mg	no	n.a	-
A	Capecitabine	Tablets : 150mg ; 500mg	yes	n.a	CMR
A+C	Carboplatin	Injection, 50mg/ml, 150mg/15ml, 450mg/45ml, 600mg/60ml	yes	n.a	CMR
A	Chlorambucil	Tablet, 2mg	yes	1	CMR
A+C	Cisplatin	Injection 50mg/50 mL; 100mg/100mL	yes	2A	CMR
A+C	Cyclophosphamide	tablet, 25mg; powder for injection, 500mg in vial	yes	1	CMR
A+C	Cytarabine	Powder for injection, 100mg in vial	yes	n.a	CMR
A+C	Dacarbazine	Powder for injection: 100mg in vial	yes	2B	CMR
A+C	Dactinomycin	Powder for injection, 500micrograms in vial	yes	3	CMR
A+C	Daunorubicin	Powder for injection, 50mg (as hydrochloride)	yes	2B	CMR
A	Docetaxel	Injection : 20mg/mL, 40mg/mL	yes	n.a	CMR
A+C	Doxorubicin	Powder for injection, 10mg, 50mg (hydrochloride) in vial	yes	2A	CMR
A+C	Etoposide	Capsule, 100mg ; injection, 20mg/mL in 5-mL ampoule	yes	1	CMR
A	Fludarabine	Powder for injection:50mg (phosphate) in vial, tablet 10mg	yes	n.a	CMR
A+C	Fluorouracil	Injection, 50mg/ml in 5-ml ampoule	yes	3	CMR
A	Gemcitabine	Powder for injection: 200mg in vial, 1g in vial	yes	n.a	CMR
A+C	Hydroxycarbamide	Capsule, 200mg, 250mg, 300mg, 400mg, 500mg ; tablet, 1g	yes	3	CMR
A+C	Ifosfamide	Powder for injection: 500 mg vial 1g vial and 2g vial	yes	3	CMR
A	Imatinib	Tablets: 100 mg, 400 mg	yes	n.a	CR
A+C	Irinotecan	Injection, 40mg/2 mL in 2-mL vial, 100mg/5 mL in 5 mL vial; 500mg/25 mL in 25mL vial	yes	n.a	CMR
A	Melphalan	Tablet 2mg; powder for injection 50mg in vial	yes	1	CMR
A+C	Mercaptopurine	Tablets: 50mg	yes	3	CMR
A+C	Methotrexate	Tablet, 2.5mg (as sodium salt); powder for injection, 50mg (as sodium salt) in vial	yes	3	CMR
A+C	Oxaliplatin	Injection 50mg/10mL in 10mL vial; 100mg/20mL in 20 mL vial, 200mg/40mL in 40mL vial; powder for injection : 50 mg, 100 mg in vial	yes	n.a	CMR
A+C	Paclitaxel	Injection 6mg in vial	yes	n.a	CMR
A+C	Pegaspargase	Injection 3,750 units/5mL in vial	-		-
A+C	Procarbazine	Capsule, 50mg (as hydrochloride)	yes	2A	-
A+C	Realgar-indogo naturalis formulation	Tablet 270mg	-		-
A+C	Tioguanine	Solid oral dosage form 40 mg	yes	n.a	CMR
A+C	Vinblastine	Injection 10mg/10mL (sulfate) in vial powder for injection, 10mg (sulfate) in vial	yes	3	CMR
A+C	Vincristine	Injection 1mg/mL (sulfate); 2mg/2mL (sulfate) in vial Powder for injection, 1mg, 5mg (sulfate) in vial	yes	3	CMR
A	Vinorelbine	Capsule 20mg; 30mg;80mg injection 10mg/mL in 1 mL vial, 50mg/5mL in 5 mL vial	yes	n.a	MR

A= Adults; C Children

8.2.2 Risks for the patients

Cytotoxic drugs are highly beneficial therapeutic medicines however extreme care should be taken due to their narrow therapeutic index and high toxicity. Their activity is often not selective, i.e., it does not differentiate between cancer cells and normal cells. Patients under chemotherapy should thus be closely monitored for any side effects or adverse events related to the treatment. The main reported effects in treated patients include pain, nausea and vomiting, alopecia, cardiotoxicity, immunotoxicity, hematopoietic toxicity, renal and hepatic toxicity, neurotoxicity, dermal toxicity, etc.(37) Other aggravating factors associated with the chemotherapy context can increase the risks, such as patient health status (immunocompromized and weak from the disease) or high-risk administration route (i.e. intravenous or intrathecal) prone to extravasations and infections.(38) Medication errors with cancer medicines are not rare and can lead to severe consequences or even to fatal events. (39) Chemotherapy drugs were reported as the second cause of death among mortalities caused by medications errors.(39) In a recent review, 1–3% of cancer patients experienced a medication error during treatment.(40) Due to the complexity of chemotherapy regimens, medication errors can occur at any step from prescribing to administration. Prescription errors were found to be the highest error rate, followed by preparation errors.(41) Findings from studies in LMICs reported even a prevalence of medication errors over 40% among cancer patients.(42,43)

To ensure patient's safety, quality assurance should be implemented to prevent, intercept and manage any errors that may happen at each step of the chemotherapy treatment. For instance, administrative supports (e.g., standardized treatment protocols for prescription-preparation-administration and standard operating

procedures), supportive infrastructure for clinical and laboratory monitoring, and specific training of the staff involved in the chemotherapy treatment should be part of any risk management program.(38,44)

8.2.3 Risks for the personnel

Beyond patient safety, cytotoxic drugs can be a safety issue for the personnel involved in their handling. Concerns about occupational risks for the personnel handling these drugs have been well described since the 1970's. (38,45) *Falck and colleagues* published the first evidence of occupational exposure in 1979, by reporting mutagenic substances in the urine of nurses who handled cytotoxic medicines.(46) Since then, numerous studies have investigated the potential hazards associated to occupational exposure. Acute and long–term toxic effects have been described. Although there is no strong scientific evidence on whether working with cytotoxic drugs can increase the risk of developing cancer, some direct adverse health effects, such as skin reactions, hair loss and alteration of normal blood cell counts, have been observed on staff where insufficient preventive measures were applied.(47) Reproductive toxicity has also been associated to occupational exposure. Several studies reported increased fetal loss, congenital malformations, low birth weights and stillbirths although statistically significant differences were only found for spontaneous abortion in nurses who handled cytotoxic medicines. (47–49)

Occupational exposure can occur through direct skin contact (e.g., splashing, spillage), inhalation of aerosols (e.g., overpressurized vials, cleaning spill), needle-stick injuries, and ingestion (e.g., contaminated hands-to-mouth contact). Secondary sources of exposure from contaminated surfaces should not be underestimated as some studies

in high-income countries have documented a substantial contamination of the preparation and administration areas. (37,50) Staff may be exposed at every stage of the handling process when receiving and transporting drugs, preparing, administering, handling patients' excreta, transporting and disposing waste and cleaning spills. (38,51,52) Table 4 summarizes the risks associated to the handling of cytotoxic drugs.

To minimize the risk of exposure in the different processes, a combination of protective measures should be applied not only regarding healthcare workers (e.g., physicians, nurses, pharmacists) but also other technicians involved in the transport, storage, cleaning or disposal of cytotoxic drugs and related waste.(52)

Table 4: Summary of the risks related to handling cytotoxic medicines(45,50,53)

	RISKS ASSESSMENT	COMMENTS
Toxicity	Carcinogenicity Mutagenicity Reproductive toxicity Irritation Hypersensitivity Others (nausea, light-headedness)	Chronic toxicity Acute toxicity
Route of Exposure	Dermal absorption Inhalation Ingestion	
Galenical form	Liquid Lyophilized powders Tablets, capsules Aerosols	
Handling activities	Handling drug-contaminated vials Reconstituting powdered or lyophilized drugs Crushing tablets, opening of capsules Handling, counting uncoated tablets Further diluting concentrated liquid forms Generating aerosol during compounding or administration Cleaning contaminated area Handling excreta and contaminated materials Handling contaminated wastes	Group of workers potentially exposed: Pharmaceutical staff, stock keepers, nursing personnel, housekeeping personnel, transporters, waste disposal personnel, maintenance personnel
Level of exposure	Duration of contact Frequency of exposure Product chemical and physical properties Applied protective measures	
Protective Measures	Engineering controls Organisational measures/administrative controls Personal protective equipment	E.g., biosafety cabinet E.g., work practices, training programs E.g., gloves, masks, gown

8.2.4 Risks for environment

Due to the toxic properties of cytotoxic drugs, improper waste management techniques are not only dangerous for staff involved in the process, but environmental contamination might have dramatic ecological consequences and constitute public health threat for the whole community.(54) A review from *Harhay and colleagues* (2009) revealed that health-care waste management remains a major challenge in numerous LMICs.(55) Therefore, particular attention should be given to cytotoxic waste management. Careful planning in term of collection, segregation, storage, transport and final disposal of cytotoxic waste should not be overlooked. Efforts should

be invested to minimize the risks of contaminating water supply and/or soil, and allow safe disposal of cytotoxic waste. Incineration at high temperature (>1200°C) is the recommended disposal method, which constitutes a real challenge in many settings as it requires particular and very costly incinerators.(54)

8.3 Safe practices for handling

8.3.1 Guidelines, recommendations and regulations

Soon after the hazards associated with occupational exposure were recognized, health professional associations developed the first guidelines on safe handling of cytotoxic drugs. [52, 53] Thus, since the 1980's, numerous professional associations and government agencies have published updated documents based on scientific evidence or best practices. The purpose of these documents might differ from one another (e.g., guidelines, national regulations, document from insurance companies) as well as their orientation and the level of details presented. While they all share the same principles, i.e., the safe handling of cytotoxic/hazardous drugs, some documents (e.g., from insurances companies or from the Occupational Safety and Health Administration) are exclusively oriented toward workers' protection and focus on minimizing the risk of occupational exposure only. (52,58,59) On other hand, others, such as the "United States Pharmacopeia (USP) chapter <800>, "ISOPP Standards of practice on safe handling of cytotoxics", "QuapoS: Quality Standards for oncology Pharmacy" cover additional aspects related to safe handling, including Good Manufacturing Practices (GMPs) principles (especially for parenteral cytotoxic drugs) to ensure the quality of the product for patient safety and to protect the environment from contamination.(38,60,61) Besides, more clinical standards were also developed and

regularly updated by the American Society of Clinical Oncology and the Oncology Nursing Society promoting safe use of chemotherapy and preventing the risks of errors that can lead to potentially harmful events in patients receiving chemotherapy. (62) In 2013, The Pan American Health Organization (PAHO) and its special program on Sustainable Development and Health Equity published “Safe Handling of Hazardous Chemotherapy Drugs in Limited-Resource Settings”. This document summarized the rational for and approaches to implementation of safe handling practices from existing recommendations and guidelines.(63) It addressed safety recommendations for specific steps of the cytotoxic drugs flow within the health facility (receipt, storage, compounding, transport, administration, cytotoxic waste and incident management). Two other WHO documents complete some specific aspects of the cytotoxic process as “WHO Good Manufacturing Practices for Pharmaceutical Products containing Hazardous Substances” and “Safe Management of Waste from Health-Care Activities”.(54,64) Although the WHO documents did not present new information, it might reinforce the message that safe handling practices are part of the cancer care. They should be implemented in any place where cytotoxic medicines are handled and used even in limited-resource settings. Indeed, promoting safe handling to prevent hazards associated with cytotoxic drugs is not only based on expensive engineering solutions but relies on a combination of three different levels of preventive measures and hazard controls: (1) engineering measures, (2) administrative and organizational measures, and (3) personal protective equipment. (38,59,63)

8.3.2 Handling practices in LMICs

Although research on safe handling practices in cancer care delivery is still limited in LMICs, a few studies have shown deficiencies and safety issues related to inappropriate practices. Unsuitable infrastructures, the unavailability of materials, multitasking, workload pressure, and high patient numbers represented the main issues.(65,66) Other studies have reported that improper working practices were due to a lack of training, a lack of awareness, and false beliefs.(67,68) In some resource-constrained settings, handling cytotoxic medicines has not yet been acknowledged to be dissimilar to other drugs. *Strother and colleagues (2012)* reported that in many LMICs, oncology practice environment did no differ from the situation of cancer care facilities of high-income countries during the 1980's, prior consideration of the risks and the development of safety guidelines and regulations.(69) Under-trained nurses mainly handle cytotoxic medicines and are responsible for drug storage, preparation and administration in the wards resulting in improper behaviors and practices, improper storage conditions and security.(67,68,70) In India, lack of national-level guidelines/recommendations and lack of administrative support or regulations were considered as major barriers to the implementation of safety standards for chemotherapy.(71) The inadequate practices described in these studies do not only endanger patients with harmful events but also workers involved with the handling of cytotoxic drugs. Furthermore, challenges in waste management and improper final disposal of cytotoxic waste expose to environmental issues. Thus, the rising use of cytotoxic drugs in LMICs associated with their unsafe handling might lead to an emerging public health issue.

Recently, these safety concerns on handling practices started being addressed and improvement experiences in African and South-East Asia countries have been reported in the literature. The AMPATH-oncology project, a collaboration between Moi University School of Medicine, Moi Teaching and Referral Hospital in Kenya and a consortium of North-American academic medical centers, was the first to publish the experience of a set-up of a centralized oncology pharmacy in a resource-constrained setting.(69) Findings from AMPATH-oncology project were similar to the results in resource-replete settings that is, well managed centralized oncology pharmacy benefits to supply chain management, patient, professional and environment safety and cost-containment. *Vaz da Conceiçao and colleagues (2015)* described a similar experience in Angola, with the establishment of oncology pharmacy units in three health care facilities in collaboration with the Institute of Oncology in Porto, Portugal.(72,73) *Keat and colleagues (2013)* described how pharmacists played an important role in improving nurse's knowledge, attitude and practices in safe handling of cytotoxic drugs in a Malaysian hospital by providing a series of technical, educational and administrative support measures. (70) More recently, in 2018, the ChemoSafe program was launched as a partnership between the Oncology Nursing Society and the American Cancer Society. ChemoSafe is a comprehensive approach to promote the safe handling of chemotherapy and quality service provision to patients in Sub-Saharan African countries.(74) Their actions focus on i) Adapting international standards and integrate them into national policies, ii) ensuring that high-quality, affordable personal protective equipment (PPE) and engineering controls are consistently available to all workers with potential exposure to hazardous drugs, iii) improving infrastructure, standard operating procedures, and documentation systems, and iv) training health workers in safe handling and administration of chemotherapy.

To date, facilities in Ethiopia, Uganda, Kenya, Tanzania, Rwanda, and Nigeria have engaged in the program.(75)

These experiences in low and middle-income countries showed encouraging results and pointed out the importance of the role of the pharmacy in improving the safe handling of cytotoxic medicines. Besides, investment in staff and their continuous training as well as equipment and facilities was required. The support from the hospital authorities and/or the Ministry of Health with policies and procedures that stress safety-related measures to handle cytotoxic medicines and related waste was also mentioned as essential.

8.4 Distance learning in Health

Worldwide, healthcare professionals' education is essential to improve the quality of care and patient management. In recent years, taking advantage of information and communication technologies, developing e-learning strategies have been strongly encouraged for healthcare workers education.(76) Distance education has grown significantly, particularly in LMICs, where there is a strong need to alleviate the shortage and retention of trained, qualified professionals.(77,78) One of e-learning's many advantages is that it can transcend the geographical, political, and time barriers to education and thus extend training opportunities and access to larger numbers of people. Those aspects are particularly interesting for low-resource contexts that face lack of infrastructure (i.e, insufficient classrooms and student housing), limited numbers of teachers, and difficulties of access for people from rural area or political instability. (79) These last two years, distance learning has shown its usefulness in time of a pandemic as well. Technological progress in hardware and software and affordable internet connectivity have enabled broader technology access and usage in

low-resource settings, even if limitation in bandwidth can still contribute to slow speed and low quality of video or pictures in some places. (79) Despite this potential for success, most studies did not produce strong scientific evidence of e-learning effectiveness in medical education in LMICs. The main reasons pointed out were the low quality methodologies (by absence of control group, use of invalidated questionnaire) and low sample size (small scale e-learning pilots) partially due to limited available funding. (77,79). Besides, distance education or e-learning are generic terms hiding a large variety of methods which make them difficult to compare. They include all kinds of educational methods, ranging from simple digital libraries to more complex distance learning networks and innovative methods such as virtual simulation or gamification.(80)

8.4.1 Instructional Design

Ideally, the effective use of educational technology requires a classic instructional design approach, a systematic method of analysing learner needs and developing appropriate instructional activities.(81–83) Among the existing frameworks, The *ADDIE (Analyse-Design-Develop-Implement-Evaluate)* model and the *Kern's Six-Step Approach for Curriculum Development for Medical Education were* commonly used in healthcare education.(83,84). These two stepwise approaches are very similar as they helps plan and organize the curriculum development. We chose to highlight the *Six-Step Approach for Curriculum Development for Medical Education* as it is presented more as a dynamic continuous cyclical process where all the steps can influence each other (figure 1).(85)

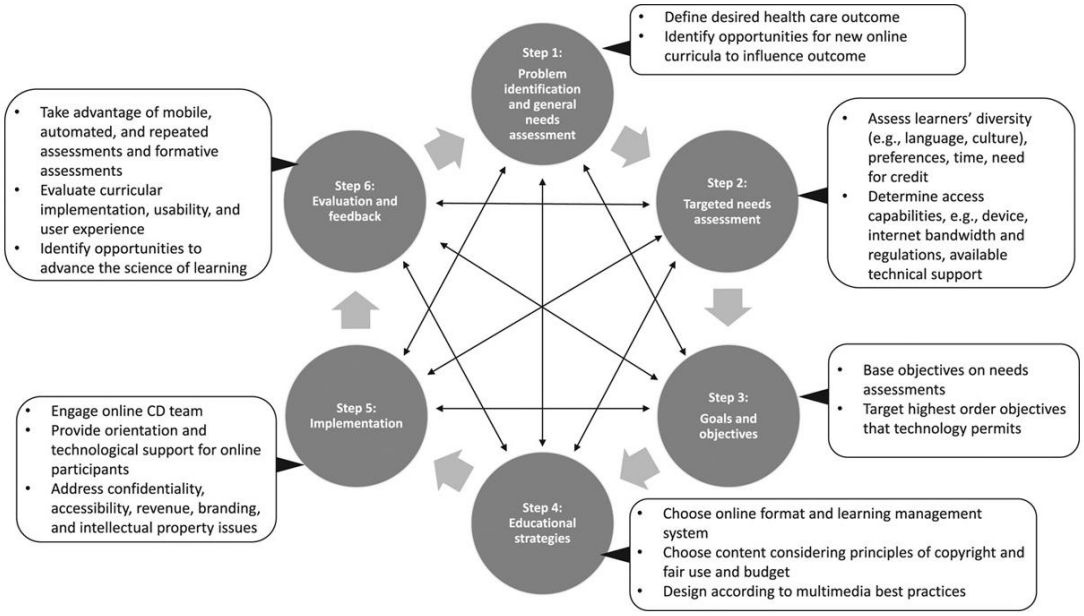

Figure 1 : Considerations for online curriculum development according to the Six-Step Approach for Curriculum Development for Medical Education**(85)**

- *Step 1 Problem identification and general needs assessment:* this key step corresponds to a critical situation analysis to identify the gaps in knowledge and issues in attitude and performance that need to be addressed by the curriculum.

- *Step 2 Targeted needs assessment:* the general needs identified in step 1 are then refined according to the different characteristics and features of the target audience to best meet their needs.

- *Step 3 Goals and objectives:* The overall objectives of the course and the specific measurable learning objectives for each lesson need to be defined in order to build structured learning resources. They provide explicit learning objectives and clear expectations of what students should learn. They are also the starting point for ensuring constructive alignment between learning objectives, content and

assessment.(86) Constructive alignment is achieved when all components are aligned, so that the objectives express the level of understanding expected from the learners, the teaching context encourages students to undertake the learning activities likely to achieve those understandings, and the assessment tell them how well the objectives have been met. Bloom's taxonomy is the most commonly used terminology for writing learning objectives. This hierarchical framework created by Benjamin Bloom in 1956 classifies cognitive skills in six major categories called *Educational Objectives*: (i) Knowledge; (ii) Comprehension; (iii) Application; (iv) Analysis; (v) Synthesis; (vi) Evaluation. In 2001, a revised Bloom's taxonomy was published suggesting a more dynamic classification reflecting on learners' cognitive process by using action verbs for categories instead (Figure 2).(87)

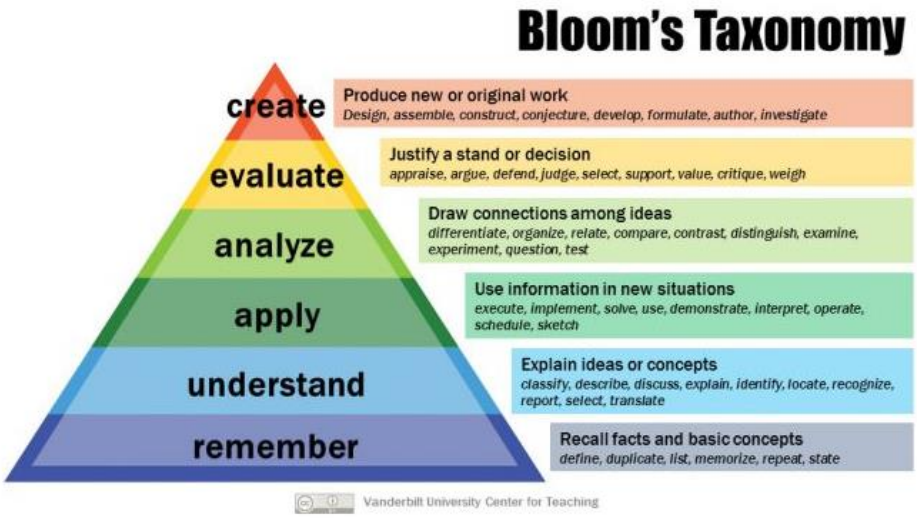

Figure 2: Revised Bloom's Taxonomy "A taxonomy for Teaching, Learning, and Assessment"**(87)**

- *Step 4 Educational strategies:* Although there is no formula for optimal online learning, the effectiveness of the training will largely depend on the educational strategy used. (88,89) Educational strategies are grounded in overarching learning theories, which provide a conceptual overview on how people learn. The three most

popular educational theoretical frameworks are behaviorism, cognitivism, and constructivism. Behaviorism, the oldest theoretical framework, sees learning as a change in behavior, whereas cognitivism is interested in the cognitive process that lead to understanding and learning. Constructivism considers learners as active, constructing their own knowledge by interacting with their environment or with others (social constructivism). Then, a number of new theories have evolved, most of which derive from these major learning theories.(90) E-learning courses often combine aspects from different theories by using several educational strategies.(91) These latter are classified in several categories according to the type of learning activities. In e-learning, the main categories are the following: expositive methods, applicative methods and collaborative.(92)

Table 5: Educational strategies in the e-learning context(92)

EXPOSITIVE METHODS	APPLICATION METHODS	COLLABORATIVE METHODS
Presentation	Demonstrations-practice methods	Online guided discussion
Case studies	Jobs aids	Collaborative work
Work examples	Case-based exercise	Peer tutoring
Demonstrations	Role plays	
	Simulations and serious games	
	Guided research	
	Project work	

The use of these different methods must enable learners to achieve the learning objectives previously defined (constructive alignment). In neurosciences, Stanislas Dehaene, a cognitive psychologist has highlighted four fundamental elements that contribute to successful learning: attention, active engagement, feedback and consolidation, referred as the “four pillars of Learning”. Attention acts as a filtering

mechanism that allows the learner to select and process information in order to remember it. Thus, learning activities should focus on catching and sustaining learners ‘attention by using a good balance of stimuli and variations in activities (e.g., with visual, sound, quizzes).(93) The design of the e-learning also plays a role. Information should be presented in a concise and logical manner with appropriate use of font, color, graphics, borders and white space. (94) The second aspect is based on the principle that a passive organism does not learn. Learners should be actively involved by interacting with the content and making decisions about the information presented, which triggers memorization and improves understanding and retention of knowledge.(94) Feedback involves considering mistakes as learning opportunities to adjust knowledge. Learners can make progress by making mistakes, provided they receive a constructive signal in return. Finally, memorizing new information or acquiring new skills is merely the first step: this knowledge must be consolidated if it is to be durable and used automatically, almost unconsciously. Although the strength of recommendation was limited, *Cook and colleagues* showed that interactivity, practice exercises, repetition, and feedback improve learning outcomes in internet-based learning for health professionals. (95)

In the e-learning context, different categories of technological tools can be used to deliver content, for example, interactive multimedia tools, synchronous/asynchronous communication tools, social tools, etc., but no one type of tool was found to be more effective than another.(83,96) It is the instructional strategy that lead to the selection of the most appropriate tools. In addition, other factors related to technological and organizational constraints as well as time and budget available influence the choice of the delivery format.

- *Step 5 Implementation:* This step should consider the human and financial resources needed for the successful implementation of the program (e.g., for the dissemination of the program to the target audience, the provision of ongoing technical support to the learners). Most online courses are delivered through a learning management system (LMS), a software that stores and delivers course content, manage user information and track learning progress.(97) Before full implementation, conducting a pilot with a small group provides the opportunity to troubleshoot remaining technical issues (in term of usability and functionality) and to clarify or readjust certain aspects according to learners 'experience.

- *Step 6 Evaluation and feedback:* this step is crucial to ensure that the instruction achieved the desired goals, to determine if the curriculum was successful and how it could be improved. It should include assessment of individual participants and evaluation of the program's structure, processes, and outcomes by collecting qualitative and quantitative data. Most training program evaluations use the Donald Kirkpatrick's Model.(98) This four-level evaluation model evaluates how participants react to the training (*Level 1*), analyses if they truly improved knowledge, skills or attitude as a result of the training (*Level 2*), observes to what extend the participants change their behavior back in the workplace (*Level 3*), and measures the impact of the training program on relevant outcomes (Level 4). Although Level 4 represents the primary goal of the program and is the most relevant level to measure its real effectiveness, it is rarely considered as it is also harder to measure. Indeed, these outcomes are often affected by multiple, complex variables and variable interactions.(89) Finally an additional level *(Level 5)* was added by Jack Phillips to calculate the Return On Investment (ROI) of the training

program, i.e comparing the monetary benefits with the cost of the training program.(99)

Figure 3: Kirkpatrick training Evaluation model and ROI **(98,99)**

8.5 Objectives

As the cancer burden increases rapidly in LMICs, more hospitals will be engaged in cancer care and more healthcare workers will handle and be exposed to cytotoxic drugs. It is thus imperative that a strong and safe foundation for the provision of chemotherapy is established in each facilities so that the expansion of treatment can occur in a qualitative and safe manner. The overarching goal of this thesis was to improve knowledge and practices on the aspect of safe handling of chemotherapy drugs in LMICs. More specifically, we aimed to create, implement and evaluate different tools that could contribute in promoting and supporting continuous implementation of safe and quality practices in cancer care centers.

8.5.1 Research question 1

"Which criteria can be used to assess quality and safety of chemotherapy handling practices in cancer care centers of LMICs?"

The first research question aimed at selecting criteria that can enable to assess chemotherapy handling practices in cancer care centers in LMICs. The specific objective was to develop, validate and pilot-test a self-assessment tool based on recognized guidelines of safe handling of cytotoxic drugs. The availability of a self-assessment tool, suitable for the use in resource-constrained settings, would facilitate the structured evaluation of the quality and safety of current handling practices in regards to international standards and best practices. It could assist LMICs facilities on how to improve handling of chemotherapy to reach higher quality standards and ensure the safety of the workers and patients. It could be used as a continuous quality improvement by tracking progress over time. In addition to the validation of items, we

intended to prioritize them. Recommendation on the priority of safety measures is important to guide appropriate resource allocation in settings with limited resources.

8.5.2 Research question 2

"What is the level of implementation of safe handling practices in cancer care centres of low- and middle-income countries?"

The second research question investigated the level of quality and safety of chemotherapy handling practices in LMICs at every steps of the process, i.e., at reception of drugs, storage, transportation, prescription, preparation, administration, cleaning and waste disposal, handling patient's excreta as well as for more transversal aspects related to the management and personnel. Literature on this topic is still scarce and this study would provid a broad overview of the different practices implemented in many low-resource settings. Findings from this overview might help highlighting the gaps and identifying needs to support the improvement of safe practices.

8.5.3 Research question 3

"How to evaluate and promote continuous improvement of safe handling of chemotherapy drugs through a quality-oriented approach?"

The introduction of a quality-oriented approach to chemotherapy handling is essential to ensure patient and staff safety. The Deming Cycle describes four iterative steps (plan, do, study, and act) and has been widely used as a model for quality improvement.(100,101) In our context, the evaluation step, which the cycle defines, is to study whether safe and quality practices are being implemented so that corrective actions can be taken when necessary. To encourage LMIC facilities to complete this

step, we aimed to develop and test a toolkit for conducting a comprehensive assessment of the safety chemotherapy handling in LMIC cancer treatment centers. The toolkit would contain several tools to facilitate a structured and methodical assessment of the various steps in the cytotoxic process.

The pilot test of this toolkit in a variety of settings would enable to verify its applicability in local contexts. The availability of such a toolkit, offering ready-to-use tools and checklists might participate to facilitate the implementation of a continuous quality approach in LMIC cancer treatment facilities to ensure patient and staff safety.

8.5.4 Research question 4

"What is the impact of an e-learning module on safe chemotherapy handling practices?"

Guidelines and recommendations are unanimous: proper education and training on cytotoxic risks and safe handling practices should be provided to all the staff involved in the cytotoxic process. However, gaps in staff education and knowledge have been reported in LMICs. To address the lack of training opportunities in this area for LMICs, the objective was to build an online training module as well as supporting resources (e.g., standard operating procedures, job aids, checklists, video tutorials and other supporting materials), leveraging international best practices. The curriculum would be defined so as to cover the main aspects of the safe handling of chemotherapies all along the chemotherapy pathway (e.g., receiving drugs, storage, transport, prescription, preparation, administration, waste management, and disposal), to ensure patient safety and reduce the risks of occupational exposure and environmental contamination. All the material would be subsequently uploaded onto our existing online educational platform "Pharm-ED" (www.Pharm-Ed.net), a platform that we

created for promoting the efficient, safe, and rational management of medicines in LMIC hospitals.(102) The development process of the e-learning followed a systematic stepwise approach in order to create resources appropriate to low-resource settings and answering the needs of the intended users.

Thus, the last research question of this thesis seeks to ensure that our e-learning module was adapted to the learners and effective for knowledge improvement.

Articles

9. Articles

Methods are described in the original articles (§ 9.2.1, § 9.2.2, § 9.2.3, § 9.2.4)

9.1 Methodological Contribution

9.1.1 Article 1 : Cyto-SAT: A self-assessment tool for the safe handling of cytotoxic drugs adapted for use in low- and middle-income countries

Authors: Sandrine von Grünigen[1,2], Antoine Geissbühler[3,4] and Pascal Bonnabry[1,5]

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The aim of the research was to develop, validate, and pilot test a self-assessment tool to support the implementation of safe handling practices and promote continuous quality improvement for cytotoxic drug management in LMICs.

Literature review and development of the tool

The author of this thesis, Sandrine von Grünigen (SVG) reviewed key sources on safe handling to derive items and create a draft checklist. This initial checklist containing 137 items addressing safety and quality aspects of every step of cytotoxic drug process (e.g., receipt, storage, transport, prescription, preparation, administration, waste management, cleaning, and patient counseling) was then submitted to a steering committee led by Pascal Bonnabry (PBY) for pre-validation.

Delphi study

SVG conducted the modified two-round Delphi survey. This survey aimed to establish consensus on the different items and prioritize them in three categories (essential, very important and desirable). SVG developed the forms to collect the information from the experts and the documents explaining the process and providing background information. SVG recruited a panel of 27 international experts in oncology pharmacy practice from 13 high-income countries and LMICs. SVG performed the descriptive statistics and analyzed the results of the two rounds according to the consensus definition that was decided by the steering committee in the study design. SVG discussed with the steering committee the comments and proposed modifications of items received from the experts and made the agreed changes where appropriate. Before the second round SVG prepared an individual report for each expert presenting the summary results and the statistical group response for each item compared with her/his individual response. At the end of the Delphi, SVG finalized the tool and named it as Cyto-SAT for its online diffusion.

Evaluation survey

SVG conducted the evaluation survey of Cyto-SAT. This included the development of the evaluation form, the recruitment of participating facilities and the results analysis.

Writing of the article

SVG drafted the article which was critically reviewed by PBY and Antoine Geissbühler (AG) before submission. SVG led its finalization according to the peer review process until acceptance by the journal.

9.1.2 Article 2: The safe handling of chemotherapy drugs in low- and middle-income countries: an overview of practices

Authors: Sandrine von Grünigen[1,2], Antoine Geissbühler[3,4], and Pascal Bonnabry[1,5]

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The aim of this survey was to obtain an overview of the level of safe handling practices implemented in LMICs' healthcare facilities who are dealing with cytotoxic medicines and to prioritize opportunities for improving them.

Survey:

The cross-sectional survey was designed by PBY and SVG. Participating facilities were asked to perform a self-assessment of their practices regarding safe handling of cytotoxic drugs by using Cyto-SAT, the tool developed and validated in the article 1. SVG repeatedly recruited the participating facilities through diverse communication channels (social media, professional association, community of practices, newsletters, professional networking etc.) and provided documents with background information and detailed instructions on how to fill in the tool. Participants were encouraged to enter

their data directly into a web-based platform (www.datapharma.ch/cyto-SAT) developed by an IT engineer. However, for facilities with limited internet access, SVG sent out by email a Microsoft Excel® version of Cyto-SAT, and subsequently transcribed the results returned onto the online platform. SVG analyzed the results and performed the descriptive statistics (median, interquartile range etc.).

Writing of the article

SVG drafted the manuscript which was critically reviewed by PBY and AG before submission. SVG led its finalization according to the peer review process until acceptance by the journal.

9.1.3 Article 3 : Development and proof of concept of an audit toolkit for the safe handling of cytotoxic drugs in low- and middle-income countries

Authors: Sandrine von Grünigen[1,2], Ludivine Falaschi[1], Nicolas Guichard[1], Sandrine Fleury-Souverain[1], Antoine Geissbühler[3,4], and Pascal Bonnabry[1,5]

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This paper describes the development and proof of concept of a toolkit to audit chemotherapy handling practices in LMIC healthcare facilities.

Development of the toolkit.

The audit method and the toolkit design were defined by a steering committee created within Geneva University Hospitals' Pharmacy Department. Besides the development of Cyto-SAT assessment tool that was discussed in article 1, SVG developed the three structured observations checklists that were part of the toolkit and allowed the data collection during audits. Each checklist was based on professional guidelines and best practices but was adapted to the contexts existing in LMICs. The prescription and the three preparation checklists were reviewed by two experts from the chemotherapy centralized preparation unit - Ludivine Falaschi (LF) and Febronia Grossrieder- and PBY. The administration of chemotherapy checklist was reviewed by two HUG nurses specialized in oncology. The methods used to perform surface-wipe sampling and analyse the cytotoxic contamination was previously developed by Nicolas Guichard (NG) and Sandrine Fleury (SF) from the quality control unit of the HUG pharmacy.

Recruitment of pilot sites

SVG recruited the healthcare facilities that participated as pilot sites. The contacts in Dakar Senegal and Yaoundé Cameroon were given by AG. SVG provided each facilities with documentation on the audit process and background information.

Conducting the audit

SVG organized and conducted the field visits to audit the three participating facilities. Using the different tools, SVG conducted structured observations of the process and

practices, interviews with the staff and performed surface-wipe sampling in the chemotherapy preparation and administration areas within the 3 pilot sites.

Data process

NG analyzed under the supervision of SF the cytotoxic contamination of the 35 samples collected. SVG processed the data collected during the audit and wrote an individual report for each health care facility summarizing the results in the different processes and highlighting the main strengths and areas for improvement. An action plan was drafted at the end of the three reports. Each of these was then critically reviewed by LF and PBY before being sent to the local pilot site coordinator.

Writing of the article

SVG drafted the manuscript which was critically reviewed by all co-authors before submission. SVG led its finalization according to the peer review process until acceptance by the journal.

9.1.4 Article 4 : Development and evaluation of an e-learning module on safe handling of chemotherapy drugs for low- and middle-income countries

Authors: Sandrine von Grünigen[1,2], Berangère Dessane[1], Pauline Le Pape[1], Ludivine Falaschi[1], Antoine Geissbühler[3,4], and Pascal Bonnabry[1,5]

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The study objectives were to develop and evaluate an e-learning training module on safe handling of chemotherapy drugs to strengthen knowledge and practices in low- and middle-income countries.

Curriculum development

A steering committee including SVG, PBY and LF developed the curriculum of the e-learning module on safe handling of cytotoxic drugs by discussing the target audience, its needs and the objectives of the module and the educational strategy.

E-learning development

SVG, Pauline le Pape (PLP) and Berangère Dessane (BD) participated in the creation of the eleven e-learning lessons and their pre/post-tests and the development of practical tools (e.g. checklist, procedure, etc.). PLP and BD were supervised by SVG. All the e-learning and tools were critically reviewed by LF and PBY before online publication. SVG managed the online platform and the learning management system with the assistance of an IT engineer.

Conduct of the study

PBY, AG and SVG agreed on the study design. SVG was in charge of conducting the study, i.e the participants' recruitment, the provision of study instructions, the data analysis and the statistics.

Writing of the manuscript

SVG drafted the manuscript which was critically reviewed by all co-authors before submission. SVG led its finalization according to the peer review process until acceptance by the journal.

9.2 Article manuscripts

9.2.1 Article 1

JOURNAL OF ONCOLOGY PHARMACY PRACTICE

Original Article

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Cyto-SAT: A self-assessment tool for the safe handling of cytotoxic drugs adapted for use in low- and middle-income countries

Sandrine von Grünigen[1,2], Antoine Geissbühler[3,4] and Pascal Bonnabry[1,5]

Abstract

Introduction: The handling of cytotoxic medicines is a high-risk process for human and environmental health. Considering the rising burden of cancer in low- and middle-income countries (LMICs), we aimed to develop, validate, and pilot test a self-assessment tool to support the implementation of safe handling practices and promote continuous quality improvement for cytotoxic drug management in LMICs.

Methods: First, the self-assessment tool Cyto-SAT was developed and validated. Key sources on the safe handling of cytotoxic medicines were reviewed to derive items addressing safety and quality aspects at every stage of the process. A two-round online Delphi survey was conducted to validate and prioritize the items. The validation rules in the first and second rounds were defined as $\geq$65% and $\geq$75% agreement, respectively. Then, intended users in healthcare facilities in LMICs evaluated the Cyto-SAT tool in a pilot test. They were asked to fill out an online evaluation questionnaire.

Results: Twenty-seven experts from 13 high-income countries and LMICs participated in the Delphi survey. Final expert consensus was achieved for 134/137 (97.8%) items. Consensus on priority was achieved for 52 of 134 (38.8%) items. The final Cyto-SAT tool comprises 134 items in 10 domains and 28 subdomains covering the whole cytotoxic drug handling process (https://pharmed.datapharma.ch/cyto-sat_en/). Staff from 34 institutions in 28 LMICs completed the Cyto-SAT evaluation. Almost all of them reported total agreement or agreement with its usefulness (96%), applicability (94%), usability (98%), and acceptability (97%).

Conclusion: Cyto-SAT is the first self-assessment tool designed to assist professionals in LMICs in the safe handling of cytotoxic drugs. The pilot test revealed that Cyto-SAT is a useful and highly appreciated tool that supports practice improvement in LMICs. Cyto-SAT will be used in an international survey to obtain a global overview of handling practices in various LMIC settings.

Keywords

cytotoxic drug, safe handling, self-assessment tool, resource constrained settings, low- and middle-income countries

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Introduction

The safe handling of cytotoxic drugs is an important aspect of cancer management. Due to their inherent toxicity, these medicines should be handled with great caution to ensure patient safety and to prevent occupational exposure and environmental contamination.[1] Since the 1980s, many professional groups and national authorities have developed handling guidelines and regulations for these drugs based on scientific evidence

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and best practices. All of them promote the implementation of safe handling programs wherever cytotoxic drugs are transported, received, stored, prepared, administered, and disposed of.[1–5]

Low- and middle-income countries (LMICs), as defined by the World bank,[6] are facing a growing burden of cancer cases. The most recent data from the International Agency for Research on Cancer indicate that the majority of new cancer cases occur in these countries. Of the 9.6 million cancer deaths worldwide in 2018, 70% occurred in LMICs.[7,8]

The economic impact and human development challenges resulting from this rising cancer burden have led the World Health Organization (WHO) and its partners to take action.[9,10] Substantial efforts have been made to prevent and manage cancer in LMICs, notably by expanding access to affordable and high-quality cytotoxic drugs for chemotherapy. More than 30 cytotoxic medicines are included in the WHO's essential medicines list.[11] Beyond patient safety, the risks of occupational exposure and environmental contamination are likely to become increasing concerns for hospital management and governments, particularly in settings with poor infrastructure and few qualified personnel. Many gaps related to the safe handling of cytotoxic drugs remain in national and international cancer control programs, and few relevant context-specific guidelines and tools exist.[12] We aimed to develop, validate, and pilot test a self-assessment tool to support the implementation of safe handling practices and promote continuous quality improvement for cytotoxic drug management in LMICs.

Methods

This study was conducted in two main phases: the development and validation of the self-assessment tool Cyto-SAT and its evaluation by intended users.

Cyto-SAT development and validation of the tool

Literature review and checklist creation. The principal investigator reviewed key sources on safe handling (Table 1) to derive items and create a draft checklist. Only publications that were accessible online at no charge were reviewed. A steering committee performed a pre-validation of the check-list before the beginning of the Delphi survey. The steering committee was assembled in the Pharmacy Department of the Geneva University Hospitals. It was composed of the department head, the pharmacist in charge of quality assurance, the pharmacist in charge of the cytotoxic drug preparation unit, and the principal investigator of this study. The committee was given the responsibility of making decisions at each step of the survey. The draft checklist was written in French and in English, and forward/backward translation was performed to ensure that the two versions matched.

The Delphi study. We conducted a two-round Delphi survey for consensual validation of the tool and to prioritize items addressing safety and quality aspects of every step of cytotoxic drug handling (e.g., receipt, storage, transport, prescription, preparation, administration, waste management, cleaning, and patient counseling).

Expert recruitment. We recruited a panel of international experts representing high-income countries and LMICs. Pharmaceutical experts with strong experience with cytotoxic medicines and oncology pharmacy were invited to participate. We identified potential experts through the steering committee's professional network and panel members' recommendations, and among country delegates listed on the websites of professional societies [e.g., the International Society of Oncology Pharmacy Practitioners (ISOPP) and the European Society of Oncology Pharmacists] and authors of relevant publications on oncology pharmacy in LMICs. Each expert participating in the study disclosed any conflict of interest.

Delphi survey rounds. An online self-administered questionnaire was submitted to the expert panel using the SurveyMonkey® website.[19] In the first Delphi round, the experts were asked to rate their agreement with the checklist items on a 5-point Likert scale (1, strongly disagree; 5, totally agree) and to prioritize them using a 3-point scale (1, essential, absolutely required even for occasional handling of cytotoxic medicines; 2, very important, required for regular use of cytotoxic medicines; 3, desirable, if regular use and/or sufficient resources). For both criteria, a "no opinion" option was available. A free text field was provided, allowing experts to add comments or references to clarify their positions and/or to suggest item amendments and/or additions. Expert's comments were reviewed and discussed by the steering committee to determine whether items needed to be modified, completed, or rephrased.

The steering committee decided arbitrarily that only items with >65% agreement (score $\geq$4) would be retained for the second round. We did not use the priority level to exclude items. This criterion was meant to guide users in designing their action plan according to the results of the self-assessment.

Before the second round, each expert received an individual feedback report presenting the summary

Table 1. References used for the elaboration of the items.

Documents	Authors	Year	Region/countries	Type de documents
Standards ISOPP[1]	International Society of Oncology Pharmacy Practitioners	2007	International	Recommendations from scientific societies
QuapoS 4: Quality Standard for the Oncology Pharmacy Service with Commentary[13]	DGOP e.V (German Society of Oncology Pharmacy)/ESOP (European Society of Oncology Pharmacy)	2009	Europe	Quality standards from scientific societies
ASHP Guidelines on Handling of Hazardous Drugs[2]	American Society of health system pharmacists	2006	USA	Recommendations from scientific societies
USP (United States Pharmacopeia) Chapter 800: Hazardous Drugs-Handling in Healthcare settings[14]	The Compounding Expert Committee	2015 (draft)	USA	Regulatory framework
Bonnes Pratiques de Préparation[15]	Afssaps (Agence française de sécurité sanitaire de produits de santé)	2007	France	Regulatory framework
Suvapro: sécurité dans l'emploi des cytostatiques[3]	Swiss Accident Insurance Fund	2004	Switzerland	Recommendations for occupational safety
WHO-Good Manufacturing Practices Annex 3[16]	WHO Expert Committee on Specifications for Pharmaceutical Preparations	2010	International	Regulatory framework
Chemotherapy Administration Safety Standards[17]	American society of clinical Oncology (ASCO)/Oncology Nursing society (ONS)	2013	USA	Quality standards from scientific societies
OSHA: Controlling Occupational Exposure to Hazardous Drugs[4]	Occupational Safety & Health Administration (OSHA) (US Department of Labour)	Consulted 2016	USA	Recommendations for occupational safety
NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings[18]	National Institute for Occupational Safety and Health	2004	USA	Recommendations for occupational safety
Safe Handling of Hazardous Chemotherapy Drugs in Limited-Resource Settings[5]	Pan American Health Organization (PAHO)	2013	PAHO	Recommendations

results and the statistical group response for each item compared with her/his individual response.

In the second round, we asked experts to rate their agreement with the median priority scores from the first round on a 5-point Likert scale (1, strongly disagree; 5, totally agree). When an expert disagreed with a score, she/he was required to indicate her/his preferred priority level in a comment in a free text field.

In accord with previous studies, final consensus was defined as $\geq$75% expert agreement (score $\geq$4).[20,21] Only items for which consensus was achieved were retained in the final tool. The expected duration of each round was about 4 weeks.

Cyto-SAT evaluation by intended users

We recruited health facilities handling cytotoxic drugs in LMICs to test the Cyto-SAT tool in various settings. We used several communication channels to disseminate the study and recruit facility staff: social media, websites, member lists of professional associations (e.g., the ISOPP and Pharm-Ed[22]), community of practice forums (e.g., for e-med and e-drugs), newsletters (e.g., of Pharm-Ed and Union for International Cancer Control), and professional networking. Staff at participating facilities were asked to use the Cyto-SAT for self-assessment of their handling practices in small multidisciplinary teams. After the assessment, they were asked to fill out an evaluation questionnaire to give feedback on the usefulness, applicability, usability, and acceptability of the tool. These data were recorded on a web-based platform (http://datapharma.ch/cytoSAT/).

Statistical analysis

Data from both phases of the study were exported into a Microsoft Excel® spreadsheet (MS office 2013). For each statement, we calculated the participation rate, the median agreement rating, the 1st and 3rd quartile, the minimum and maximum and the percentage of experts who rated 4 or 5. After the first round we calculated the median item priority scores; when a score was between two whole numbers (e.g., 1.5) the priority level that had received the most votes was chosen.

Results

Cyto-SAT development and validation

The chronology of the Delphi survey is presented in Figure 1.

Literature review. The principal investigator derived 138 items from the literature review. These items were classified into 10 domains and 28 subdomains representing cytotoxic medicine handling in healthcare facilities (Table 2). After revision by the steering committee members, 137 items were included in the draft checklist submitted to the expert panel. One item was deleted due to its low relevance.

Expert panel. Of 55 international pharmaceutical experts in oncology practice invited to be part of the panel, 33 (60%) agreed to participate; 28 (85%) of these experts completed the first Delphi round and 27 of these 28 (96%) completed the second round (Table 3). Thirteen high-income countries and LMICs (Algeria, Belgium, Canada, Chile, Egypt, Estonia, France, Germany, Morocco, New Zealand, South Africa, Switzerland, and Tunisia) were represented. No expert reported a conflict of interest relevant to the study.

Delphi rounds. In the first Delphi round, 135 of 137 (98.5%) items were validated (i.e., >65% expert agreement). Thus, two items were removed. The mean participation rates for agreement and priority rating were $98.5\% \pm 2.7\%$ and $96.9\% \pm 4.8\%$, respectively. The experts provided 385 comments. After revision and discussion of the comments' relevance, the steering committee modified 56 items. Agreement on priority (>65%) was achieved for only 19 of the 137 (14%) items.

In the second round, consensus on content and formulation was achieved for 134 of 135 items. The mean participation rates for agreement on content and median priority rating were $99.7\% \pm 1.0\%$ and $95.8\% \pm 1.4\%$, respectively. The experts provided 185 comments, which led to the clarification (primarily the addition of information) of 28 items. Consensus on priority ($\geq$75% agreement with the median priority score) was achieved for only 51 of 134 (38%) items. The final tool contains 76 (57%) "essential" items and 58 (43%) "very important" items. No item was ranked as "desirable."

Cyto-SAT evaluation by intended users

Thirty-three institutions from 26 LMICs (from the 51 institutions that participated in Cyto-SAT testing) completed the evaluation questionnaire (Table 4 and Figure 2). A median of 3 (range, 1–12) persons per facility participated in the self-assessment. Most of the team reporters were pharmacists (91%), no information were collected on the other members of the team. Staff at almost all facilities reported agreement or total agreement with the usefulness (96%), applicability (94%), usability (98%), and acceptability (97%) of the tool. Staff from some facilities noted the lack of detailed questions about the equipment used for drug

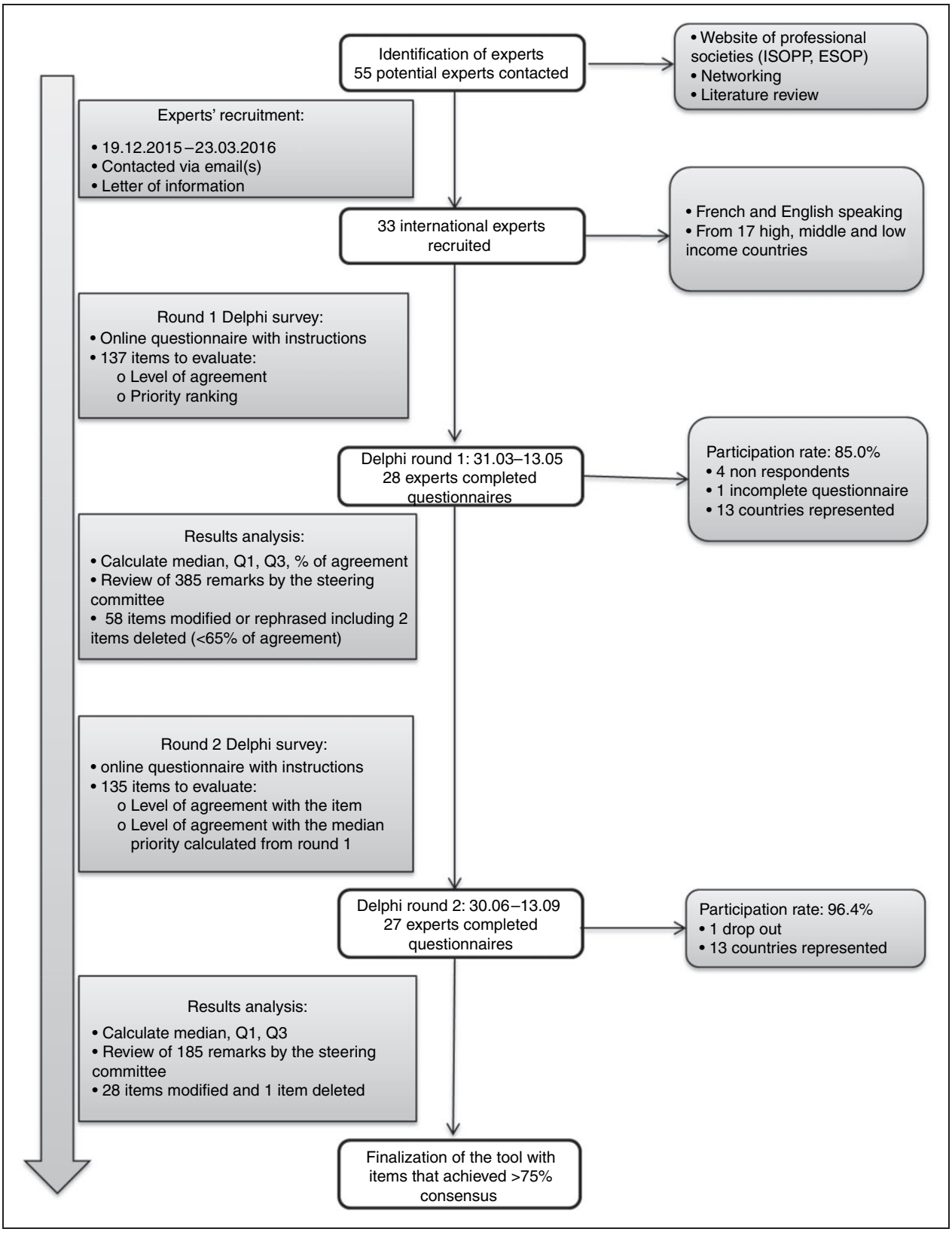

Figure 1. Chronology of the Delphi survey.

Table 2. Domains and subdomains classification with number of items in the draft checklist.

Domains	Sub-domains	Number of items submitted to the DELPHI PANEL
1. Management		11
2. Personnel	• Education and training	4
	• Medical surveillance	4
3. Logistics	• Receipt	6
	• Storage	6
	• Transport	5
4. Prescription		5
5. Preparation	• Management and organization	4
	• Preparation area of parenteral medicines	10
	• Hygiene and personal protective equipment	6
	• Preparation process set up	4
	• Preparation technique	10
	• Packaging and labelling	3
	• Checking procedure	2
	• Documentation	3
	• Maintenance	2
	• Non sterile preparation	1
6. Administration	• Management	2
	• Hygiene and safety measures	5
	• Documentation	3
	• Work practices	4
7. Incidents management	• Surface contamination	6
	• Staff contamination	3
	• Extravasations	3
	• Quality assurance	1
8. Waste management	• Waste disposal	7
	• Patients' excreta	3
9. Cleaning	• Management and organization	2
	• Cleaning practices	6
	• Laundry	2
10. Patients counselling		4
	TOTAL	137

preparation and administration, about premedication preparation, and about the home use of cytotoxic medicines. Other staff teams recommended the summary of certain points and reduction of the number of questions. Finally, staff at some facilities mentioned that training, mentoring, collaboration between institutions, sharing of experience in other contexts, support for equipment provision (e.g., biosafety cabinets, personal protective equipment, and spill kits), and support from national authorities could help them to improve their practices.

Discussion

We developed the first self-assessment tool designed to assist staff at healthcare facilities in LMICs safely handle cytotoxic medicines (online Appendix 1). The Cyto-SAT consists of 134 items in 10 domains and 28 subdomains covering the entire process of cytotoxic drug handling in healthcare facilities. The high level of satisfaction reported by intended users confirms its usefulness and acceptance as an ongoing quality improvement tool, which might enhance future use of this tool in resource-constrained settings.

Study strengths and weaknesses

The Cyto-SAT was validated using the Delphi technique, which is used widely to elicit experts' opinions about and agreement with quality indicators in healthcare.[20] We achieved broad geographical and economic representation, with the participation of experts in 13 countries with incomes of all levels. The availability of the survey in English and French permitted the involvement of experts from various regions of the world, which enriched the results based on their different cultures and experiences. The participation of experts from high-income countries was essential to benefit from these experts' extensive expertise in the field, and the assembly of a mixed panel with experts from LMICs was important to ensure the adaptability of the

Table 3. Characteristics of the pharmaceutical experts involved in the Delphi survey.

Experts' characteristics		
Experts: n (%)	28	
French-speaking	19	(68%)
English speaking	9	(32%)
High-income countries	15	(53.6%)
Low & middle-income countries	13	(46.4%)
Gender: n (%)		
Men	10	(35.7%)
women	18	(64.3%)
Type of health facilities: n (%)		
University/Academic Hospital	21	(75%)
Regional Hospital	5	(17.9%)
Private Facility	2	(7.1%)
Other	1	(3.6%)
Countries: n (%)	13	
High-income	7	(53.8%)
Low & Middle-income	6	(46.2%)
Experience with cytotoxics (years): median (Q1–Q3)	10	(4–18)

Table 4. Characteristics of participating facilities in Cyto-SAT evaluation survey.

Participants' characteristics	**Number**	**(%)**
By country income level		
Upper middle-income	7	21%
Lower middle-income	14	43%
Low income	12	36%
Types of institution		
Academic/University hospital	19	58%
Non-profit private healthcare facility	2	6%
For-profit Private healthcare facility	3	9%
Regional Hospital	4	12%
District Hospital	3	9%
Health Center	1	3%
Unknown	1	3%
Members of ISOPP	12	36%
	Median (Q1–Q3)	
Nb of departments that administer chemotherapies	2 (1–4)	
Nb of chemotherapies administered/month	300 (70–1150)	
Number of staff involved in the preparation and administration of chemotherapies	9 (5–20)	

tool to their settings. However, the identification of pharmaceutical experts in oncology from the least-developed countries was difficult, as this specialty has barely been established in those countries.

Very high participation rates (mean, 99.7%) and strong consensus (mean agreement, 94.8%) were achieved for all final Cyto-SAT items. However, consensus on item priority was difficult to achieve in this study; final consensus was achieved for only 38.5% of items. The threshold of $\geq$75% for final consensus was chosen based on similar studies,[21] but lower thresholds have also been used.[21,23] With a threshold of 70%, consensus would have been achieved for more than two-thirds of items in this study. We considered performing a third Delphi round to increase the level of consensus through the provision of additional feedback, but we decided not to do so because the experts did not follow the instructions to provide arguments and preferred priority ratings in case of disagreement with the proposed priority scores in the second round. Thus, a third round would probably not have significantly increased the degree of consensus, and might have led to expert fatigue and dropout.

Comparison with other tools

Cyto-SAT is the only self-assessment tool adapted to LMIC settings that enables rapid appraisal of the whole process of cytotoxic drug handling. It covers more domains (e.g., administration and patient counseling) than other assessment tools, which focus on oncology pharmacy unit activities.[24,25] To ensure its suitability for use in LMICs, Cyto-SAT does not include items requiring integrated information technologies, although the computerization of some processes is always listed as a desirable objective. In contrast to tools designed for use in the inspection of national or regional facilities, the Cyto-SAT tool does not contain context-specific items, which enables its application in multiple settings. Moreover, Cyto-SAT entails the innovative prioritization of items. In settings with limited resources, knowledge of the priority of safety measures is important to guide appropriate resource allocation. Cyto-SAT is complementary to the International Medication Safety Self-Assessment® for Oncology[26] which was designed to reduce medication errors and improve patient safety in oncology.

Implications for practice

Cyto-SAT is available on a free online platform: https://pharmed.datapharma.ch/cyto-sat_en/. The high level of user satisfaction in the pilot test demonstrates that Cyto-SAT is useful and appropriate for the assessment of cytotoxic drug handling in many resource-constrained settings. Almost all users found that the time invested in the assessment was worth it, and stated that they would repeat such assessment in the future (92% and 94%, respectively). These very

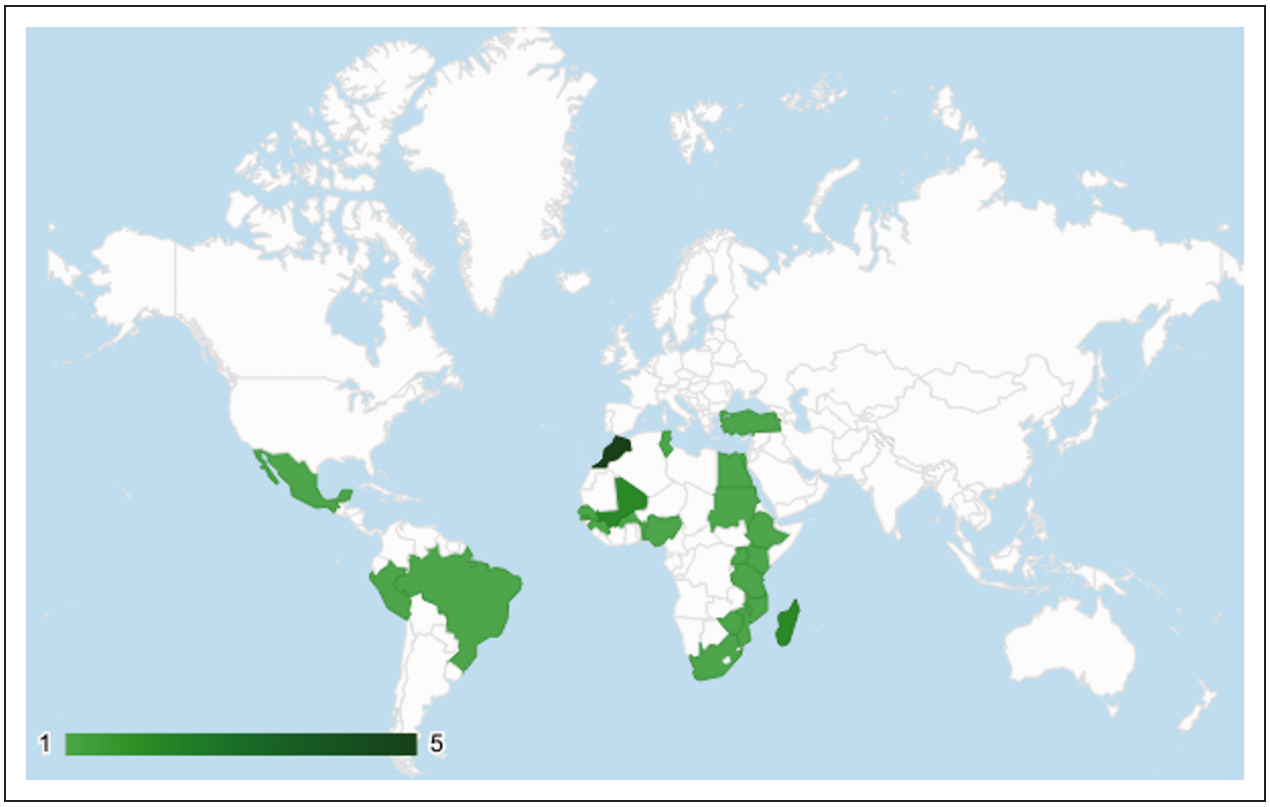

Figure 2. Geographical participants' distribution of the evaluation survey.

positive results confirm the relevance of Cyto-SAT for measuring improvement over time in these facilities. Staff at 97% of the participating facilities agreed or totally agreed that Cyto-SAT, in addition to the primary goal of ongoing quality improvement, is useful for knowledge strengthening. Cyto-SAT could thus also be used as an educational tool and to raise awareness about safe handling practices. Additional translation of the tool into Spanish and/or Portuguese might help to expand its use in more countries.

Unanswered questions and future research

Our next step will be to disseminate the tool and perform an international survey to obtain a global overview of cytotoxic drug handling practices in various LMIC settings. This research could provide information about variability in actual safety levels. By highlighting strengths and weaknesses of the tool, it might help to identify the need for the development of additional tools or educational resources to further support practice improvement. Cyto-SAT will then be used to evaluate the impact of a blended learning module on the safe handling of cytotoxic drugs in several pilot sites in Africa in a before/after study.

Conclusion

Cyto-SAT is the first tool developed for the self-assessment of cytotoxic drug handling in LMICs. It consists of 134 items covering this whole process in healthcare facilities. The pilot test revealed that Cyto-SAT is a useful and highly appreciated tool that supports practice improvement in LMICs.

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Supplemental material

Supplemental material for this article is available online.

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APPENDIX

Appendix 1: Cyto-SAT

N°	ITEM	ADDITIONAL INFORMATION
MANAGEMENT AND ORGANIZATION		
1	A risk analysis has been conducted in order to evaluate the working environment and to identify and assess hazards related to the flow of cytotoxic medicines within the facility (from the receipt to the use of the products)	A risk assessment approach is used to determine the containment strategies and/or work practices. This considers: overall working environment; equipment (i.e. ventilated cabinets, closed-system drug transfer devices, needleless systems and personal protective equipment); physical layout of work areas; volume, frequency and form of drugs handled (coated or uncoated tablets, powder or liquid); equipment maintenance; decontamination and cleaning; waste handling; potential workplace exposure; routine operations; spill response; and waste segregation, containment. and disposal, training and level of experience of the staff
2	A comprehensive safety management programme has been put in place to deal with all aspects of the safe handling of cytotoxic drugs	A staff member is responsible for coordinating the implementation of preventive measures and preparing guidelines, in close collaboration with other relevant staff within the facility.
* 3	Policies and procedures ensure that guidelines for the safe handling of medicines are applied to all processes in which cytotoxic drugs are handled.	Policies and procedures are updated regularly. The frequency of update is to be defined by the local institution, according of the context. Any changes must be documented.
* 4	A self-assessment of compliance with safety guidelines regarding the safe handling of cytotoxic medicines is carried out regularly.	Each institution should define its frequency according to local context.
* 5	Material Safety Data Sheets (MSDS) are readily available for all cytotoxic medicines used in the facility.	MSDS can be kept in a file, be available on a computer or be consulted via the internet.
*		The list can be kept in a file or be available on a computer.

6	A list of the cytotoxic medicines used in the facility is available and regularly updated.	
* 7	Smoking, drinking and eating are forbidden in areas where cytotoxic medicines are prepared, stored and administered	
* 8	All staff know and understand the facility's policies and approach on quality assurance.	Documents are readily available and written in an easily understandable manner.
* 9	There is a regularly updated organigram (organizational chart) indicating the roles and responsibilities of all the staff members involved in processes using chemotherapies, as well as their contacts details.	
* 10	There are written job descriptions detailing the responsibilities, skills and tasks of each staff member.	Required national or international qualifications to handle cytotoxic can also be added
* 11	There is a sufficient number of competent staff to ensure that high quality care is carried out safely.	The staff available daily should enable to fulfill the tasks and responsibilities according to this repository and to maintained an acceptable workload.
PERSONNEL		
Eduction and training		
* 12	Based on their tasks and responsibilities, all staff involved in the handling of cytotoxic medicines have received adequate initial training on the type of products they are dealing with, cytotoxic risks, suitable protective measures and proper handling methods.	This includes pharmacy and nursing staff and doctors, plus support staff such as porters, cleaners, stock managers and waste management staff.
13	There is regular continuous education for staff.	Training sessions are specific to the category of staff. An annual training plan should be prepared

14	Both theoretical knowledge and practical skills are validated following training (according to the tasks and responsibilities of the staff)	E.g. oral or written tests; assessment using simulation exercises; or practical audits on the following subjects: - Knowledge of cytotoxic medicines handled and their risks; - Knowledge of SOPs related to their handling; - Proper use of personal protective equipment; - Proper handling and use of equipment and devices; - Managing incidents such as breakages, spills and exposure to cytotoxic medicines.
15	All training and skill validations are documented.	Training records are kept for at least 5 years.
Medical surveillance		
* 16	An occupational health surveillance programme is available for staff members who handle cytotoxic medicines	The occupational health surveillance includes: the evaluation of protective measures for pregnant and breastfeeding women; risk assessments in case of accidental exposure or proven or suspected deficiencies in technical protection systems; and investigations that must be carried out in suspected cases of disorders associated with exposure to cytotoxic medicines
17	No pregnant and breastfeeding women are involved in the handling of cytotoxic medicines.	Pregnant or breastfeeding women must not take part in the preparation, reconstitution, administration, cleaning or disposal of cytotoxic medicines (consult also the stipulations of the national labor law if available)
* 18	Staff involved in the preparation of cytotoxic medicines, with an upper respiratory tract infection or a cutaneous infection informs their superior before any manipulation	The decision to exclude temporarily or not the person from the preparation should be evaluated one by to avoid a risk of microbiological contamination of the preparation. A medical advice can be eventually sought
LOGISTICS		
Receipt of cytotoxic drugs		
* 19	Cytotoxic medicine deliveries are only received and unpacked by trained staff.	The staff responsible for receiving cytotoxic medicines has been trained about the possible surface contamination of primary packaging and vials, the risks of breakages and the appropriate precautions to apply.

* 20	Staff use appropriate personal protective equipment when receiving and unpacking cytotoxic medicines	Protective gloves
* 21	The reception of cytotoxic medicine deliveries is carried out appropriately.	Product deliveries are handled by trained staff who visually check the integrity of the packaging to identify any breakages or fissures. If products seem to be intact, reception and unpacking are carried out immediately, or the boxes are placed in a secure area (adequately labeled and with restricted access) until this can be done. Medicines that must stay in the cold chain are unpacked and refrigerated upon receipt.
22	The staff receiving and unpacking cytotoxic medicines know the procedures to adopt in cases of accidental spills or leakages.	They are also able to apply those procedures in practice
* 23	Staff washes their hands with soap after handling cytotoxic medicines.	Wearing gloves is not a substitute for washing hands.
Storage		
* 24	Cytotoxic medicines are stored separately from the rest of the inventory, in a dedicated storage area (including those requiring storage in a refrigerator).	Product segregation prevents contamination and the risk of exposure. If segregation in a separate room for cytotoxics is impossible, storage of cytotoxics is in a clearly identified area.
* 25	The storage area for cytotoxic medicines is clearly defined and labeled. Access is restricted to authorized personnel only.	Easily recognizable warning labels should be placed to alert staff (e.g. "Danger/caution cytotoxics"), and security measures should limit access (e.g. locks, badges).
* 26	Storage areas contain equipment and monitoring system in order to ensure the correct storage conditions (temperature, light, humidity, exhaust air ventilation) and fulfill safety precautions.	Temperature is monitored and recorded on a logbook.
* 27	The storage area has sufficient general exhaust ventilation	
*		

28	Only trained staff have access to the storage area for cytotoxic medicines, and they wear appropriate personal protective equipment when resupplying or stocktaking	Gloves should be worn when handling cytotoxic medicines, even in primary packaging and vials. Numerous studies have reported surface contamination of vials and primary packaging.
* 29	Staff wash their hands with soap after handling cytotoxic medicines when resupplying or stocktaking	Wearing gloves is not a substitute for washing hands.
Transport		
30	Cytotoxic medicines are transported in a manner that will prevent damage to and contamination of the environment, and maintain the integrity of the medicines themselves and the safety of the transporter.	This includes all in-house or inter-facility transport.
* 31	Cytotoxic medicines are transported in exclusively dedicated containers/boxes.	
* 32	Transport containers/boxes for cytotoxic medicines are easily recognizable for any person who might handle them.	Easily recognizable warning labels must be attached to the containers and provide specific instructions regarding storage and measures to be taken in case of breakage.
* 33	Cytotoxic medicines are transported in very tough, leak proof containers that can be sealed and are made of a material that can easily be cleaned and decontaminated.	Vials must also be securely positioned within their containers in order to minimize impacts and risks of breakage. Ready-to-use preparations must first be placed in leak-proof bags
* 34	Personnel transporting cytotoxic medicines know the procedures to carry out in case of an accidental spill.	Staff knows who to contact in case of an emergency.
PRESCRITPION		
35	Only authorized healthcare practitioners can prescribe chemotherapy treatment.	The facility has a readily available, up to date list of authorized prescribers.
*		

36	Prescriptions are based on standard pre-prepared chemotherapy treatment protocols dependent on the diagnosis, available in the facility (these have either been developed in-house or with reference to external review board or nationally approved clinical research protocols or guidelines).	Standard treatment protocols are regularly revised and updated. They are readily available to all the staff involved in prescribing and validating the prescription. Any prescriptions that are off-protocol must be accompanied by the physician in charge of the chemotherapy's written justifications
* 37	Prescriptions are done in a structured way, with the use of standardized, formatted (pre-printed or electronic) prescription forms. They are nominative, readable, contain no abbreviations and clearly identify the prescriber, the department giving care and the facility.	No prescription (or prescription modification) that was only communicated orally should be validated
38	Prescriptions include the following information: patient identity (name, sex, date of birth) weight, height, body surface area, diagnosis, relevant laboratory results (e.g. clearance), name of the protocol, product INN, dosage regimen, dates and times of administration, start and duration of the treatment, pharmaceutical formulation and route of administration, solvent and infusion volume, premedications.	Use of standardized, pre-printed or electronic prescription forms for chemotherapy treatment protocols is recommended.
39	Before preparation, all prescription/orders are analyzed, cross-checked using the standard agreed chemotherapy protocol and then validated by the signature of a qualified person (e.g. a pharmacist).	Independently verify each order for chemotherapy before preparation, including confirming: that the prescription corresponds with standards protocols; drug names, regimen and volume; route and rate of administration; product/solvent and product/product compatibilities; dose calculations (including the variables used in this calculation), treatment cycle and day of cycle and cumulative doses.
PREPARATION		
Management and organization		

40	Only trained, qualified personnel prepare cytotoxic medicines.	Each operator should be individually validated for both aseptic working methods and proper compounding techniques. (see Chapter on "Personnel")
41	Preparation of oral or parenteral cytotoxic medicines takes place in a controlled area dedicated to this activity. Signs designating the hazard must be prominently displayed at the entrance.	It is recommended that the preparation of cytotoxic medicines should be centralized in order to minimize the risks of contamination and limit the number of people exposed. The preparation area should be located away from breakrooms and refreshment areas.
42	Access to preparation areas is restricted to authorized personnel involved in preparation of cytotoxic medicines and wearing appropriate personal protective equipment.	
* 43	The quality, safety and aseptic conditions (if cleanroom) of the entire preparation process for parenteral/sterile cytotoxic medicines have been validated.	The objective of validation is to demonstrate that the processes used ensure to reproducibly obtain a cytotoxic preparation, with the correct products, within acceptable concentration limits, and that chemical and microbiological integrity of the product will be maintained for the established conservation period.
Preparation area of parenteral drugs		
44	An administrative area is available for examining prescriptions, preparing production sheets and storing documentation and patient files.	This area is outside the preparation room, but close to it.
* 45	The preparation room only contains the necessary materials for the preparation	The objective is to limit the risk of confusion and to minimize the contamination in case of cleanroom
* 46	The preparation of sterile cytotoxic (parenteral) medicines takes place in a cleanroom	The preparation of sterile cytotoxic drugs can be defined as an aseptic preparation and should follow GMP and PIC/S guidelines for aseptic procedures. Preparations realized in non-aseptic conditions (without a cleanroom) even with a BSC must not be kept more than 24h.
*		

47	The preparation room surfaces are designed to minimize particle shedding and prevent the build-up of particulate matter as per Good Manufacturing Practices.	Work surfaces and all other surfaces in the preparation room should be smooth and facilitate effective cleaning and disinfection.
* 48	Ergonomic guidelines for the workspace are closely followed.	Notably, these include guidelines on air conditioning, lighting and the workspace, essential for the well-being of the staff and risk minimization of incidents
* 49	The preparation of cytotoxic medicines is performed in a class II b or class III (vertical laminar-airflow hood) biosafety cabinet (BSC) or in an isolator with system externally vented through HEPA filters (high-efficiency particulate air).	A continuous monitoring device ensures confirmation of adequate airflow and/or cabinet performance. If the preparation is not done in a BSC or an isolator, it is only extemporaneous
* 50	Access to the preparation room is through airlocks only, with adequate procedures to prevent simultaneous door opening (doors to the cytotoxic preparation room and to the external environment).	The airlock should provide facilities for gowning prior to personnel entering the preparation room.
* 51	A pass-through hatch enables the transfer of cytotoxic preparations between the cytotoxic preparation room and the external environment.	Ideally distinct from the staff airlock.
* 52	Pressure gradients are maintained between the different rooms in the preparation zone and monitored continuously.	The compounding room has negative pressure compared to the adjacent positive pressure airlock, thus providing inward airflow to contain any contamination in the compounding room. The positive pressure of the airlock also protects the preparation room from the outside environment.
* 53	Preparation rooms are ventilated effectively.	Air exchanges should be frequent enough to prevent room contamination and an accumulation of toxic products (at least 12 air exchanges/hour).
Hygiene and protective equipment		

54	The personnel follow the general hygiene procedures related to medicine preparation.	Staff pay attention to hand hygiene (washing and disinfection) before and after drug preparation activity; they wear no jewelry, wrist-watches or makeup.
* 55	Operators and assistants wear appropriate personal protective equipment during the preparation or reconstitution of cytotoxic medicines according to the working environment and collective protective equipment	
56	During compounding, gloves in contact with cytotoxic vials are regularly changed or are immediately replaced when torn, punctured or directly contaminated.	According to recommendations, gloves should be changed every 30 minutes.
* 57	Personal protective equipment is removed (either discarded or laundered according to the appropriate procedure) before exiting the preparation area (in the airlock's "dirty area")	
* 58	Appropriate measures are used to avoid insects or other animals entering preparation areas.	
59	The storage and use of leftover cytostatic solutions, i.e. vials containing solution residues, is carried out according to a validated procedure that takes into account chemicophysical stability and the risk of microbiological contamination	The conservation and use of leftover cytotoxics more than 24 hours is only possible if the preparation is performed under strict aseptic conditions (cleanroom).
Preparation process set up		
* 60	Doors and windows are closed during compounding.	In an aseptic area, windows should be sealed anyway

61	Before and after compounding, all unnecessary items are removed from the work surface and it is cleaned and/or disinfected	Cleaning with an alcohol -soaked wipe should be done before and after each work session. Periodic cleaning with a detergent solution and rinse with water and then disinfecting with alcohol should be done according to the local context (e.g. daily, weekly, monthly). Ventilation should be switched on at least 30 minutes before drug preparation starts and not stopped earlier than 30 minutes after work ends.
* 62	All the materials and products required for the preparation are assembled and checked by a certified person before work starts.	Production materials are prepared based on protocol. The drug and its strength, dosage, quantity, reconstitution fluid, as well as equipment and cleanliness, the expiry dates of all component materials, the accuracy of the labels generated and worksheets must all be verified. This verification must be documented.
63	All equipment is sterile or disinfected before use.	All items of equipment are sprayed or wiped down with alcohol or another appropriate disinfectant immediately before being placed in the BSC or the isolator pass-through. Materials with secondary sterile packaging should be "peeled off" (not applicable if isolators) and placed in the BSC without coming into contact with hands or other non-sterile objects.
Preparation Techniques		
* 64	The preparation of cytotoxic medicines takes place on a impermeable-plastic-backed absorbent preparation mat in order to avoid contamination of the workbench.	Mats should be changed immediately a spill occurs and regularly during use; they should be discarded at the end of production.
65	During preparation, adequate precautions are applied to avoid confusion or mix-up of patients' treatment.	Only one patient's treatment is prepared at a time, and only one particular drug is on the workbench at a time. Preparation of a series of doses, i.e. a batch of the same drug at the same dose (fixed dose), can be performed simultaneously.
66	The operator compounds preparations by strictly following the operating instructions.	

67	The operator uses proper working techniques under a BSC to maintain product asepsis.	There should be no disturbances or interruptions in airflow, minimum work distances from the grills must be respected, benches should be tidy, clean/dirty areas must be separate, vial septums must be disinfected using an alcohol swab, exiting and entering the work area during compounding should be avoided.
* 68	The operator uses proper working techniques to reduce the risks of chemical contamination or needle stick injuries or cuts.	The operator should for example: either use Luer-lock connections on needles and syringes to minimize the risk of separation in case of over pressurization or use a needless system or closed-system transfer devices; possibility to use a sterile swab when opening an ampoule, or at the injection port of a vial or infusion bag. A safety box should be available for needles and sharp waste. Evacuating residual air from syringes should be carried out carefully using a sterile swab to limit the risks of contamination.
* 69	The operator uses proper working techniques to prevent the build-up of pressure differentials between the inside and outside of cytotoxic vials.	E.g: air venting device fitted with a 0.2 micron hydrophobic filter; wide bore needles (18G/1.2 mm).
70	The operator uses a syringe size appropriate to the sample volume.	The syringe should not be less than one-third full, in order to ensure the precision of the volume measured.
71	I.V tubing is primed prior to adding the cytotoxic product in the infusion bag.	
72	Once filled, chemotherapy infusion bags are ready for immediate use, that is, with the infusion set or administration system already connected and the tubes primed with the dilution solvent. The air has already been evacuated from syringes.	The aim is to avoid risk of exposure to the cytotoxic for the nurse when starting the administration
Packaging and labeling		
* 73	There are packaging instructions for each different preparation	Primary packaging must be suitable for the dosage form and volume that it is intended to contain. Container/content interactions must be avoided.

* 74	The preparation is packed in adequate, sealed secondary packaging.	The use and characteristics of secondary packaging should be determined according to the risks of deterioration of the primary packaging until use, especially where there is a risk of breakage or leakage and is essential during transport of the preparation
* 75	The final product's primary packaging is adequately and unambiguously labelled according to Best Practices and local regulation	For example the label should include: name and address of the pharmacy that produced the preparation; the patient's family name, given name, date of birth; name of ward, department or therapeutic facility ordering the product; names, quantities and qualities of all the cytostatics and other active substances; type and volume of carrier solution; method of administration; day of administration in the course of treatment; instructions for use; instructions for storage; time and date of production; expiry date; and other quality control information such as transport information (cold chain), batch number (or logbook register number).
Checking procedure		
76	Identity and volume of the drugs used are double-checked by the operator and using a reconciliation method	Checks should be performed either by visual inspection by another qualified person during the preparation; or using appropriate technology that directly, automatically records volumes on the container; or using weighing procedures with integrated balances and software that produce weighing tickets during the preparation process and for the final product; or by an analytical control on the final product. Whichever method is used, proof of the check must be recorded and attached to the production worksheet.

77	No preparations are released and dispensed before the person in charge has reconciled and validated the final product in order to certify that the product fulfills the established specifications.	The following factors should be cross-checked: patient information on the label must match the medical prescription (if nominative prescription); the medicine information on the label must match the medical prescription and the preparation protocol; the dilution solvent must be appropriate (nature, quantity and compatibility); the container must be adequate for its content; the completeness of labelling; the product's organoleptic properties (e.g. color, clarity, particle free); and finished pack integrity via a visual inspection.
*		
78	Specific production protocols exist for each different cytotoxic medicine.	Protocol specifications must include the following information: the cytotoxic medicine's name, pharmaceutical form and dosage; the types and names of the products to be used; types and names of the medical devices and equipment to be used; the proper preparation procedure; maximum permissible deviation from the value specified in the prescription; packaging and labelling types; information to appear on the label; information on shelf life; and information about special precautions to apply when handling the finished preparation.
*		

79	Production worksheets (describing the work done) are completed for each product prepared. This allows complete traceability at every step in preparation. Worksheets are stored for at least 1 year after the preparation's expiry date (or according to national regulations)	A standardized worksheet should be developed and it should record at least the following information: the preparation's name and, where appropriate, the name of the person who cross-checked its production; the batch number being manufactured; the date and time of the preparation; the operator's name; the names, batch numbers and expiry dates of the different products used (solvents and cytotoxic medicines); the theoretical and actual quantities of each starting product used; the in-process checking performed and the results obtained; the final quantity of product obtained; the type of packaging and number of units packaged, a specimen product label; the expiry date of the final product; notes on any special problems or deviations from normal preparation, including details; a signed authorization for any deviation from the master formula; and signature of the person responsible of production.
* 80	Each preparation is recorded on a preparation logbook	The logbook can also be electronically available
Maintenance		
* 81	Equipment used to prepare cytotoxic medicines and air-treatment systems are serviced according to a planned maintenance schedule.	Each intervention during a service must be recorded on a maintenance log, e.g. replacement of HEPA filters, equipment calibration, etc.
* 82	Surrounding conditions (microbiological contamination, particulate contamination) are regularly monitored according to a planned monitoring programme.	if cleanroom
Non sterile preparation		
* 83	All activities likely to result in particle generation, for example, crushing tablets, mixing or filling capsules, should be performed in a Biological Safety Cabinet (BSC)	Whenever possible, sterile and non-sterile preparation activities should not be performed within the same BSC.
ADMINISTRATION		

Management and organisation		
* 84	Written administration and surveillance protocols exist and are updated for every chemotherapy available in the facility.	Protocols should include: products' generic names and their different dosages; administration route (if necessary precision of medical device to be used) with the duration and chronology of administration of cytotoxic products and supporting medication; surveillance instructions; and what actions to take in case of complications.
85	Only trained, entitled personnel are permitted to administer cytotoxic medicines to patients.	See chapter on "Personnel".
Hygiene and safety measures		
* 86	Access to the chemotherapy administration area is limited to healthcare personnel, patients and a limited number of relatives, if essential; the latter are informed of the potential risks.	Children and pregnant and breastfeeding women should avoid the chemotherapy administration area.
87	Healthcare personnel correctly apply hand hygiene measures during treatments and respect the rules for ensuring asepsis.	Hand hygiene (washing and disinfection) should be compliant with WHO recommendations, including no jewelry.
* 88	When administering parenteral cytotoxic medicines, staff wears appropriate personal protective equipment (PPE) and removes them before leaving the chemotherapy administration area.	PPE should include trousers, a long-sleeved gown and gloves. If there is a risk of splashing or an aerosol, protective googles and a mask are also recommended.
89	If a direct contact occurs between a cytotoxic product and gloves or a gown, they are immediately changed and hands are thoroughly rinse with water washed.	Some experts recommend that soap or disinfectant should not be used as they can alter the skin's protective barrier. Gloves should also be changed between treating each patient.
90	After administration of the chemotherapy, staff wash their hands with soap and water.	
Documentation		
*		

91	Traceability of chemotherapy administrations is ensured by treatment administration sheets developed based on protocols. All the fields on the sheet are completed and signed by the personnel who administer treatment.	The use of standardized/pre-printed or electronic forms are recommended. These documents should include the products administered (generic name), their dosage, the time, chronology and duration of administration, surveillance and clinical parameters monitored and the signature of the administering personnel.
92	Before administering chemotherapy, the personnel verify the accuracy of information on the prepared product against the administration protocol. The verification is documented.	A check-list should be used to verify: the patient's identity; the drug name, dosage and volume; route of administration; date of administration; information regarding product conservation; expiry date until end of administration; and the medicine's appearance and physical integrity.
93	The personnel question the patient to verify that his/her identity (given name, family name, date of birth) matches the administration plan and the information written on the product.	A checklist should be used to verify and document the control.
Work practices		
94	Personnel administer cytotoxic medicines safely by using work practices that reduce the risk of exposure and contamination dependent on the different routes of administration: intravenous (infusion or direct injection), subcutaneous, intramuscular, vesical, intraperitoneal, intrathecal, aerosolization, oral or topical.	Administration techniques should use infusion sets and pumps with Luer-lock fittings, or needleless administration system. A disposable plastic-backed absorbent pad should be placed on the work surface or the patient's arm during administration to absorb any leakage. Sterile gauze should be placed around any IV push or connection sites before injection and during removal in order to contain any possible leakage.
* 95	Priming IV sets or evacuating air from syringes containing cytotoxic medicines is not carried out in the chemotherapy administration area but in the preparation room.	Alternative methods (e.g retro priming) are possible as far as the risk of exposure of the healthcare personnel is minimized during the administration
*		This is done to avoid the risk of aerosolization

96	The infusion is safely removed from the patient and the entire infusion line discarded intact into the cytotoxic waste container. Needles are never disconnected from syringes; they are disposed of together in a sharp container for cytotoxic medicines.	
97	Crushing cytotoxic tablets or opening capsules in an open mortar should be avoided.	This is done to avoid the risk of generating airborne particles of the products. The extemporaneous preparation of oral cytotoxic drugs should be performed with appropriate personal protective equipment associated with containment measures and under a collective protective equipment.
INCIDENT MANAGEMENT		
Surface contamination		
98	There is a standard operating procedure in place in the facility regarding cleaning up spills or breakages involving cytotoxic medicines that is known by every staff who handle cytotoxics.	Any accidental leak or spillages must be contained (the zone must be identified and marked out) and cleaned up immediately by trained staff wearing appropriate personal protective equipment.
* 99	All staff members who might be involved in handling cytotoxic medicines have received training appropriate to their roles regarding the procedures and measures to be taken in case of a spill or a breakage.	Staff should undergo training and simulation exercises.
100	Fully equipped spill kits are readily available wherever cytotoxic medicines are handled (in receipt, storage, transport, production and reconstitution, and administration zones).	The spill kits' locations are known, signposted and easily accessible if needed.

101	Clearly signposted spill kits contain all the materials needed to clean up cytotoxic medicine spills.	Content: instructions for use of the kit, warning material for identifying and marking out the contaminated area, an impermeable protective gown, boots or overshoes, goggles, P3-type respirator mask, at least 2 pairs of appropriate gloves, plastic dustpan and broom or squeegees, cotton wool and absorbent swabs, liquid soap and alcohol, absorbent granules for liquids, containers for sharp waste, clearly labeled cytotoxic waste containers, spill report form.
102	Used materials are directly discarded according to the waste management procedure.	If economic issues, some objects could be cleaned and decontaminated according to an adequate procedure (e.g. safety glasses, shovel etc.)
* 103	Spill kits are replaced as soon as possible in case of future incidents.	Ideally, a replacement kit should be available in advance.
Staff contamination		
104	There is an established standard operating procedure for managing accidental staff chemical contamination. It is displayed in areas where cytotoxic medicines are compounded or administered.	All contaminated clothing should be immediately removed and appropriately discarded or laundered. Contaminated areas of skin should be immediately thoroughly rinsed with water. Medical attention should be sought rapidly.
105	The equipment and materials for managing the emergency treatment for chemical contaminated staff are located in areas where cytotoxic medicines are prepared, administered	Close proximity of an emergency shower or water supply. For eyes, a sterile isotonic solution (0.9% sodium chloride) is recommended
106	All staff members involved in handling cytotoxic medicines have received appropriate training according to their tasks. They know the procedures and measures to take in case of staff contamination.	
Extravasation		
107	There is an established standard operating procedure for managing extravasation of cytotoxic medicines	Treatment protocols for managing extravasations might differ depending on the agents: "non vesicant", "irritant" and "vesicant" agents.

* 108	Nursing, medical and pharmacy staff are trained to apply preventive measures and to manage and follow-up after extravasation.	Any extravasation must be documented on a monitoring form.
* 109	An emergency kit for dealing with extravasation is readily available in areas where chemotherapies are administered.	The kit must contain written instructions on how to treat affected areas and how to use the specific antidotes contained in it.
Quality assurance		
* 110	All incidents involving cytotoxic medicines are reported, monitored, analyzed, recorded and any corrective measures applied are followed up on and evaluated.	All incidents must be reported on an incident report form. Its causes should be analyzed in order to avoid future repetition.
WASTE MANAGEMENT		
Waste disposal		
111	The facility's cytotoxic waste disposal is compliant with current local regulations and is described in a written procedure.	Some countries differentiate between slightly contaminated and heavily contaminated waste.
* 112	Cytotoxic waste disposal is handled separately. Specific segregation, packaging, collection, transport, storage exist to protect staff, patients and the environment from contamination.	Cytotoxic waste is considered to be all those materials which have come into contact with cytotoxic drugs during the processes of reconstitution and administration. This should include syringes, needles, empty or partially used vials, gloves, single-use personal protective equipment and materials used to clean-up of cytotoxic spills. In addition, cytotoxic drugs which have expired, or which must be destroyed for any other reason, are also treated as cytotoxic waste. Some regulations differentiate between slightly contaminated (traces of cytotoxics) and heavily contaminated (leftovers, expired vials, etc) waste

113	Suitable, clearly labelled cytotoxic waste containers are available in all areas of the facility where cytotoxic medicines are handled.	Cytotoxic waste containers should be of a specific colour and labelled with a danger symbol at all times. Thick, leak-proof plastic bags placed inside a covered waste container should be used for collection of cytotoxic waste solely. The lid should always be closed, except when disposing waste.
114	Needles and syringes are disposed in puncture-resistant containers. Syringes and needles are not separated after the injection but discarded together	Needles and syringes are disposed in puncture-resistant containers. Syringes and needles are not separated after the injection but discarded together
* 115	Only trained personnel handle cytotoxic waste containers; they wear appropriate personal protective equipment.	a minima :gloves
116	The facility's storage areas for containers of cytotoxic waste awaiting destruction remain locked and are clearly identified. Storage areas are sheltered, protected from bad weather, cool, have adequate ventilation and are far away from patients and personnel areas in order to minimize the risk of exposure	Cytotoxic waste should only be stored at the facility for a short duration before being transferred for final destruction.
* 117	Cytotoxic waste is incinerated at 1200°C	Depending on national regulations, waste with low levels of chemical contamination can follow different types of disposal
Patients'excreta		
* 118	Trained personnel handle the excreta (vomit, urine, feces, blood, or puncture liquid) of patients undergoing chemotherapy (for at least 7 days after treatment), they wear the appropriate personal protective equipment, including for cleaning toilets.	Gown and gloves and if necessary a mask and protective boots. For the management of excreta at home, information should be provided to the patients' family and caregivers (see chapter patient information)
* 119	Contaminated linen should be placed in a bag clearly identified and forwarded to the laundry	See chapter on "Cleaning".
120	Mattresses and pillows are protected with plastic covers and wiped-down between patients.	

CLEANING		
Management and organization		
* 121	Cleaning and maintenance tasks are only carried out by trained personnel.	Cleaning staff have received appropriate training on cytotoxic medicines and safety measures they should apply.
* 122	Cleaning activities are conducted in accordance with the established procedure and documented in cleaning logs.	Cleaning and disinfection procedures provide detailed information on which areas require cleaning (logistics, preparation and administration rooms) cleaning frequency (e.g. daily, weekly), and the products and cleaning techniques to be used. They should be reviewed regularly and updated when required.
Cleaning practices		
* 123	Cleaning staff wears the personal protective equipment appropriate to the various tasks to be performed.	The level of personal protection differs according to the type of area to be cleaned. For instance, cleaning of the preparation room requires the same PPE as for the preparation activities. For other areas, staff should at least wear gloves that are chemically resistant to cleaning agents, as well as a splash proof gown. (note: for cleaning up accidental spills, see chapter on "Incidents")
124	Single-use, disposable cleaning equipment is used preferably. Should this be impossible, the equipment used must be used exclusively for cleaning and disinfecting of cytotoxic areas.	Cleaning materials (e.g. wipes, mops and disinfectants) for use in the clean room should be made of materials that generate low amounts of particles.
125	Cleaning is only carried out using moistened materials.	No vacuum cleaners, no dry sweeping.
126	Staff washes their hands thoroughly with soap immediately after cleaning activities.	
	The cleanroom is cleaned in an appropriate manner.	

127		Cleaning should proceed from the cleanest area in the room to the dirtiest. This should imply a cleaning workflow from the ceiling to the floor, moving outwards from the ventilation tool to the exit.
128	The inside of the biosafety cabinet or the isolator is cleaned by the preparation operators	In addition to daily cleaning of the workbench before and after a work session, a comprehensive cleaning process (included the lower part of the BSC, under the workbench) is performed weekly. Inside the BSC, cleaning should start from the top (upstream), close to the HEPA filter, to move down, starting with the rear wall of the BSC, its sides and lastly, the work surface (downstream). The cleaner should be very careful not to wet HEPA filters. If working with isolators, independently of the cleaning at each working session, they should be thoroughly cleaned and regularly sterilized according to a validated frequency (daily, weekly or monthly) depending on the level of activity and the microbiological monitoring of the environment
Laundry		
129	Contaminated, reusable protective clothing (gowns) and linen soiled with patient excreta are placed in clearly labelled laundry bags and are washed separately from other clothing.	Laundry should start with a cold prewash cycle and then continue using the normal washing process
* 130	Laundry staff and patient relatives have received instructions and know the procedure on how to handle contaminated linen and clothing and wear adequate personal protective equipment	resistant gloves, gown with long sleeves
PATIENT COUNSELING		
*		

131	The patient's informed consent for chemotherapy treatment is obtained	Before the initiation of a chemotherapy treatment, patient is given information about the diagnosis, the treatment and its goals, as well as the potential risks and necessary follow-up. The consent process follows appropriate professional and legal regulations.
132	Patients and/or caregivers are taught about the treatment including possible side effects and how to manage them, the risks of possible drug interactions and the precautionary measures to take with regard to a patient's excreta. For oral chemotherapy at home, information related to storage, handling, administration, and planning for missed doses and disposal are also provided.	Patient information materials are appropriate for the patient's and the caregiver's levels of understanding and literacy.
133	Patients and/or their caregivers are informed about warning signs and know who to contact and how in case of an emergency or other specific circumstances.	
* 134	Any patient counseling session is documented and added to the patient's file.	

essential Very important Desirable * =No consensus (<75% of agreement on the level of priority)

9.2.2 Article 2

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The safe handling of chemotherapy drugs in low- and middle-income countries: An overview of practices

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Abstract

Introduction: The rising burden of cancer in low- and middle-income countries (LMICs) has led to substantial efforts to improve access to chemotherapy. The present study's objectives were to obtain an overview of the safe handling practices implemented in LMICs' healthcare facilities when dealing with chemotherapy drugs and to prioritize opportunities for improving them.

Methods: We conducted an online survey, from June 2018 to April 2019, among LMIC healthcare facilities dealing with chemotherapy drugs. Facilities were asked to self-assess their chemotherapy handling processes using Cyto-SAT, a self-assessment tool incorporating 134 items organized into 10 domains (management, personnel, logistics, prescription, preparation, administration, incident management, waste management, cleaning, and patient counselling). Data were recorded on an online platform (www.datapharma.ch/cyto-SAT).

Results: The survey enrolled 53 healthcare facilities (15 from low-income, 26 from lower-middle-income, and 12 from upper-middle-income countries). The median level of implementation of safe practices was 63% (Q1:39%–Q3:77%). Facilities in low-income countries (LICs) reported lower median levels of safe practices than middle-income countries (MICs) [LICs: 32% (Q1:24%–Q3:62%), Lower-MICs: 63% (Q1:49%–Q3:70%), Upper-MICs: 85% (Q1:77%–Q3:93%)]. The biggest differences between country categories were observed in the domains related to personnel, preparation processes, and incident management.

Conclusion: This overview of practices highlighted a large variability and major gaps in the safe handling of chemotherapy drugs in LMICs. Improvement strategies are needed to increase patient and staff safety and limit environmental contamination, especially in LICs. Safe handling programs should be part of continuing efforts to improve access to quality cancer drugs and should be integrated into national cancer control programs.

Keywords

Safe handling practices, cytotoxic drugs, low- and middle-income countries, oncology, chemotherapy

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Introduction

It is well known that handling chemotherapy drugs is a high-risk process for human and environmental health. These drugs have long been considered hazardous and require special precautions.[1,2] Due to their inherent toxicities, their narrow therapeutic index, and the fragility of cancer patients, any incident resulting from a medication error can have dramatic consequences on patient health.[3–5] Beyond patient safety, risks related to occupational exposure are also a major concern. In the 1970s and 1980s, acute, long-term toxic effects were

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reported among the personnel handling these products without specific precautions.[6,7] Since then, the risks of occupational exposure have been widely discussed in the literature.[8] Professional associations, national authorities, insurance companies, and other organs have developed guidelines to protect workers as well as recommendations on safe handling practices.[2,9–14] Protective measures should be applied not only to healthcare workers (e.g. physicians, nurses, and pharmacists) but also to other technicians involved in the transport, storage, cleaning, or disposal of chemotherapy drugs and related waste. Protection relies on a combination of three different levels of preventive measures and hazard controls: engineering measures, administrative and organizational measures, and personal protective equipment.[2,9,10] Besides the risk of occupational exposure, improper cytotoxic waste management could also have dramatic, long-term ecological consequences and constitute a community-wide public health threat.[15] Careful planning in terms of the collection, separation, storage, transport, and final disposal of cytotoxic waste should not be overlooked. Efforts should be made to minimize the risks of contaminating water supplies and soil and facilitate the safe disposal of cytotoxic waste. Thus, implementing safe handling practices are of utmost importance to prevent occupational exposures, ensure patient safety, and limit environmental contamination.

Cancer was long considered as an issue reserved for wealthy countries. However, in recent years, the rising burden of cancer has become a great concern in low- and middle-income countries (LMICs). According to estimates from the International Agency for Research on Cancer (IARC), 10.6 million new cancer cases and 6.7 million cancer-related deaths occurred in LMICs in 2018.[16] To address this heavy economic burden and related human development issues, the World Health Organization (WHO) endorsed a "Global Action Plan for the Prevention and Control of Non-communicable Diseases 2013–2020."[17] Reducing premature deaths from cancers and implementing cancer prevention initiatives were two objectives set out in both the WHO's plan and the United Nations Sustainable Development Goals.[17,18] In 2017, the desire to accelerate those initiatives and boost hopes of reaching the targets set for 2030 was reflected in the World Health Assembly resolution (WHA 70.12) entitled "Cancer prevention and control through an integrated approach."[19,20] As part of global monitoring strategies, great efforts were made to improve access to chemotherapy. More than 30 chemotherapy agents were included in the WHO's model list of essential medicines.[21] In the coming years, the number of patients and the use of chemotherapy are both expected to increase significantly; therefore, the potential health hazards related to the handling of chemotherapy drugs must be promptly and fully addressed. To the best of our knowledge, the current literature on handling practices in LMICs settings remains scarce. The present study's objectives were thus to obtain an overview of the safe handling practices implemented in LMICs' healthcare facilities when dealing with cytotoxic medicines and to prioritize opportunities for improving them.

Methods

Instrument design and dissemination

We conducted a cross-sectional study among volunteer healthcare facilities dealing with cytotoxic medicines in LMICs designated as such by the World Bank.[22] Participating facilities were asked to form a small, multidisciplinary team and assess their chemotherapy drug handling practices by using the Cyto-SAT self-assessment tool. This free online tool consists of 134 items organized into 10 domains and 28 sub-domains (Table 1) covering all the steps of chemotherapy drug handling (e.g., receipt, storage, transport, prescription, preparation, administration, waste management, cleaning, and patient counseling). Cyto-SAT was validated using a two-round Delphi process involving a panel of 27 pharmaceutical experts in oncology practice from 13 LMICs and high-income countries.[23]

The survey was distributed internationally through social media, professional websites, professional associations' membership lists (e.g., the International Society of Oncology Pharmacy Practitioners and Pharm-Ed[24]), community of practice forums (e.g., e-med[25] and e-drugs), newsletters (e.g., Pharm-Ed and Union for International Cancer Control), and professional networking.

Healthcare facilities which decided to participate were provided with detailed written instructions about the survey and how to perform the self-assessment. Data were collected between June 2018 and April 2019. Participants were encouraged to enter their data directly into a web-based platform (www.datapharma.ch/cyto-SAT). However, for facilities with limited internet access, a Microsoft Excel® version of Cyto-SAT was sent out by email, and the principal investigator subsequently transcribed the results returned onto the online platform.

Scoring system

Participants assessed each item on the tool using a scoring system from 1 (no activity) to 4 (fully implemented). The scoring system (Table 2) was based on the one used by Institute for Safe Medication Practices (ISMP) tools.[26]

Table 1. Cyto-SAT domain and sub-domain classifications and their number of items.

Domains	Sub-domains	Number of items accepted by the Delphi panel
1. Management		11
2. Personnel	• Education and training	4
	• Medical surveillance	3
3. Logistics	• Receipt	5
	• Storage	6
	• Transport	5
4. Prescription		5
5. Preparation	• Management and organization	4
	• Parenteral medicine preparation areas	10
	• Hygiene and personal protective equipment	6
	• Preparation process set-up	4
	• Preparation technique	9
	• Packaging and labeling	3
	• Checking procedure	2
	• Documentation	3
	• Maintenance	2
	• Non-sterile preparation	1
6. Administration	• Management	2
	• Hygiene and safety measures	5
	• Documentation	3
	• Work practices	4
7. Incident management	• Surface contamination	6
	• Staff contamination	3
	• Extravasation	3
	• Quality assurance	1
8. Waste management	• Waste disposal	7
	• Patients' excreta	3
9. Cleaning	• Management and organization	2
	• Cleaning practices	6
	• Laundry	2
10. Patient counseling		4
	Total	134

Table 2. Scoring system.

Scoring system	
1	There has been no implementation activity for this item.
2	This item has been discussed and considered, but it has not been implemented yet. There may be a document, but there has been no implementation and only some staff awareness-raising.
3	The item has been partially implemented in the facility or implemented only in some areas, or for some patients and/or staff.
4	The item has been fully implemented throughout the facility for all patients, drugs, and/or staff.

N.A.: not applicable. This item cannot be considered in the local context.
Note: Scores 3 and 4 can only be selected if there has been real implementation. Unapplied procedures or guidelines are not enough.

Analysis

Data were exported into Microsoft Excel® 2013 (Microsoft Corporation, Redmond, WA, USA) for the calculation of descriptive statistics. Items with the "not applicable" were not considered answers and were therefore not counted in the data analysis.

Results

Characteristics of the participating facilities

Of the 82 healthcare facilities that registered on the Cyto-SAT web platform, 53 (65%) facilities from 34 countries met the inclusion criteria (Figure 1) and 29 were excluded (26 facilities only completed the general information and 3 were from high-income countries).

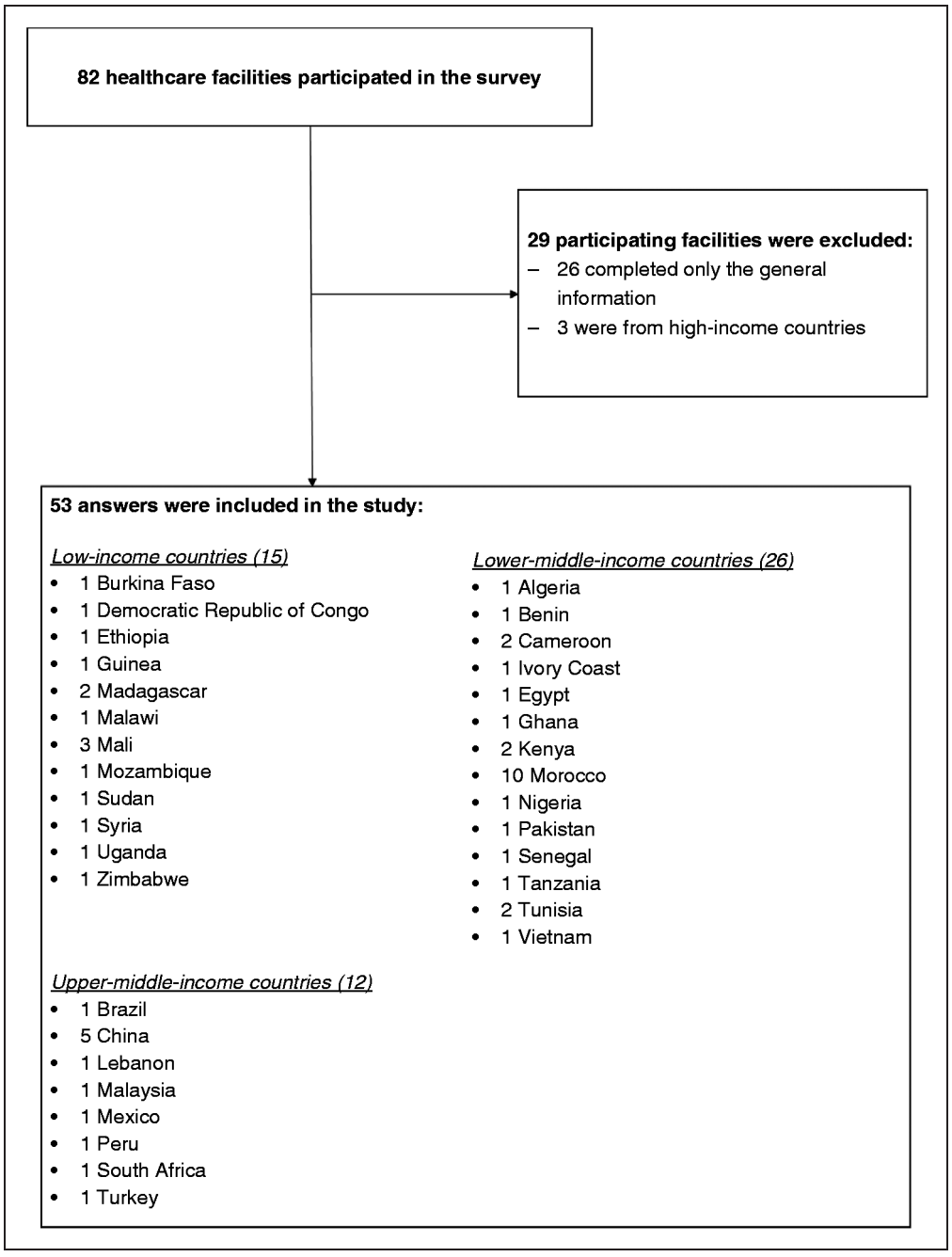

Figure 1. Study flow diagram.

Among the 53 respondents, 15 (28%) were from low-income countries, 26 (49%) from lower-middle-income countries, and 12 (23%) from upper-middle-income countries (Figure 2).

Different types of healthcare facilities participated in the survey, with the highest proportion of the respondents (51%) being university hospitals (Table 3). A median number of 300 chemotherapies were reported to be administered monthly, with a great variation among the respondents (Q1:87.5–Q3:950)[27].

General findings

The median level of the implementation of safe practices was 63% (Q1:39%–Q3:77%)[27]. Facilities from LICs reported a lower level of implementation of safe practices than MICs [LICs: 32% (Q1:24%–Q3:62%), lower-MICs: 63% (Q1:49%–Q3:70%), upper-MICs: 85% (Q1:77%–Q3:93%)].

The greatest differences in median implementation levels between country categories were observed in the

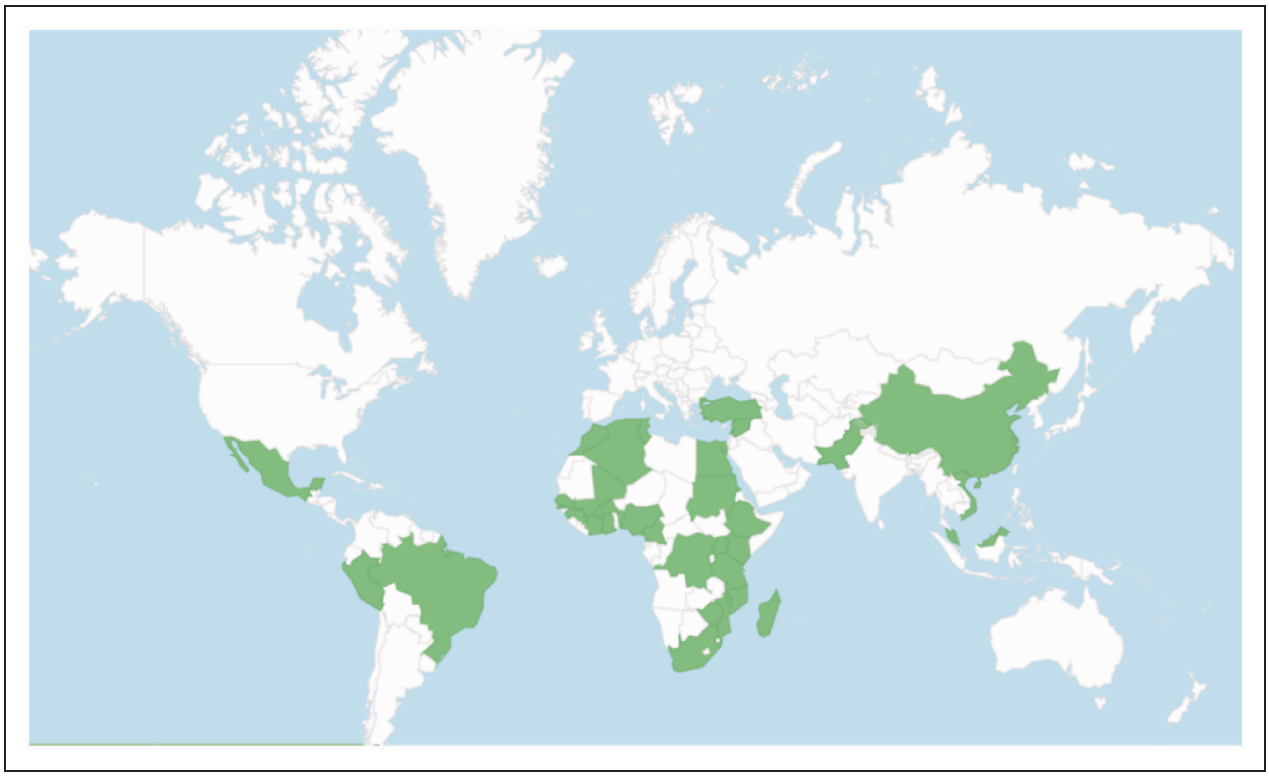

Figure 2. Geographical locations of included survey participants.

Table 3. Characteristics of participating healthcare facilities.

Characteristics of participating healthcare facilities	Number	(%)
TOTAL respondents	53	
By country income level[a]		
Upper-middle-income	12	23%
Lower-middle-income	26	49%
Low-income	15	28%
Types of healthcare facility		
Academic/university hospital	27	51%
Non-profit private healthcare facility	3	6%
For-profit private healthcare facility	3	6%
Regional hospital	8	15%
District hospital	2	4%
Healthcare center	1	2%
Unknown	9	17%
	Median (Q1–Q3)	
Number of departments administering chemotherapies	1 (1–4)	
Number of chemotherapies administered/month	300 (87.5–950)	
Number of staff involved in the preparation and administration of chemotherapies	6 (5–14.25)	

[a]According to the World Bank classification for the 2021 fiscal year.

domains of personnel [LICs: 19% (Q1:14%–Q3:36%), upper-MICs: 86% (Q1:71%–Q3:92%)], preparation processes [LICs: 27% (Q1:17%–Q3:63%), upper-MICs: 92% (Q1:84%–Q3:98%)], and incident management [LICs: 18% (Q1:7%–Q3:65%), upper-MICs: 86% (Q1:82%–Q3:96%)] (Figure 3). Median results for all the domains and sub-domains are presented in Appendix 1.

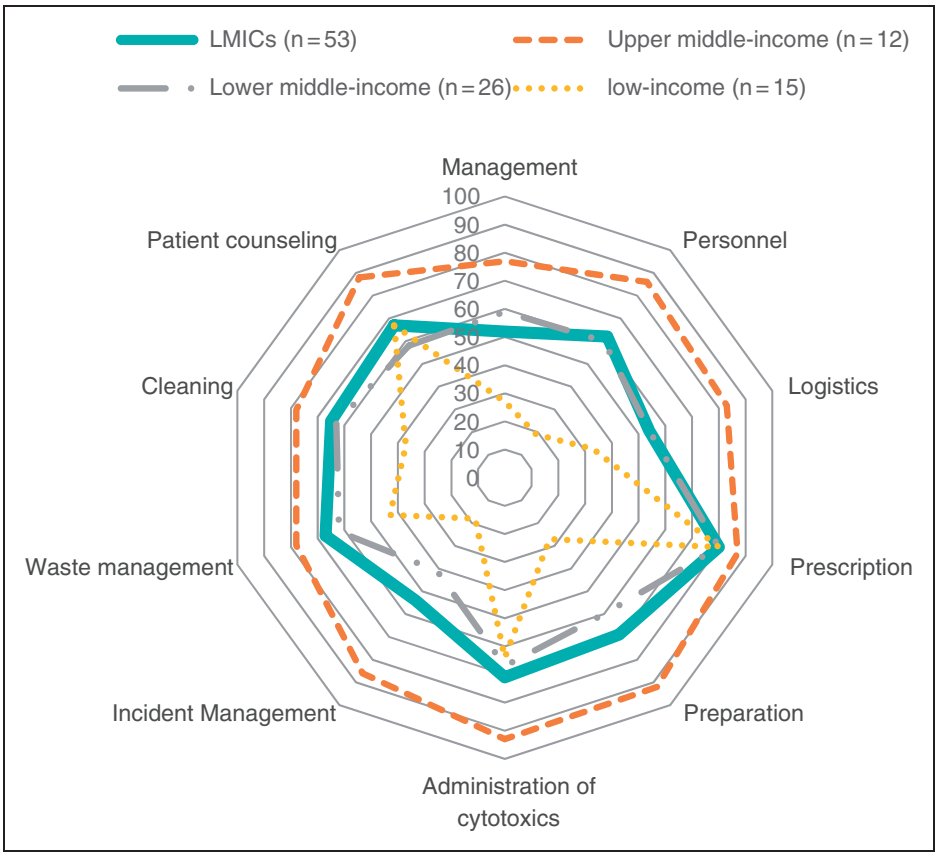

Figure 3. Median percentage level of implementation of safe practices, by domain.

The five highest-scored items in the survey were in the domains of prescription (2 items), management (2), and personnel (1), for which 64%–87% of participating facilities self-scored 4 (*fully implemented*). The five lowest-scored items were in the domains of cleaning (2 items), management (2), and personnel (1), for which 47%–55% of participating facilities self-scored 1 (*no activity*). Details of these item scores are presented in Table 4.

Focus on preparation sub-domains

As pharmacists, we were particularly interested in the results from the items in the preparation domain. Figure 4 presents the median percentages of the level of implementation of safe handling practices in the ten preparation sub-domains. Large variations in the levels of safe handling practices were observed between country's income classification categories for all sub-domains. Of the 53 participating facilities, 21 reported having no centralized preparation area (11 in LICs, 8 in lower-MICs, and 2 in upper-MICs). In 20 of the 53 facilities (12 in LICs, 8 in lower-MICs), chemotherapies were prepared without biosafety cabinets or isolators. The use of inappropriate protective personal equipment (PPE) was reported by 13 facilities (8 in LICs, 5 in lower-MICs), and 12 facilities (4 in LICs, 8 in lower-MICs) reported that the use of appropriate PPE was only partially implemented. Twenty-five of 53 facilities (10 in LICs, 15 in lower-MICs) had no in-process controls to ensure that the right cytotoxic agent had been selected or to verify its volume and dosage during the preparation of the chemotherapy, and they made no analytical checks on the final preparation. In more than half of the participating facilities (32 of 53: 12 in LICs, 16 in lower-MICs, 4 in upper-MICs), no production worksheet was completed to ensure the preparation's traceability.

Discussion

This survey gives a snapshot of the level of safe handling practices implemented in LMICs. Although the median level of safe handling practices was quite good (63%), the survey revealed great disparities in practices between healthcare facilities depending on their country's World Bank level of income categorization or whether they were supported by an NGO or international collaboration. One major gap was observed in the domain of preparation, which is one of the chemotherapy process's riskiest steps.[28,29] Any calculation, dosing, or sampling error made during the

Table 4. Top five highest and lowest self-scored items in the survey.

Top 5 of the highest scored items

Item n°	Domain	Description	Number of answers	% of 4 s	Median score (Q1–Q3)
35	Prescription	Only authorized healthcare practitioners can prescribe chemotherapy treatments.	53	87%	4 (4–4)
7	Management	Smoking, drinking, and eating are forbidden in areas where cytotoxic medicines are prepared, stored, and administered.	51	71%	4 (3–4)
17	Personnel	No pregnant or breastfeeding women are involved in the handling of cytotoxic medicines.	53	66%	4 (3–4)
6	Management	A list of the cytotoxic medicines used in the facility is available and regularly updated.	53	66%	4 (3–4)
36	Prescription	Prescriptions are based on standard, pre-prepared chemotherapy treatment protocols dependent on the diagnosis and available in the facility (these have either been developed in-house or with reference to an external review board or nationally approved clinical research protocols or guidelines).	53	64%	4 (3–4)

Top 5 of the lowest scored items

Item n°	Domain	Description	Number of answers	% of 1 s	Median score (Q1–Q3)
130	Cleaning	Laundry staff and patients' relatives have received instructions and know the procedures for handling contaminated linen and clothing, and they wear adequate personal protective equipment.	46	54%	1 (1–2.75)
52	Preparation	Pressure gradients between the different rooms in the preparation zone are maintained and monitored continuously.	52	54%	1 (1–3)
4	Management	A self-assessment of compliance with safety guidelines regarding the safe handling of cytotoxic medicines is carried out regularly.	51	51%	1 (1–3)
129	Cleaning	Contaminated, reusable protective clothing (gowns) and linen soiled with patients' excreta are placed in clearly labelled laundry bags and are washed separately from other clothing.	44	48%	2 (1–3)
50	Preparation	Access to the preparation room is through airlocks only, with adequate procedures to prevent simultaneous door-opening (doors to the cytotoxic preparation room and the external environment).	53	47%	2 (1–3)

chemotherapy preparation process could have potentially dramatic consequences for the patient. Furthermore, the risk of occupational exposure is particularly high as it involves handling concentrated cytotoxic drugs. Improvements in this domain should be facilities' top priority. Major opportunities for improvement were also highlighted in essential cross-cutting domains such as personnel and incident management. Initial and continuous staff education about safe handling, with proper knowledge checks and supervision, is a core element of safety and the quality of care—it should never be neglected. In case

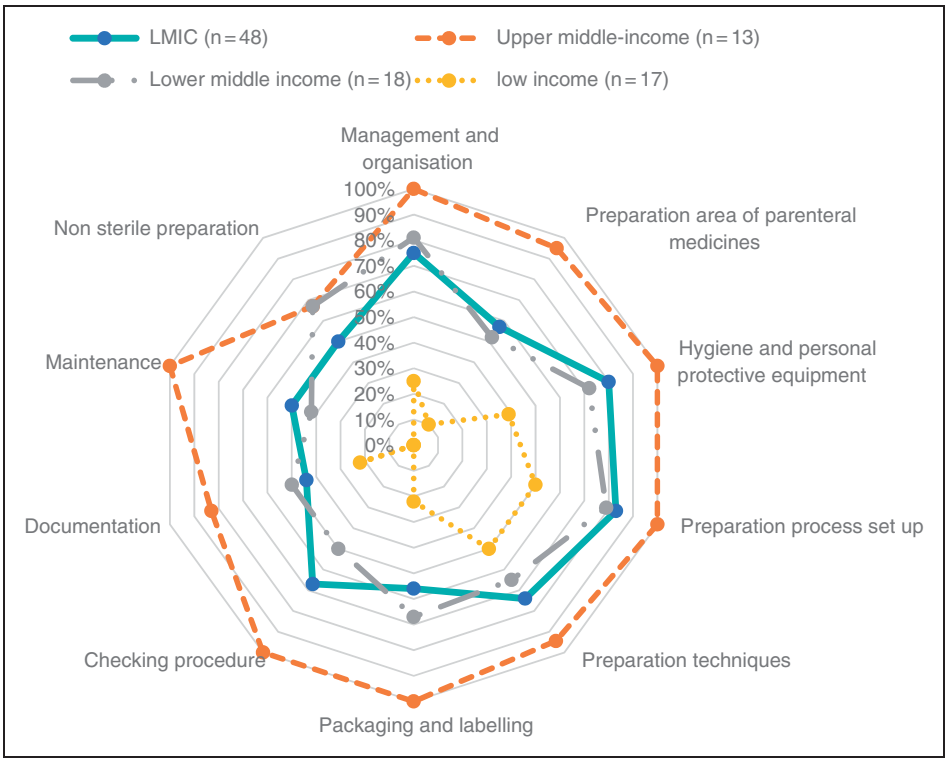

Figure 4. Median percentage of implementation of safe handling practices for the preparation sub-domain.

of a spill, contamination of personnel, or extravasation, the lack of clear written procedures and the unavailability of emergency management kits in many facilities from lower-middle and low-income countries also revealed important weaknesses in procedures. When such an incident occurs, staff should always be able to act safely and rapidly. Thus, standard operating procedures and regular simulation exercises are essential to ensuring appropriate incident management.

Study strengths and limitations

The broad geographical distribution of the survey's participants, the different types of facilities, and the variety of contexts in which they worked enriched the study's results. The survey material's availability in French and English allowed us to reach countries on different continents, but the absence of a Spanish version may have limited the participation of facilities in South America.

The survey's convenience sampling methodology (with no information on non-respondents) and sample size do not allow for the generalization of its results across LMICs. In addition, the data was collected based on hospital self-assessments; therefore, the recorded data's validity cannot be measured. We did not test how cultural differences may have influenced how self-assessments were conducted, nor did we test respondents' reliability (such as test–retest or inter-rater reliability). For all these reasons, any broad interpretations of the present results should be made with caution.

Comparison with other studies

To the best of our knowledge, no similar international surveys have been conducted in LMICs. However, several studies conducted locally in resource-poor settings have previously shown unsatisfactory levels of knowledge and unsafe practices regarding the preparation and use of chemotherapy drugs.[30–33] In particular, weaknesses were revealed during the preparation and administration of chemotherapy. Although the present survey did not examine the reasons or challenges behind inappropriate practices, other studies have identified insufficient knowledge, unsuitable infrastructure, the unavailability of materials, multitasking, work pressures, and high patient loads as barriers to safety.[29,30,32] Other studies have reported that improper work practices were due to a lack of training, a lack of awareness, and false beliefs. In India, for example, the lack of national-level guidelines or recommendations and the lack of administrative support or regulations were considered as major difficulties in the implementation of safety standards for chemotherapy.

Implications for practice

The present survey shows that there remain many safety deficiencies in chemotherapy handling practices, particularly in countries with limited resources. There are thus many potential health hazards which will have

to be fully addressed as patient numbers are expected to significantly increase in LMICs, as will the use of and exposure to chemotherapy drugs. The WHO's endorsement of safe handling guidelines and the integration of safe handling practices recommendations into National Cancer Control Plan models could help raise standards through advocacy and encourage the allocation of resources for the improvement of practices. There is a great need for financial, managerial, organizational, and human resources.

Each cancer care facility has a mission to provide safe, high-quality care. To design appropriate risk management strategies, every institution administering chemotherapies should conduct a comprehensive risk assessment. As part of this process, the Cyto-SAT tool could be a useful one with which to assess handling practices and help design action plans to address gaps and improve safety.

Future research

To pursue our work on the safe handling of chemotherapy in LMICs, we recently developed an online training package on this subject. Eleven e-learning lessons covering the ten domains addressed by the Cyto-SAT tool are available for free on our www.Pharm-Ed.net platform. A set of practical tools has also been developed to support the implementation of safe practices (e.g., videos, checklists, procedures, etc.). In the near future, we hope to evaluate this program's impact on facilities in LMICs.

Conclusion

The present study's overview of safe handling practices for chemotherapy showed that unsafe practices remain a significant risk issue in low- and middle-income countries. Strategies to remedy and improve this situation are needed in order to increase patient and staff safety and limit the risks of environmental contamination, especially in lower-income countries. The promotion of safe handling programs should be part of the efforts to improve access to quality cancer drugs and must be integrated into National Cancer Control Plans.

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Appendix 1

Table 5. Median percentages of the implementation of safe practices in the different domains and sub-domains by country income level.

Domains	Sub-domains	LMICs Median (Q1–Q3) (%)	LICs Median (Q1–Q3) (%)	Lower-MICs Median (Q1–Q3) (%)	Upper-MICs Median (Q1–Q3) (%)
Management		**52 (30–79)**	**27 (23–42)**	**59 (33–79)**	**77 (69–95)**
Personnel		**62 (24–76)**	**19 (14–36)**	**60 (44–70)**	**86 (71–92)**
	Education and training	50 (25–67)	17 (8–29)	50 (27–58)	79 (67–94)
	Medical surveillance	67 (44–89)	33 (22–56)	67 (58–89)	94 (75–100)
Logistics		**54 (38–77)**	**33 (18–53)**	**54 (43–70)**	**83 (72–94)**
	Receipt	70 (37–93)	33 (13–63)	67 (53–93)	90 (80–100)
	Storage	67 (33–89)	33 (31–46)	72 (61–89)	83 (64–90)
	Transport	40 (17–80)	13 (7–53)	33 (23–63)	83 (65–100)
Prescription		**80 (60–93)**	**80 (53–87)**	**80 (73–93)**	**87 (79–93)**
Preparation		**69 (29–84)**	**27 (17–63)**	**60 (45–76)**	**92 (84–98)**
	Management and organization	75 (25–100)	25 (10–46)	81 (44–83)	100 (98–100)
	Parenteral chemotherapy preparation areas	57 (17–80)	10 (3–42)	52 (23–70)	95 (85–100)
	Hygiene and personal protective equipment	80 (39–100)	39 (22–69)	72 (44–88)	100 (97–100)
	Preparation process set-up	83 (50–100)	50 (29–71)	7 (58–92)	100 (100–100)
	Preparation techniques	74 (48–93)	50 (27–78)	65 (49–88)	94 (87–97)
	Packaging and labelling	56 (22–100)	22 (0–44)	67 (36–97)	100 (81–100)
	Checking procedures	67 (0–100)	0 (0–83)	50 (4–79)	100 (96–100)
	Documentation	44 (22–78)	22 (0–50)	50 (33–78)	83 (58–100)
	Maintenance	50 (33–100)	0 (0–92)	42 (33–67)	100 (92–100)
	Non-sterile preparation	50 (0–67)	0 (0–33)	67 (33–100)	67 (67–100)
Administration		**71 (48–83)**	**64 (32–78)**	**67 (49–75)**	**93 (81–98)**
	Management	83 (50–83)	67 (33–83)	75 (50–83)	92 (79–100)
	Hygiene and safety measures	80 (60–93)	73 (43–87)	73 (60–87)	97 (85–100)
	Documentation	67 (67–100)	67 (39–78)	67 (67–89)	100 (67–100)
	Work practices	67 (33–92)	42 (19–83)	63 (42–75)	100 (79-100)
Incident Management		**54 (23–82)**	**18 (7–65)**	**41 (24–59)**	**86 (82–96)**
	Surface contamination	50 (22–89)	22 (6–61)	39 (24–65)	100 (93–100)
	Staff contamination	56 (11–78)	22 (0–72)	39 (3–67)	89 (78–100)
	Extravasations	56 (22–78)	11 (6–67)	44 (36–67)	83 (67–100)
	Quality assurance	33 (0–67)	0 (0–50)	33 (0–67)	100 (67–100)
Waste management		**67 (33–79)**	**43 (23–70)**	**62 (33–73)**	**78 (69–90)**
	Waste disposal	67 (33–86)	38 (24–79)	62 (31–80)	90 (83–100)
	Patients' excreta	44 (33–67)	44 (6–67)	53 (33–67)	56 (28–92)
Cleaning		**65 (37–80)**	**37 (22–63)**	**63 (44–77)**	**78 (70–92)**
	Management and organization	67 (33–92)	33 (0–67)	50 (33–67)	83 (58–100)
	Cleaning practices	78 (44–90)	44 (33–75)	72 (58–83)	97 (88–100)
	Laundry	17 (0–54)	0 (0–25)	33 (0–50)	42 (0–88)
Patient counseling		**67 (48–83)**	**67 (46–83)**	**58 (42–75)**	**88 (67–100)**
Total		**63 (39–77)**	**32 (24–62)**	**63 (49–70)**	**85 (77–93)**

According to the World Bank classification of countries LMICs: low- and middle-income countries; LICs: low-income countries; lower-MICs: lower-middle-income countries; upper-MICs: upper-middle-income countries; Q1: first quartile; Q3: third quartile.
Bold values summarize results for the domains.

9.2.3 Article 3

HEALTH SERVICES RESEARCH

original reports abstract

Development and Proof of Concept of an Audit Toolkit for the Safe Handling of Cytotoxic Drugs in Low- and Middle-Income Countries

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PURPOSE Chemotherapies are considered high-risk drugs for patient and staff safety. Considering the rising burden of cancer and the increasing use of chemotherapy drugs in low- and middle-income countries (LMICs), promoting continuous improvements in the safety and quality of practices in these settings is essential. This paper describes the development and proof of concept of a toolkit to audit chemotherapy handling practices in the health care facilities of LMICs.

METHODS A steering committee defined the audit method and the toolkit content. Several checklists were developed to facilitate the audit and data collection. Items included in checklists were derived from key reference works on safe handling. Different tools were validated using Delphi surveys and expert reviews. Audits of pilot sites were performed to test the toolkit's applicability and relevance.

RESULTS The toolkit contains a 134-item global assessment tool for the different processes at each step of the medication pathway and three step-specific observation checklists to assess different health workers' practices during the prescription, preparation, and administration of chemotherapies. The toolkit also proposes using a surface-wipe sampling method to measure any cytotoxic contamination of the immediate environment. The toolkit was tested in three teaching hospitals in Africa.

CONCLUSION The toolkit developed was successfully implemented in a variety of LMIC settings, providing a comprehensive evaluation of the quality and safety of the chemotherapy drug handling practices in participating health care facilities. This toolkit can help facilities in LMICs to implement a new approach to continuously improving the quality and safety of their practices and ultimately ensure patient and staff safety.

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INTRODUCTION

Chemotherapies are considered high-risk drugs, not only for patients but also for the staff handling them. The risks related to occupational exposure were first described in the literature in the late seventies in the study by Falck et al[1] that reported mutagenic activity in the urine of nurses handling chemotherapy drugs without specific protection. Over the years, the risks of this ongoing challenge were studied and addressed by many experts, from professional organizations, national authorities, and even insurance companies.[2-7] As a result, several recommendations, guidelines, and regulations on safe handling practices were developed. In high-income countries, implementing preventive and control measures wherever chemotherapy drugs were transported, received, stored, prepared, administered, and disposed of became standard professional practice or a legal obligation.

The use of chemotherapy drugs in low- and middle-income countries (LMICs) is much more recent. For many years, LMICs shouldered a great burden of infectious diseases and little attention was given to noncommunicable diseases. But recently, the increase in premature cancer deaths in LMICs can no longer be ignored and the burden of cancer has become a public health issue in these countries as well.[8-10] In 2020, GLOBOCAN statistics produced by the International Agency for Research on Cancer estimated 2,977,172 new cases of cancer, 5,720,384 cases of 5-year prevalence, and 1,953,071 cancer-related deaths in countries with medium- and low-human development indexes.[11,12] The economic impact and human development challenges resulting from this rising burden have led the WHO and other stakeholders to take action.[8,13] Substantial efforts have been made to prevent and manage cancer in LMICs, notably by expanding access to affordable, high-quality chemotherapy drugs.

In the coming years, increasing numbers of patients, combined with improved access to chemotherapy, will

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

How to evaluate and promote continuous improvement of safe handling of chemotherapy drugs through a quality-oriented approach in low- and middle-income countries (LMICs)?

Knowledge Generated

The audit method and the different tools developed via this project enabled a comprehensive assessment of the safety of chemotherapy handling in three health care institutions in LMICs. Its implementation in a variety of settings enabled us to verify its applicability by future users.

Relevance

The audit toolkit offers health care facilities in LMICs ready-to-use tools and checklists to assess their safe handling of cytotoxic medicines and ensure patient and staff safety.

increase the use of these hazardous drugs. A recent survey on handling practices in LMICs showed that unsafe practices remained a significant safety risk to patients and staff in many places.[14] Strategies to remedy and improve this situation are needed, therefore, especially in lower-income countries.

Introducing a quality-oriented approach to the handling of chemotherapies is essential for ensuring patient and staff safety. The Deming cycle describes four iterative steps (plan, do, study, and act) and has been widely used as a quality improvement model.[15,16] In our context, the assessment or evaluation step consists of ensuring that the good practices that the cycle defines are implemented. Simply disseminating these recommendations is insufficient: their implementation must be ensured. Indeed, several works have highlighted the gap between current scientific knowledge and actual practices, as well as the significant variability in those practices.[14,17-19] There are currently few tools available to assess safe practices in LMICs. Their availability would facilitate the implementation of a continuous quality approach within LMIC institutions. This paper describes the development and proof of concept of a toolkit to audit chemotherapy handling practices in LMIC health care facilities.

METHODS

A steering committee was created within Geneva University Hospitals' Pharmacy Department to lead the project and define the audit method and toolkit. It was composed of the department head, the pharmacist in charge of the cytotoxic drug preparation unit, and the study's principal investigator. Toolkit design was guided by the objectives that it should first provide an overview of the processes and practices implemented throughout the chemotherapy circuit (eg, receiving drugs, storage, transport, prescription, preparation, administration, waste management, disposal, etc) and then compare them with existing best practices and guidelines. Various audit evaluation methods were chosen, such as interviews with key informants, structured observations, and surface-wipe sampling.

Instrument Design

Several tools were developed to facilitate the audit and data collection.

Assessment tool. The kit's first tool makes a full assessment of every step involved in the processes and practices of handling chemotherapy drugs (eg, receipt, storage, transport, prescription, preparation, administration, waste management, cleaning, and patient counseling). Items addressing aspects of quality and safety were derived from key sources (Table 1) and underwent a first review by the steering committee. A panel of 27 pharmaceutical experts in oncology practices from 13 low-, middle-, and high-income countries subsequently validated those items via a two-round online Delphi survey. A previous publication described the development of this tool in detail.[26]

Structured observation checklists. Additionally, we developed three structured observation checklists for noting how different staff applied safety and quality practices during the three main steps of the cytotoxic treatment process: prescription, chemotherapy preparation, and administration. Each checklist was based on professional guidelines and best practices but was adapted to the contexts existing in LMICs (Table 1); each item was reviewed and validated by two or three experts from within our institution.

Surface-Wipe Sampling

Surface-wipe sampling has been widely used in health care settings handling hazardous drugs.[27] This methodology has been recommended for evaluating contamination trends, implementing corrective measures, and increasing workers' awareness about the risks related to handling chemotherapy drugs.[22,27] A variety of surfaces should be selected depending on the setting and how the health care facility works (eg, preparation workbenches and adjacent areas, drug administration areas, etc). For this section of the toolkit, we chose to use methods previously developed and validated by Guichard et al.[28-30]

Sampling was performed by wiping polyester swabs (TX716, Texwipe, Kernersville, NC) moistened with

TABLE 1. Toolkit Design References

Document	Authors	Year	Region or Country	Document Type
ISOPP Standards[4]	International Society of Oncology Pharmacy Practitioners	2007	International	Scientific society's recommendations
QuapoS 4: Quality Standard for Oncology Pharmacy Services, With Commentary[20]	German Society of Oncology Pharmacy and European Society of Oncology Pharmacy	2009	Europe	Quality standards from a scientific society
ASHP Guidelines on Handling of Hazardous Drugs[21]	American Society of Health-System Pharmacists	2006	United States	Scientific society's recommendations
USP (United States Pharmacopeia), Chapter 800: Hazardous Drugs—Handling in Healthcare Settings[22]	The Compounding Expert Committee	2015 (draft)	United States	Regulatory framework
Good Preparation Practices[23]	Afssaps (Agence française de sécurité sanitaire de produits de santé)	2007	France	Regulatory framework
Mesures de protection relatives à la manipulation de médicaments (Protective measures related to the handling of medicines)[24]	Swiss Accident Insurance Fund	2018	Switzerland	Occupational safety recommendations
WHO Good Manufacturing Practices, Annex 3[25]	WHO Expert Committee on Specifications for Pharmaceutical Preparations	2010	International	Regulatory framework
Chemotherapy Administration Safety Standards[7]	American Society of Clinical Oncology/ Oncology Nursing Society	2016	United States	Scientific society's quality standards
OSHA: Controlling Occupational Exposure to Hazardous Drugs[3]	Occupational Safety and Health Administration (US Department of Labor)	Consulted 2016	United States	Occupational safety recommendations
NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings[2]	National Institute for Occupational Safety and Health	2004	United States	Occupational safety recommendations
Safe Handling of Hazardous Chemotherapy Drugs in Limited-Resource Settings[5]	Pan American Health Organization (PAHO)	2013	PAHO	Recommendations

isopropanol 75% over a surface of 100 cm^2. After sampling, each swab was preserved separately in a small closed glass container. Samples were transported in insulated envelopes, with ice packs (for < 24 hours), and then frozen to $< -20°C$ until analysis. Samples were analyzed in Switzerland by Cytoxlab[31] using an ultrahigh pressure liquid chromatography coupled with mass spectrometry method, enabling the simultaneous identification of 23 antineoplastic drugs.[29]

Proof of Concept

The principal investigator organized audits in several hospitals in LMICs to test the toolkit's applicability and relevance. Facilities were chosen through professional networks, and participation was voluntary. The same investigator performed audits at the different sites during 4-day visits (Table 2). Data were collected through observations, interviews, and surface-wipe sampling.

RESULTS

The final toolkit consisted of one assessment tool, three observation checklists, and a surface-wipe sampling method. The Cyto-SAT assessment tool encompasses 134 items in 10 domains and 28 subdomains covering the entire cytotoxic drug handling process in health care facilities (Table 3). A free online service was developed to allow any LMIC hospital to self-assess its practices.[32]

Unlike Cyto-SAT, the three structured observation checklists focus on one process each.

The prescription checklist includes items evaluating whether the chemotherapy prescription is clear and unambiguous and includes all the necessary information to provide safe treatment. It addresses prescription format, prescriber identification, patient-related information, and the chemotherapy protocol (Data Supplement).

The preparation checklist items assess the preparation process and operators' practices to ensure traceability throughout chemotherapy preparation, thus maintaining product integrity, preventing potential medication errors, and limiting the risks of occupational exposure (Data Supplement). This checklist exists in three versions so as to cover every possible situation found in LMICs: (1) chemotherapy preparation in environments without biosafety cabinets

TABLE 2. Example of a 4-Day Audit Visit Program

Days of Visit	Morning	Afternoon	Remarks
Day 1	Meeting with the local audit coordinator Presentation and description of the local cancer patient management context Facility tour Introduction of the auditor to staff and presentation of the 4-day audit's objectives and program	Start of the audit Data collection according to the Cyto-SAT tool Review of different prescribers' prescription practices (checklist)	Before the visit, each pilot site had to appoint a local audit coordinator
Day 2	Structured observation of chemotherapy preparation practices (checklist) Structured observation of chemotherapy administration practices (checklist)	Data collection according to the Cyto-SAT tool (end) Prescription review of the different prescribers with the prescription observation checklist	Timetable for observing prescriptions, preparation, and administration according to the activity in the facility
Day 3	Structured observation of chemotherapy preparation practices (checklist)	Structured observation of the chemotherapy administration practices (checklist)	
Day 4	Feedback from the auditor to the medical representative, nurse, and pharmacist to discuss results	Collection of the surface-wipe samples Return to airport	An audit report would be sent a few days later (including results of the surface-wipe contamination tests)

(BSCs) and cleanrooms, (2) chemotherapy preparation under a BSC but without a cleanroom, and (3) chemotherapy preparation under a BSC inside a cleanroom.

The administration checklist considers the entire course of care, with items assessing practices before, during, and after chemotherapy administration. It addresses aspects related to hygiene measures, the protection of nurses, checking procedures to limit treatment errors, patient surveillance, and waste management (Data Supplement). This checklist was developed for peripheral intravenous administration (infusion or a direct intravenous route) solely, as this is by far the most common route of administration. Administration via a central venous catheter is very rarely used in LMIC public hospitals because of its high cost.

We tested the toolkit in three teaching hospitals in Africa (Yaoundé in Cameroon, Fès in Morocco, and Dakar in Senegal) between November 2019 and February 2020. All three hospitals treated inpatients and outpatients for cancer. One of the institutions had a centralized chemotherapy preparation unit with two isolators located in a nonclassified room inside the hospital pharmacy. At the other two hospitals, nurses prepared chemotherapies in patients' rooms just before administration, directly at the bedside in one and on a workbench in the other. In each hospital, the investigator used all four data collection tools and took 10-15 surface-wipe samples. The tools developed enabled measurement of how well standards of practice were applied (Table 3) and provided the levels of cytotoxic contamination in the real-world environments of all three sites (Fig 1). All 35 samples revealed some cytotoxic contamination, with a total contamination level of the different drugs tested ranging from 74 ng to 12,401 ng, with a median of 856 ng (first quartile: 255 ng-third quartile: 3, 104 ng). The safety and procedural gaps and points requiring improvement that were identified enabled us to draw up an action plan for implementing improvement measures in each hospital (Table 4).

DISCUSSION

The audit method and the different tools developed via this project enabled a comprehensive assessment of the safety of chemotherapy handling in three health care institutions in LMICs. The toolkit contains one 134-item global assessment tool to evaluate the different processes at each step of the medication pathway and three step-specific observation checklists to assess the practices of different health workers during the prescription, preparation, and administration of chemotherapies. The toolkit also proposes the use of a surface-wipe sampling method to measure any cytotoxic contamination of the immediate environment. The implementation of this audit method in a variety of settings enabled us to verify its applicability by future users.

The different tools enable a quick comparison between the practices currently used and those that are recommended, making it easy to identify areas for improvement. An action plan can then be drawn up on the basis of this thorough evaluation.

In general, the tools developed proved easy to use and were applicable in different contexts. Following our visits to the different hospitals, two additional versions of the observation checklists will be added to the toolkit in the future. The first is a specific version for chemotherapy preparation in an isolator, and the second is a version for the administration of chemotherapy by a central venous catheter for those countries with sufficient resources.

Surface-wipe sampling allowed us to highlight the levels of contamination in the different hospitals' working environments. Contamination levels differed significantly depending on the surfaces sampled. The most contaminated

TABLE 3. Results of the Cyto-SAT Evaluation: Percentage of Safe Practices Implemented in the Different Domains and Subdomains at the Three Hospitals

Domain	Subdomains	No. of Items	Hospital 1 (%)	Hospital 2 (%)	Hospital 3 (%)
Management		11	24	18	85
Personnel	Education and training	4	25	0	58
	Medical surveillance	3	78	22	67
Logistics	Receipt	5	27	NA	60
	Storage	6	50	NA	67
	Transport	5	0	0	40
Prescription		5	80	73	100
Preparation	Management and organization	4	0	8	83
	Parenteral medicine preparation areas	10	0	7	70
	Hygiene and personal protective equipment	6	11	22	72
	Preparation process setup	4	25	17	83
	Preparation technique	9	33	21	81
	Packaging and labeling	3	11	56	56
	Checking procedure	2	0	0	50
	Documentation	3	0	33	67
	Maintenance	2	NA	NA	67
	Nonsterile preparation	1	NA	NA	100
Administration	Management	2	33	83	50
	Hygiene and safety measures	5	60	73	73
	Documentation	3	11	67	100
	Work practices	4	11	11	75
Incident management	Surface contamination	6	0	11	28
	Staff contamination	3	0	0	33
	Extravasation	3	11	0	44
	Quality assurance	1	0	0	33
Waste management	Waste disposal	7	19	10	57
	Patients' excreta	3	11	22	44
Cleaning	Management and organization	2	17	33	67
	Cleaning practices	6	17	58	61
	Laundry	2	0	0	17
Patient counseling		4	42	50	25
Total		**134**	**23**	**24**	**62**

Abbreviation: NA, not applicable.

spots were found to be inside the isolators and on the equipment used for preparation. It was both interesting and valuable for each hospital to see which surfaces were the most contaminated and where occupational exposure risks were highest. Compared with the results obtained from samples from European or Swiss hospitals analyzed by Cytoxlab, the amounts of contamination we sampled were much higher (internal data). Although there are no acceptable or recommended limits, the precautionary principle implies reducing environmental contamination by chemotherapies to a minimum, notably through better working techniques, process reorganization, the use of equipment that limits the risks of contaminating personnel, and the application of adequate cleaning or chemical decontamination procedures. Unfortunately, local analysis of the surface-wipe samples was impossible as it required specialist, high-cost equipment. Transporting samples was also challenging as no professional transport company could guarantee to get them to Cytoxlab within 24 hours to ensure their stability.

Although the literature on safe handling practices in LMICs is still scarce, several studies have reported unsafe practices and the need for improvements.[14,18,19,33,34] Our study's findings confirmed that the level of safe practices in some institutions remained very low. Thus, implementing safety standards and continuous quality improvement

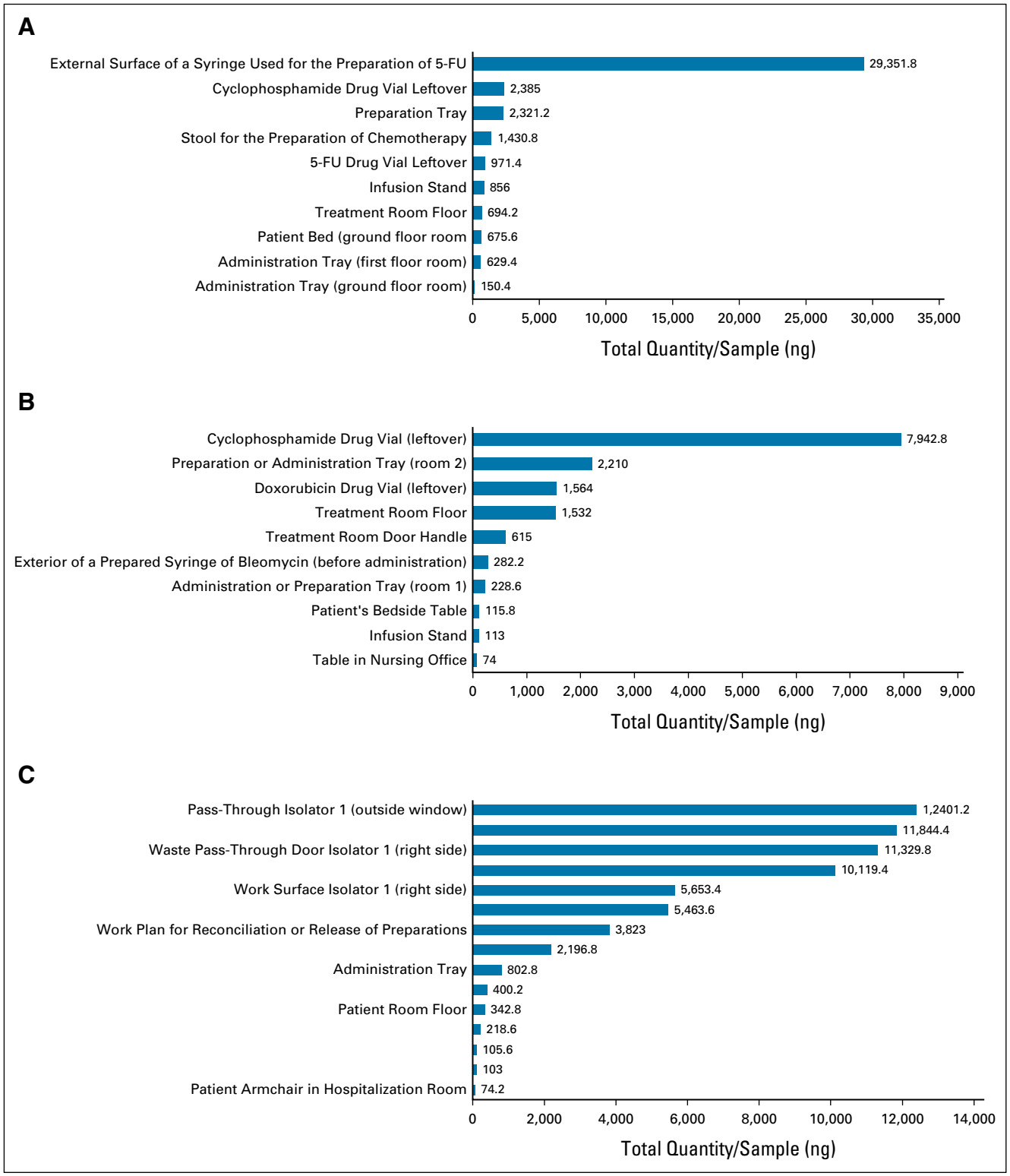

FIG 1. Surface-wipe sampling results in the three hospitals (sum of the 23 cytotoxics tested). (A) Hospital 1: total cytotoxic contamination by surface sample (ng). (B) Hospital 2: total cytotoxic contamination by surface sample (ng). (C) Hospital 3: total cytotoxic contamination by surface sample (ng). FU, fluorouracil.

approaches in this area is of utmost importance as the number of cancer treatments will continue increasing in the coming years. The audit toolkit (available in the Data Supplement) offers LMIC health care facilities ready-to-use tools and checklists to assess their safe handling of cytotoxic medicines and ensure patient and staff safety. Our

TABLE 4. Summary of the Three Hospitals' Strengths, Areas Requiring Improvement, and Actions Required Following Their Audit

Audit Results	Hospital 1	Hospital 2	Hospital 3
Main strengths	Storage Dedicated storage area for cytotoxic drugs, separate from other medicines, in a closed cupboard Prescription Only by authorized prescribers Use of standard protocols Use of preformatted forms, with the minimum recommended information Preparation and administration Same-day laboratory results are verified before authorizing preparation of the chemotherapy The staff wear work clothes (not civilian clothes) Access to treatment room is limited to authorized staff and patients The nursing staff are kind and empathetic with patients Always one staff member present in the treatment room for patient surveillance Hygiene Staff respect basic hygiene (no smoking, drinking, and eating in the administration and preparation areas) The bins are emptied regularly	Prescribing Only by authorized prescribers Use of standard protocols Use of preformatted forms, with the minimum recommended information Preparation and administration The staff wear work clothes (not civilian clothes) and a lab coat during preparation and administration During the preparation and administration of chemotherapies, family and caregivers leave the room Patients are comfortably seated on individual beds Nurses report what has been done and any potential side effects that they observe on the back of the prescription Hygiene Staff respect basic hygiene (no smoking, drinking, and eating in the administration and preparation areas) The bins are emptied regularly	A continuous improvement approach to the quality and safety of the chemotherapy circuit was implemented Prescribing Electronic prescribing of chemotherapies Only by authorized prescribers Use of standard protocols Validation of the prescription by a pharmacist before preparation Preparation Centralized unit for chemotherapy preparation in the pharmacy, with separate areas for each step of the process Preparation in isolators Regular maintenance of the isolators according to a preventive maintenance plan Reconciliation of preparations with prescriptions before dispatch to the wards Hygiene Staff respect basic hygiene (no smoking, drinking, and eating in the administration and preparation areas) The bins are emptied regularly Administration Verification that the preparation and its administration plan match Patients are comfortably seated on individual chairs Final check of the patient's identity carried out at bedside
Main areas requiring improvement	Storage Gloves not used to handle chemotherapy drugs Preparation Many hygiene issues leading to potential risks of microbiologic contamination of the chemotherapy formulation and a high risk of occupational exposure Lack of appropriate personal protective equipment No BSC Lack of control, traceability, and inadequate labeling of the chemotherapy formulation Lack of specific staff training on good preparation practices Administration Lack of hand sanitizing Gloves not changed between patients No cross-checking between patient prescription and the chemotherapy formulation given to the patient Lack of a clear procedure in the case of extravasation Incident management No spill kit available and no specific procedure No clear procedure in the case of staff contamination Waste management Waste management process not safe	Preparation Many hygiene issues leading to potential risks of microbiologic contamination of the chemotherapy formulation and a high risk of occupational exposure Lack of appropriate use of personal protective equipment Preparation at patient's bedside No BSC Lack of control, traceability, and inadequate labeling of the chemotherapy formulation Lack of specific staff training on good preparation practices Administration Lack of hand sanitizing Gloves not changed between patients No cross-checking between patient prescription and the chemotherapy formulation given to the patient Lack of a clear procedure in the case of extravasation Incident management No spill kit available and no specific procedure No clear procedure in the case of staff contamination Waste management Use of inappropriate containers for the disposal of sharps waste	Storage Cytotoxic drugs stored in the same room as other drugs Gloves not always worn to handle drugs Preparation Labeling of the preparation done outside the isolator by another staff member when doing the reconciliation (risk of error) Lack of information on the label (eg, batch number, storage conditions etc) Lack of in-process control of drug volume and dosage Lack of regular microbiologic monitoring of equipment and the environment to ensure preparation in aseptic conditions High level of cytotoxic contamination in the isolator and on the reconciliation table (inadequate cleaning procedure) Administration Insufficient use of PPE during administration and handling of excreta Lack of clear written procedure in the case of extravasation and no extravasation kit available Incident management No spill kit available and no specific procedure No clear procedure in the case of staff contamination

(Continued on following page)

TABLE 4. Summary of the Three Hospitals' Strengths, Areas Requiring Improvement, and Actions Required Following Their Audit (Continued)

Audit Results	Hospital 1	Hospital 2	Hospital 3
Summary of actions required	Storage Wearing of gloves when receiving, storing, and dispensing anticancer drugs Preparation Establishment of a procedure for double-checking the doses of the anticancer drugs prescribed Staff training on good preparation practices with regular supervision Wearing of appropriate PPE during preparation Centralization of preparation in a separate area from other activities and limitation of access to it Preparation of chemotherapy in a type IIb BSC or isolator Improvement of hygiene measures during preparation Implementation of an in-process control procedure for the dose of anticancer drugs Introduction of a traceability system for chemotherapy formulations Improvement of chemotherapy formulation labeling Administration Improvement of hygiene measures during administration Implementation of a process for a final verification that the patient, their prescription, and their drugs (identities and dosage) match at the patient's bedside Establishment of a procedure for managing extravasations Incident management Availability of spill kits wherever chemotherapies are handled Staff training on spill management procedures Establishment of a procedure in the case of staff contamination Waste management Making the waste management process safe Use of lidded bins to maintain contamination (pedal system recommended) Training for cleaning and waste management staff Making the transport of waste to its destruction site safe by using closed containers	Preparation Establishment of a procedure for double-checking the doses of the anticancer drugs prescribed Staff training on good preparation practices with regular supervision Wearing of appropriate PPE during preparation Centralization of preparation in a separate area from other activities and limitation of access to it Preparation of chemotherapy in a type IIb BSC or isolator Improvement of hygiene measures during preparation Implementation of an in-process control procedure for the dose of anticancer drugs Introduction of a traceability system for chemotherapy formulations Improvement of chemotherapy formulation labeling preparations Administration Improvement of hygiene measures during administration Implementation of a process for a final verification that the patient, their prescription, and their drugs (identities and dosage) match at the patient's bedside Establishment of a procedure for managing extravasations Incident management Availability of spill kits wherever chemotherapies are handled Staff training on spill management procedures Establishment of a procedure in the case of staff contamination Waste management Making the waste management process safe Procurement of appropriate sharp waste containers Use of lidded bins to maintain contamination (pedal system recommended) Training for cleaning and waste management staff Making the transport of waste to its destruction site safe by using closed containers	Storage Storage of anticancer drugs in a separate room from other drugs Preparation Strengthening of operator training and supervision Strengthening proper use of PPE Limiting access to the preparation room to authorized staff only Improvement of the traceability of chemotherapy formulation (batch number, volume, expiry date etc) Improvement of chemotherapy formulation labeling procedures (directly in the isolators) Implementation of an in-process control procedure for the dose of anticancer drugs Introduction of regular microbiologic monitoring of equipment and the environment Implementation of annual checks of the preparation room according to the room's classification Adapting the cleaning procedures for isolators and the preparation room to reduce chemical contamination Administration Establishment of a written procedure for dealing with extravasations Provision of an extravasation kit Strengthening proper wearing of PPE during chemotherapy administration and excreta handling Incident management Availability of spill kit wherever chemotherapies are handled Staff training on spill management procedures Establishment of a procedure in the case of staff contamination

Abbreviations: BSC, biosafety cabinet; PPE, personal protective equipment.

goal would be for any health facility using our toolkit to conduct regular audits and measurements of their environmental contamination to monitor their progress as they implement their action plan.

Safe chemotherapy handling practices are an essential element in cancer management and ensuring staff and patient safety. Besides this audit toolkit, which is available free of charge through our Pharm-Ed platform,[35] we also provide e-learning courses on various aspects of safe chemotherapy handling practices. Many practical tools (eg, procedures, checklists, etc) and video tutorials are also available to facilitate the implementation of good practices. The overall impact of such a training program on practice improvements within a health care institution or a group of health care institutions is yet to be studied.

In conclusion, the toolkit described in the present work was successfully applied in a variety of LMIC settings and provided comprehensive evaluations of the quality and safety of the chemotherapy drug handling practices in three health care facilities in Africa. The toolkit can help facilities in LMICs to implement a continuous quality improvement approach, implement better practices, and, ultimately, ensure patient and staff safety.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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ANNEX 1: Structured observation checklist for Prescriptions

	Rating *Circle the appropriate rating*	
I. PRESCRIPTION FORMAT		**Comments**
Prescription exists in a written form, on a pre-formatted, printed prescription form or on prescription software	C PC NC NA	
No abbreviations	C PC NC NA	
II. PRESCRIBER IDENTIFICATION		**Comments**
Prescriber's family name and given names	C PC NC NA	
Prescriber's telephone number	C PC NC NA	
Date of the prescription and prescriber's signature	C PC NC NA	
III. PATIENT INFORMATION		**Comments**
Family name, given names, sex, identification number	C PC NC NA	
Date of birth (day/month/year)	C PC NC NA	
Inpatient/outpatient department	C PC NC NA	
Size and weight, body surface	C PC NC NA	
Diagnostic or diagnosis	C PC NC NA	
Relevant clinical parameters (renal or hepatic insufficiency)	C PC NC NA	
IV. PROTOCOL		**Comments**
Protocol name (identification)	C PC NC NA	
Premedication and adjuvant treatments	C PC NC NA	
Chemotherapy drug(s) prescribed using INN	C PC NC NA	
Standard dosage and patient-adapted dosage	C PC NC NA	
Type and volume of solvent	C PC NC NA	
Pharmaceutical form and route of administration	C PC NC NA	
Cycle number and day	C PC NC NA	
Date and time of administration	C PC NC NA	
Duration and/or speed of administration	C PC NC NA	
Chronology of administration if several chemotherapy drugs	C PC NC NA	

C = Compliant; PC = Partially Compliant; NC = Non-Compliant; NA = Not Applicable

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Standards of Practice, International Society of Oncology Pharmacy Practitioners

2016 Updated American Society of Oncology/Oncology Nursing Society Chemotherapy Administration Standards, including Standards for Pediatric Oncology

ANNEX 2: Structured observation checklists for Preparation

A. Observation checklist for preparation without a biosafety cabinet or a cleanroom.

B. Observation checklist for preparation under a biosafety cabinet but without a cleanroom.

C. Observation checklist for preparation under a biosafety cabinet and inside a cleanroom.

A. Observation checklist for preparation without a BSC or a cleanroom

	Rating *Circle the appropriate rating*	
I. RECEIPT AND TRACEABILITY OF MATERIALS		**Comments**
Preparation of compounding worksheet (calculation of the volume of the anticancer drug to be drawn from the vial)	C PC NC NA	
Preparation of the chemotherapy formulation's label (identification of the patient, the product, the dosage, the route of administration, storage conditions, and time and date of expiry)	C PC NC NA	
Collection of equipment and ingredients for compounding based on the compounding protocol	C PC NC NA	
Documentation of product batch numbers and expiry dates on the compounding worksheet	C PC NC NA	
Double checking of the equipment and ingredients for compounding: verification of the drug name, dosage, quantity, type of solvent, equipment used, cleanliness, product batch n° and expiry dates, exactitude of the worksheets and the labels prepared	C PC NC NA	
II. HYGIENE AND PPE		**Comments**
Operator wearing hospital uniform (not private clothes)	C PC NC NA	
Operator not wearing make-up or false nails	C PC NC NA	
Operator wearing no jewelry	C PC NC NA	
Operator washed hands hygienically (using soap and water as per WHO guidelines)	C PC NC NA	
Operator dried hands using single-use paper towels	C PC NC NA	
Donning of the following PPE	C PC NC NA	
□ hair cap		
□ N95 or FFP2 mask		
□ laboratory coat/coveralls		
□ hospital clogs and/or overshoes		
□ protection goggles		
Operator disinfected hands with hydro-alcoholic solution	C PC NC NA	
Operator put on two pairs of gloves	C PC NC NA	
III: PREPARATION ROOM		**Comments**
Room cleanliness (dust, waste, insects)	C PC NC NA	
No open windows or doors	C PC NC NA	
No concurrent activity occurring in the same room	C PC NC NA	
IV. WORKBENCH SURFACE PREPARATION		**Comments**
No materials or equipment unnecessary to the drug preparation process are present	C PC NC NA	
Workbench surface decontaminated using ethanol 70% and then left to dry	C PC NC NA	
Presence of a waste bin	C PC NC NA	
Workbench surface is clean and tidy	C PC NC NA	
Only one drug at a time is in preparation on the workbench surface	C PC NC NA	
Preparation equipment and materials are properly laid out (following the correct preparation process)	C PC NC NA	
V. HANDLING TECHNIQUES		**Comments**
Operator disinfects the vial septum and dries it if necessary (with sterile swabs)	C PC NC NA	

The operator does not touch the different equipment tips (syringes, needles)	C PC NC NA	
Air pressure levels between the vials and the work area are correctly balanced (no pressure spikes, or air intake)	C PC NC NA	
Operator uses swabs when withdrawing needles from vials	C PC NC NA	
Operator properly recaps needles	C PC NC NA	
In-process monitoring procedure for volumes withdrawn from vials and in syringes (double-checking, gravimetry or otherwise)	C PC NC NA	
Strong management of supplies and production materials used (immediately thrown into waste bin or put far enough out of reach so as not to impede the order of drug preparation)	C PC NC NA	
VI. END OF COMPOUNDING		**Comments**
The chemotherapy has been correctly labeled (identification of the patient, product, dosage, route of administration, conservation, date of administration, expiry time and date)	C PC NC NA	
The compounding process has been documented on the compounding worksheet	C PC NC NA	
Workbench cleanliness (elimination of waste products, spraying and cleaning with ethanol 70%)	C PC NC NA	
Appropriate management of left-over, unused drugs (labeling, expiry date in < 24 h, storage and conservation, sachets)	C PC NC NA	
VII. REMOVING PPE		**Comments**
Operator removed PPE before leaving the drug preparation room area	C PC NC NA	
VIII. RECONCILIATION before dispensing		**Comments**
There is a process for verifying that the chemotherapy formulation, the prescription and the compounding protocol match (verification of the compounding worksheet and the label)	C PC NC NA	
There is a visual inspection of the drug's container, its intactness and seals (also verify the type of tubing—with or without a filter)	C PC NC NA	
Visual inspection of the contents (color, clearness, lack of visible particles)	C PC NC NA	
Documentation of the reconciliation process on the compounding worksheet	C PC NC NA	

C = Compliant; PC = Partially Compliant; NC = Non-Compliant; NA = Not Applicable

B. Observation checklist for preparation under a biosafety cabinet but without a cleanroom

	Rating *Circle the appropriate rating*	
I. RECEIPT AND TRACEABILITY OF MATERIALS		**Comments**
Preparation of a compounding worksheet (calculation of the volume of the anticancer drug to be drawn from the vial)	C PC NC NA	
Preparation of the chemotherapy formulation's label (time and date of expiry (> 24 h), identification of the patient, the product, the dosage, the route of administration, storage and conservation)	C PC NC NA	
Collection of equipment and ingredients for compounding based on the compounding protocol	C PC NC NA	
Product batch numbers and expiry dates are traceable on the compounding worksheet	C PC NC NA	
Double checking of the equipment and ingredients for compounding: verification of the drug name, dosage, quantity, type of solvent, equipment used, cleanliness, product batch n° and expiry dates, exactitude of the worksheets and the labels prepared	C PC NC NA	
II. HYGIENE AND PPE	PC	**Comments**
Operator wearing hospital uniform (not private clothes)	C PC NC NA	
Operator not wearing make-up or false nails	C PC NC NA	
Operator wearing no jewelry	C PC NC NA	
Operator washed hands hygienically (using soap and water as per WHO guidelines)	C PC NC NA	
Operator dried hands using single-use paper towels	C PC NC NA	
Donning of the following PPE	C PC NC NA	
□ hair cap		
□ mask		
□ laboratory coat/coveralls		
□ hospital clogs and/or overshoes		
Disinfection of hands using an hydro-alcoholic solution	C PC NC NA	
Operator put on first pair of gloves	C PC NC NA	
III: PREPARATION ROOM		**Comments**
Room cleanliness (dust, waste, insects)	C PC NC NA	
No open windows or doors	C PC NC NA	
No concurrent activity occurring in the same room	C PC NC NA	
IV. PREPARING THE WORKBENCH		**Comments**
Laminar flow turned on at least 15 minutes before beginning any drug handling	C PC NC NA	
The biosafety cabinet is decontaminated (surfaces and sides) and allowed to dry	C PC NC NA	
Waste bin is correctly positioned beneath BSC	C PC NC NA	
Supplies and compounding ingredients placed under the laminar flow: one drug preparation at a time	C PC NC NA	
The operator removed outer packaging of sterile supplies (peeling technique) when placing them under the BSC	C PC NC NA	
Decontamination (spraying) of non-sterile supplies before placing them under the BSC	C PC NC NA	
Operator correctly put on sterile gloves	C PC NC NA	
Supplies and ingredients are correctly laid out (respecting clean zone, dirty zone, spacing)	C PC NC NA	
V. HANDLING TECHNIQUES		**Comments**

The ventilation extraction grills have no obstructions	C	PC	NC	NA	
Operator makes no overly rapid movements	C	PC	NC	NA	
Vial septa are disinfected and dried if necessary (using sterile swabs)	C	PC	NC	NA	
Operator does not touch the different equipment tips/points (syringes, needles)	C	PC	NC	NA	
Air pressure levels between the vials and the work area are correctly balanced (if no spikes)	C	PC	NC	NA	
Operator uses swabs when withdrawing needles from vials	C	PC	NC	NA	
Needles are appropriately capped after use	C	PC	NC	NA	
In process verification of the volumes withdrawn from vials (double checking, gravimetry or otherwise)	C	PC	NC	NA	
Strong management of supplies and production materials used (immediately thrown into waste bin or put far enough out of reach so as not to impede the order of drug preparation)	C	PC	NC	NA	
VI. END OF COMPOUNDING					**Comments**
Chemotherapies are correctly labeled (time and date of preparation, for extemporaneous use, identification of the patient, product, dosage, route of administration, storage and conservation)	C	PC	NC	NA	
The BSC is cleaned at the end of the drug preparation session (waste removal, spraying with ethanol 70%, appropriate S-shaped cleaning technique)	C	PC	NC	NA	
Appropriate management of left-over, unused drugs (labeling, expiry date in < 24 h, storage and conservation, sachets)	C	PC	NC	NA	
VII. REMOVAL OF PPE					**Comments**
Operator removed PPE before leaving the drug preparation room area	C	PC	NC	NA	
VIII. RECONCILIATION before dispensing					**Comments**
There is a process for verifying that the chemotherapy formulation, the prescription and the compounding protocol match (verification of the compounding worksheet and the label)	C	PC	NC	NA	
There is a visual inspection of the drug's container, its intactness and seals (also verify the type of tubing—with or without a filter)	C	PC	NC	NA	
Visual inspection of the contents (color, clearness, lack of visible particles)	C	PC	NC	NA	
Documentation of the reconciliation process on the compounding worksheet	C	PC	NC	NA	

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C. Observation checklist for preparation under a biosafety cabinet and inside a cleanroom

	Rating *Circle the appropriate rating*	
I. RECEIPT AND TRACEABILITY OF MATERIALS		**Comments**
Preparation of compounding worksheet (calculation of the volume of the anticancer drug to be drawn from the vial)	C PC NC NA	
Preparation of the chemotherapy formulation's label (identification of the patient, the product, the dosage, the route of administration, storage and conservation, and time and date of expiry)	C PC NC NA	
Collection of equipment and ingredients for compounding based on the compounding protocol	C PC NC NA	
Product batch numbers and expiry dates are traceable	C PC NC NA	
Double checking of the equipment and ingredients for compounding: verification of the drug name, dosage, quantity, type of solvent, equipment used, cleanliness, product batch n° and expiry dates, exactitude of the worksheets and the labels prepared	C PC NC NA	
Decontamination of all equipment / and ingredients / and preparations before they are brought the cleanroom	C PC NC NA	
II. HYGIENE AND PPE		**Comments**
Operator wearing hospital uniform (not private clothes)	C PC NC NA	
Operator not wearing make-up or false nails	C PC NC NA	
Operator wearing no jewelry	C PC NC NA	
Operator washed hands hygienically (using soap and water as per WHO guidelines)	C PC NC NA	
Operator dried hands using single-use paper towels	C PC NC NA	
Donning of the following PPE (in the airlock)	C PC NC NA	
□ hair cap		
□ mask		
□ laboratory coat/coveralls		
□ hospital clogs		
Operator put on overshoes on passing between the clean and dirty zones	C PC NC NA	
Operator disinfected hands using a hydro-alcoholic solution	C PC NC NA	
Operator put on first pair of gloves	C PC NC NA	
Sanitize gloves with ethanol 70%	C PC NC NA	
III. PREPARATION OF THE WORKBENCH		**Comments**
Laminar flow turned on at least 15 minutes before beginning any drug handling	C PC NC NA	
The biosafety cabinet is decontaminated (surfaces and sides) and allowed to dry	C PC NC NA	
Waste bin is correctly positioned beneath the BSC	C PC NC NA	
Supplies and compounding ingredients placed under the laminar flow: one drug preparation at a time	C PC NC NA	
The operator removed outer packaging of sterile supplies (peeling technique) when placing them under the BSC	C PC NC NA	
Decontamination (spraying) of non-sterile supplies	C PC NC NA	
Operator correctly put on sterile gloves	C PC NC NA	
Supplies and ingredients are correctly laid out (clean zone, dirty zone, spacing)	C PC NC NA	
IV. MANIPULATION TECHNIQUES		**Comments**
The ventilation extraction grills have no obstructions	C PC NC NA	

Operator makes no overly rapid movements	C PC NC NA	
Vial septa are disinfected and dried if necessary (using sterile swabs)	C PC NC NA	
Operator does not touch the different equipment tips/points (syringes, needles)	C PC NC NA	
Air pressure levels are correctly balanced (no pressure spikes or air intake)	C PC NC NA	
Operator uses swabs when withdrawing needles from vials	C PC NC NA	
Needles are appropriately capped after use	C PC NC NA	
In process verification of the volumes withdrawn from vials (double checking, gravimetry or otherwise)	C PC NC NA	
Strong management of supplies and production materials used (immediately thrown into waste bin or put far enough out of reach so as not to impede the order of drug preparation)	C PC NC NA	
V. END OF COMPOUNDING		**Comments**
The chemotherapy has been correctly labeled (identification of the patient, product, dosage, route of administration, conservation, date of administration, expiry time and date)	C PC NC NA	
The BSC is cleaned at the end of the drug preparation session (waste removal, spraying with ethanol 70%, appropriate S-shaped cleaning technique)	C PC NC NA	
Appropriate management of left-over, unused drugs (labeling, expiry date in < 24 h, storage and conservation, sachets)	C PC NC NA	
VI. REMOVING PPE		**Comments**
Operator removes PPE before leaving the preparation area (in the airlock's "dirty" area)	C PC NC NA	
VII. RECONCILIATION before dispensing		**Comments**
There is a process for verifying that the chemotherapy formulation, the prescription and the manufacturing protocol match (verification of the manufacturing worksheet and the label)	C PC NC NA	
There is a visual inspection of the drug's container, its intactness and seals (also verify the type of tubing—with or without a filter)	C PC NC NA	
Visual inspection of the contents (color, clearness, lack of visible particles)	C PC NC NA	
Documentation of the reconciliation process on the compounding worksheet	C PC NC NA	

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ANNEX 3: Structured observation checklist for the administration of iv chemotherapy

Circle the appropriate rating

A	**BEFORE ADMINISTRATION**				
I	PREPARATION OF EQUIPMENT AND MATERIALS				
1	Nurse disinfects hands using a hydro-alcoholic solution (as per WHO recommendations) throughout the treatment and care procedures	8 stages, 20–30 seconds Hand disinfection must take place at the WHO's Five Moments for Hand Hygiene		C PC NC NA	
2	Disinfection of the drug administration trolley or drug administration tray using an ad hoc disinfectant			C PC NC NA	
3	Preparation of the equipment and supplies necessary for administration	e.g., swabs, waste bins, catheters, etc.		C PC NC NA	
II	NURSES CLOTHING				
4	Appropriate PPE			C PC NC NA	
	Long-sleeved laboratory coat and/or coveralls □	Pulled tight at the cuffs			
	Mask □	Surgical			
	First pair of gloves □	Non-sterile			
	Protection goggles □	If there is a risk of splashing or spillage			
III	VERIFICATION THAT THE TREATMENT PROTOCOL MATCHES THE PRODUCT: checklist				
5	Verification that the treatment protocol matches the product administered	Possibly use a checklist		C PC NC NA	
	Methods of product storage and conservation □	Refrigeration, room temperature, light sensitivity			
	Patient identification □	(e.g., family name, given names, date of birth, patient identification number)			
	Name of the product to be administered □				
	Dosage □				
	Route of administration □	Intravenous, intramuscular			
	Today's date corresponds to the date of administration in the protocol □				
	Date and time of treatment match □				
	The drug will not expire before the end of the treatment □	Date and time			

6	Removal and disposal of gloves as per the waste disposal plan	To avoid any contamination of the working environment, gloves must be removed and disposed of as soon as the drug administrator must touch any piece of equipment or material not used in drug administration		C PC NC NA
7	Nurse disinfects hands using a hand disinfectant solution			C PC NC NA
IV	PREPARING THE PATIENT			
9	Verification of the patient's identity (family name, given names, date of birth) and that it matches with the patient identity on the drug treatment protocol	Family name, given names, date of birth		C PC NC NA
10	Ensure that the patient has been informed and educated about the treatment he/she is going to receive	Effects, risks, and side-effects		C PC NC NA
B	**DURING ADMINISTRATION**			
V	CHECKS			
11	Verification that the modalities of the drug's administration (route of administration, duration of administration, flow rate, etc.) agree with the medical treatment protocol, the nurse's protocol, and the product's specificities	Possibly use a checklist		C PC NC NA
12	Documentation on the verification (point 11) is in the patient's record			C PC NC NA
VI	INTRAVENOUS ADMINISTRATION			
13	Nurse disinfects hands using an hydro-alcoholic solution			C PC NC NA
14	Nurse puts on the first pair of gloves	Non-sterile, non-powdered		C PC NC NA
15	Placement and securing of a new, short peripheral venous catheter at a site with no prior puncture	Avoid the wrists, the elbow crease, and the backs of the hand, legs and feet. If there is a prior puncture site, it is preferable to choose the other arm or, if this is impossible, a puncture site proximal to the first one **Note: if the catheter was placed on the same day and there was venous reflux**		C PC NC NA
16	Monitoring for potential venous reflux and rinsing of the catheter with 10 mL of NaCl			C PC NC NA
17	Nurse puts on the second pair of gloves over the first	Ensure that all appropriate PPE are being worn		C PC NC NA
ADMINISTRATION VIA PERFUSION				

18	Connection of the perfusion to the catheter, which has been flushed using an isotonic solution			C PC NC NA
19	The infusion rate is set as per the protocol			C PC NC NA
20	Removal of both pairs of gloves and disposal as per the waste management plan			C PC NC NA
21	Disinfection of hands using an hydro-alcoholic solution			C PC NC NA
22	Clinical monitoring of the patient during the perfusion as per the drug administration plan	Pulse, blood pressure and body temp.		C PC NC NA
23	Regular monitoring to ensure that there are no signs of extravasations	Attentive listening to the patient and monitoring of the puncture and for potential reflux		C PC NC NA
24	Nurse puts on a new pair of gloves	Non-sterile, non-powdered		C PC NC NA
25	The perfusion catheter is flushed with 50 mL of a compatible isotonic solution between each product and after the final one			C PC NC NA
26	The precise order of administration of the products is followed			C PC NC NA
27	At the end of the treatment, the catheter is withdrawn, and the puncture site is dressed using a dry bandage or the catheter is closed and left in place for the duration of the hospital stay			C PC NC NA
INTRAVENOUS ADMINISTRATION using a short venous catheter				
32	Sterile swabs soaked in chlorhexidine alcohol or povidone-iodine are placed beneath the i.v. connector	This is unnecessary if it is a Luer-Lock syringe		C PC NC NA
34	Connection of the cytotoxic drug's syringe			C PC NC NA
35	The injection duration indicated on the protocol is adhered to			C PC NC NA
36	Clinical monitoring of the patient during the injection as per the drug administration plan	Heart rate, blood pressure and temperature		C PC NC NA
37	Monitoring to ensure that there are no signs of extravasations	Attentive listening to the patient and monitoring of the puncture and for potential reflux		C PC NC NA
38	The perfusion catheter is flushed using 50 mL of a compatible isotonic solution between each product and after the final one			C PC NC NA
39	The order of administration of products is properly respected			C PC NC NA
40	At the end of the treatments, the catheter is withdrawn, and the puncture site is dressed using a dry bandage or the catheter is closed and left in place for the duration of the hospital stay			C PC NC NA
C	**AFTER ADMINISTRATION**			
VII	WASTE MANAGEMENT			

41	All used consumable equipment and materials are disposed of directly into waste bins as per the waste management plan	(cytotoxic drugs, needles and sharps, infectious waste, PPE, excreta)		C PC NC NA
42	Disinfection of the drug administration trolley or drug administration tray using an ad hoc disinfectant			C PC NC NA
43	Disinfection of the patient's armchair, bed, seat, and the base of the perfusion stand using an ad hoc disinfectant			C PC NC NA
44	Nurse removes and disposes of gloves			C PC NC NA
45	Nurse washes hands using soap and water as per WHO recommendations, then, after drying, disinfects hands using an hydro-alcoholic solution			C PC NC NA
VIII	DOCUMENTATION			
46	Details about the drug's administration are traceable in the patient's hospital records			C PC NC NA
47	There is appropriate documentation on patient monitoring (vital signs, health status etc.)			C PC NC NA

C = Compliant; PC = Partially Compliant; NC = Non-Compliant; NA = Not Applicable

9.2.4 Article 4

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Development and Evaluation of an e-Learning Module for Low- and Middle-Income Countries on the Safe Handling of Chemotherapy Drugs

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Abstract
Despite the growing use of chemotherapy drugs in resource-constrained settings, training opportunities on safe handling practices are lacking. This study's objectives were to develop and evaluate an e-learning training module on the safe handling of chemotherapy drugs to strengthen knowledge and practices in low- and middle-income countries (LMICs). The module's curriculum was developed using the *Six-Step Approach for Curriculum Development for Medical Education*. Asynchronous, self-paced, e-learning lessons within the module were created and uploaded onto a free online platform, Pharm-Ed. The study ran online from January to April 2021. Participant recruitment was done using convenience sampling through various channels (social media, communities of practice). Training module effectiveness was evaluated using knowledge assessments (a pre-test and post-test study design) and participant satisfaction. We developed a comprehensive e-learning module on the safe handling of chemotherapy drugs comprising 11 asynchronous, self-paced, e-learning lessons. Eighty-two participants (68% pharmacists and 17% pharmacy students) from 17 countries completed at least one lesson, with a total of 259 lessons completed. Evaluation of the different lessons showed significant improvements in theoretical knowledge ($p < 0.01$) in all except one lesson and a high degree of participant satisfaction. As the use of anti-cancer drugs in LMICs will continue to increase, this e-learning module is an effective means to address the lack of training opportunities on the safe handling of chemotherapies for healthcare workers in these countries. The module could be integrated into a multi-modal approach aimed at reducing occupational exposure and increasing patient safety in cancer care centers.

Keywords Safe handling practices · Cytotoxic drugs · Low- and middle-income countries · Chemotherapy · e-Learning

Introduction

In recent years, the use of chemotherapy drugs has increased tremendously in low- and middle-income countries (LMICs). Indeed, in response to the rising burden of cancer and its economic and human-related development threat, cancer management has become a priority for many LMICs [1–3]. Among various strategies and actions, the international community has made considerable efforts to improve patient access to anti-cancer medicines [4, 5]. Due to their inherent toxicity, however, these drugs require great precautions in handling and use [6]. Patient safety and occupational exposure have been areas of great concern for many years for the professional associations and national authorities in high-income countries [7–9]. Indeed, there are several reasons why cancer treatment management is a high-risk process: the complexity of treatment regimens, patient fragility,

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the very nature of the drugs, their administration routes, and so on. Over the years, numerous best practice guidelines and recommendations have been developed. Unfortunately, in countries where cancer management is more recent, the conditions for the safe use of chemotherapies are not always met [5, 10]. Several studies have reported safety risks, including insufficient knowledge, unsuitable infrastructure, the unavailability of materials, multitasking, work pressures, and high patient numbers [11, 12]. Other studies have reported that improper working practices were due to a lack of training, a lack of awareness, and false beliefs [13, 14]. As the GLOBOCAN statistics produced by the International Agency for Research on Cancer (IARC) predict a sharp increase in cancers by 2040, particularly in LMICs, more healthcare workers and more hospitals will be engaged in cancer care and chemotherapy drug use. It is thus imperative to take actions to promote and improve safe chemotherapy handling practices [1].

In recent years, taking advantage of information and communication technologies and developing e-learning strategies have been strongly encouraged for healthcare workers education [15, 16]. Distance education has grown significantly, particularly in LMICs, where there is a strong need to alleviate the shortage of trained, qualified professionals. One of e-learning's many advantages is that it can transcend the geographical, political, and time barriers to education and thus extend training opportunities and access to larger numbers of people. Besides, technological progress in hardware and software and affordable internet connectivity have enabled broader technology access and usage in low-resource settings [17]. Distance education and e-learning are generic terms that include all kinds of educational methods, ranging from digital libraries to more complex distance learning networks and innovative methods such as virtual simulation or gamification [18]. However, achieving a real impact requires high-quality, relevant, and adaptable educational programs.

The present study's objectives were to develop and evaluate an e-learning training module on the safe handling of chemotherapy drugs for strengthening knowledge and practices in LMICs.

Methods

A steering committee created within the Geneva University Hospitals' Pharmacy Department led the project and defined the module's curriculum. It was composed of the department head, the pharmacist in charge of the cytotoxic drug preparation unit, and the study's principal investigator. The module's curriculum was developed based on the widely recognized and systematic *Six-Step Approach for Curriculum Development for Medical Education* [19].

Curriculum and e-Learning Development

Step 1—Problem identification and needs assessment: Needs assessment was based on an online survey evaluating the safe handling practices in many different settings in LMICs and on audits the authors conducted in four African hospitals (unpublished data) [10].
Step 2—Target audience: The e-learning module was principally aimed at healthcare professionals (physicians, nurses, pharmacists, pharmacy technicians) handling chemotherapies and working in low-resource settings. The module was developed in French to target French-speaking LMICs.
Step 3—Goal and objectives: The module's goal was to cover the main aspects of the safe handling of chemotherapies all along the chemotherapy pathway (e.g., receiving drugs, storage, transport, prescription, preparation, administration, waste management, and disposal), to ensure patient safety, and reduce the risks of occupational exposure and environmental contamination. The learning objectives for each lesson within the module were set using Bloom's Revised Taxonomy [20]. Lesson content was based on best practice guidelines and recommendations, and all content was reviewed and validated by the steering committee members before being published online. We followed the principle of constructive alignment to ensure coherence between the learning objectives, content, and the evaluation [21].
Step 4—Educational strategy: The lessons were developed so that they could be followed using an asynchronous, self-paced learning format, meaning that participants can access, start, interrupt, and restart the different lessons at any time that suits their professional and personal schedule. Each lesson lasted from 10–30 min. e-Learning lessons were developed using the Articulate Storyline 3 (Articulate Global inc.) authoring tool, which enables publication in the HTML5 markup language. The module is thus compatible with most devices, including tablets and smartphones. To keep the lessons engaging and interactive, there are many embedded questions and answers with instantaneous feedback. Graphics such as stick figures were obtained from PresenterMedia® (Eclipse Digital Imaging Inc). Video tutorials were also filmed to better teach good practices in chemotherapy preparation and were then uploaded onto the Pharm-Ed YouTube channel.
Step 5—Implementation: The entire e-learning module was subsequently uploaded onto the Pharm-Ed platform (www.Pharm-Ed.net), a collaborative online educational platform for promoting the efficient, safe, and

rational management of medicines in hospitals. Access to the platform is free, but registration is required to participate in the e-learning module. The LearnDash® learning management system—a WordPress plugin—was used to manage and track the learning process.

Step 6—Evaluation and feedback: We based our evaluation on the first two levels of Kirkpatrick's training program evaluation model, i.e., reaction and learning [22]. At the end of each lesson, an online satisfaction questionnaire evaluated participants' reactions, with satisfaction measured on 5-point Likert scales for various aspects of the lesson (content, courseware, level of difficulty, and overall satisfaction). The last part of the questionnaire contained open-ended questions on the lesson's perceived strengths and weaknesses. Participants' knowledge was assessed before (pre-test) and after (post-test) each lesson. These tests came in the form of multiple-choice questions that were identical for each lesson and integrated into our learning management system. The multiple-choice questions were developed to match the lesson's pedagogical objectives and content (constructive alignment). The differences between the pre-test and post-test scores were used to calculate participants' learning gain in each lesson.

Conduct of the Study

This study used a one-group pre-test–post-test design. The e-learning module evaluation occurred from January to April 2021. Participant recruitment was done using convenience sampling via various channels, such as social media, communities of practice like the *e-med forum*, newsletters like *Pharm-Ed community*, and professional networking. Because the e-learning module was in French, only French-speaking participants were selected.

Statistical Analysis

Data were exported from the LearnDash® learning management system to a Microsoft Excel® 2013 spreadsheet (Microsoft Corporation, Redmond, WA, USA). Participant characteristics were described using descriptive statistics. Participants' pre-test and post-test score differences were assessed using the Wilcoxon signed-rank test. Statistics were calculated using R4.0.3 software (R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/).

Results

The e-learning module encompassed 11 lessons covering the main aspects of the safe handling of chemotherapy drugs: (1) risks related to chemotherapy drugs, (2) logistical aspects specific to chemotherapy drugs, (3) safe chemotherapy prescription practices, (4) premises, (5) biosafety cabinets and isolators, (6) personal protective equipment, (7) ensuring preparation process safety, (8) ensuring chemotherapy administration safety, (9) incident management, (10) extravasations, (11) waste management. The average duration of the lessons varies between 10 to 30 min and the number of multiple choice questions in the pre/post-tests between five and twelve.

Participants

Of the 125 participants, 82 (66%) completed the pre-test and post-test for at least one lesson. The other 43 participants did not complete a lesson, as they filled in either only the pre-test or the post-test. In total, 259 lessons were completed (an average of 3 lessons per participant), and 82 incomplete lessons were excluded (i.e., only the pre-test or post-test was filled in). Participants came from 17 countries and most were pharmacists (68%) or pharmacy students (17%) (Table 1).

Effectiveness on Improvements in Knowledge

Figure 1 shows the mean pre-test and post-test scores for each lesson. In general, participants' pre-test knowledge levels were mostly moderate across the different lessons (i.e., around 50% of answers correct), except for three lessons where baseline knowledge was lower: prescribing (37%), biosafety cabinets and isolators (26%), and extravasations (29%). Post-test results showed significant improvements in knowledge ($p < 0.01$) after all the lessons except for the one on ensuring chemotherapy administration safety, where the number of participants was too low to detect any potential effect ($n = 4$).

Satisfaction

Of the 259 completed lessons, only 75 (29%) were accompanied by their respective completed satisfaction forms, of which 38 (51%) had been filled in by pharmacists, 25 (33%) by pharmacy students, 6 (8%) by pharmacy technicians, and 5 (7%) by nurses. All the lessons received feedback, but the majority of the results concerned the lessons on the risks related to chemotherapy drugs (43%) and the logistical aspects specific to chemotherapy drugs (21%). Overall, participants expressed a high level of satisfaction with the course content and the courseware (Fig. 2). Almost every participant (99%) would have recommended the lesson to a colleague. The level of difficulty of the concepts presented and the tests were considered "appropriate" on the majority of the forms (81% and 85%, respectively), whereas very few reported that the level of difficulty was too low (15% and 7%, respectively) or too high (1% and 4%, respectively).

Table 1 Participants' characteristics

	No. of participants	No. of lessons
Countries		
Algeria	11 (13%)	33 (12.7%)
Belgium	1 (1%)	1 (0.4%)
Benin	1 (1%)	2 (0.8%)
Burkina Faso	1 (1%)	2 (0.8%)
Cameroon	3 (4%)	15 (5.8%)
Canada	1 (1%)	1 (0.4%)
Cote d'Ivoire	1 (1%)	1 (0.4%)
Democratic Republic of Congo	3 (4%)	4 (1.5%)
France	17 (21%)	45 (17.4%)
Gabon	1 (1%)	1 (0.4%)
Greece	1 (1%)	2 (0.8%)
Guinea	1 (1%)	2 (0.8%)
Madagascar	1 (1%)	2 (0.8%)
Mauritania	1 (1%)	2 (0.8%)
Morocco	10 (12%)	40 (15.4%)
Senegal	20 (24%)	90 (34.8%)
Tunisia	8 (10%)	16 (6.2%)
Profession		
Pharmacist	56 (68%)	179 (69.1%)
Pharmacy student	14 (17%)	38 (14.7%)
Pharmacy technician	3 (4%)	3 (1.2%)
Nurse	5 (6%)	33 (12.7%)
Physician	1 (1%)	1 (0.4%)
Other	1 (1%)	1 (0.4%)
Unknown	2 (2%)	4 (1.5%)
Type of institution		
University teaching hospital	19 (23%)	62 (23.9%)
Regional hospital	4 (5%)	15 (5.8%)
District hospital	4 (5%)	19 (7.3%)
Military hospital	3 (4%)	4 (1.5%)
Private institution	4 (5%)	18 (6.9%)
Student	14 (17%)	37 (14.3%)
Other (NGO, health ministry, university)	13 (16%)	39 (15.1%)
Unknown	21 (26%)	65 (25.1%)
Total	**82**	**259**

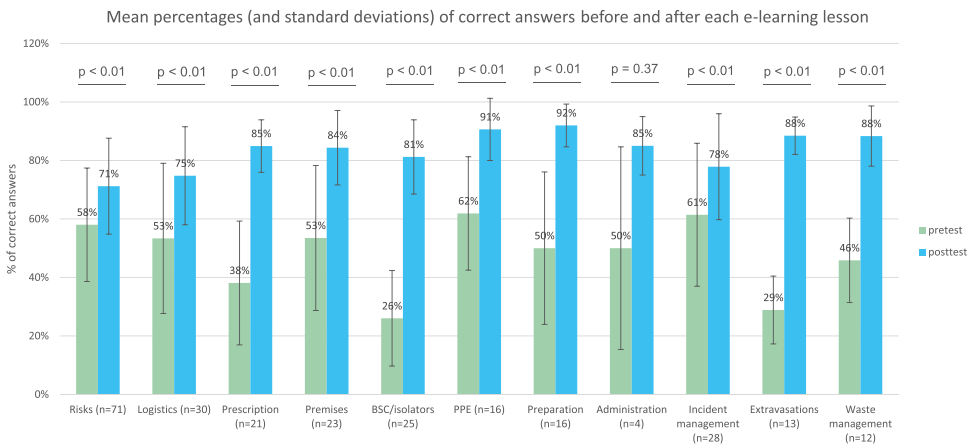

Fig. 1 Pre-test and post-test results for each lesson expressed as mean percentage of correct answers with standard deviation

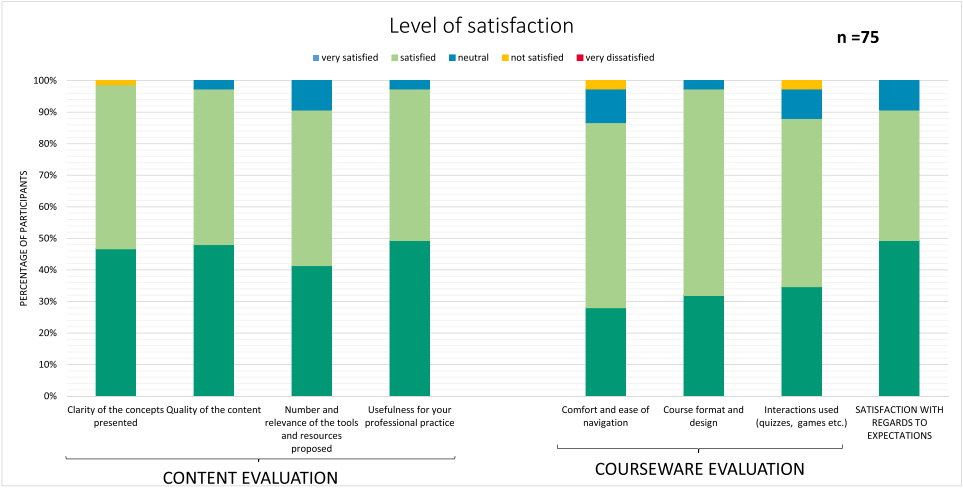

Fig. 2 Participants' reported levels of overall satisfaction (for all lessons)

Discussion

Summary of Results

We developed a comprehensive e-learning module on the safe handling of chemotherapy drugs comprising 11 asynchronous, self-directed e-learning lessons. The evaluation of these different lessons revealed significant improvements in participants' theoretical knowledge in all but one lesson (which had insufficient statistical power) and a high degree of participant satisfaction in terms of content and courseware. In general, the post-test scores for the different lessons were relatively high. These findings reflect the positive effects of the constructive alignment principle that we followed in the module's development phase. Lessons with slightly lower post-test scores (e.g., for risks and logistics) will therefore be reviewed in more detail to verify their constructive alignment. Future multiple-choice questions for the tests will be pilot-tested to detect any issues related to their structure or formulation.

Comparison with the Relevant Literature

As with the majority of the studies included in the systematic review by Barteit et al. (2019), we used a pre-test and post-test design to assess participants' knowledge using multiple-choice questions [17]. Although several studies have assessed nurses' knowledge and practices in the safe handling of cytotoxic drugs in LMICs, our study is, to the best of our knowledge, the first to evaluate an e-learning module on the safe handling of chemotherapy drugs in these countries [11, 12, 23, 24]. Indeed, our study participants were also predominantly pharmacists (89%), with only 6% being nurses. This difference was due to the communication channels used to build our convenience sample: these did not permit large numbers of nurses to be reached. The participation of a larger number of nurses would have been desirable, however, as they are directly concerned by many of the aspects addressed in this module.

Strengths and Limitations

This study involves participants from a wide diversity of settings, not only geographically but also in terms of working environments. The high level of satisfaction thus reflects the module's adaptability and applicability across these different contexts. Making these courses available in additional languages, such as English and Spanish, could be very beneficial to healthcare workers in other LMICs where these languages are spoken.

The present study had some limitations, including the lack of a control group. In addition, the sample size differed from lesson to lesson and, for some, the number of participants was relatively low, making it difficult to analyze sub-groups or interpret results. Because not all of the participants completed the entire e-learning module, it was impossible to measure its overall effectiveness. Regarding the individual lessons, we limited our evaluation to the Kirkpatrick model's first two levels, namely user satisfaction and knowledge acquired; the competencies evaluated in levels 3 and 4—resulting from the transposition of knowledge into professional practice and its impact at the institutional level—were not assessed. In addition, we assessed knowledge directly after each lesson in the training module. It would be interesting to study knowledge retention over time.

Implications for Practice

The present study demonstrated some of the effectiveness and appropriateness of this e-learning module for healthcare

professionals in LMICs. Implementing this type of training for all the staff involved in handling chemotherapies should become mandatory as it could help reduce the risks of occupational exposure and improve patient safety. To the best of our knowledge, there are very few opportunities for training healthcare workers in this field in resource-limited countries. This training module can be followed for free on the Pharm-Ed e-learning platform. It is a beneficial and appropriate training module for a variety of settings. It could also be integrated into a blended learning approach with one or more face-to-face modules used to emphasize specific skills and behaviors; it could encourage the exchange of best practices during focus groups and the discussion of barriers to institutional change. However, although improving individual knowledge levels and behaviors is essential, the adoption of safety measures and the application of safe practices at the institutional level require broad changes in the approach to workplace safety. Using a multi-modal approach should include implementing recommended safety policies and procedures, the availability of safety equipment, knowledge reinforcement, supervision, and managerial support for safety programs [25].

Future Research

To address some of the present study's limitations, it would be interesting to retest the participants' knowledge several months after their training to measure knowledge retention over time. Secondly, to complete the evaluation of the module's effectiveness, a field study involving the participating healthcare institutions could be conducted to observe actual changes in behaviors and practices: this would represent the third level in Kirkpatrick's evaluation model for training programs. The use of other qualitative methods, such as in-depth interviews and focus groups, could help to investigate the barriers and facilitators to improving practices.

Conclusion

The systematic and thorough approach used in the development of this training module led to very positive results, not only in terms of participant satisfaction but also in terms of their improved knowledge. The results from the satisfaction questionnaire underlined the e-learning module's relevance and appropriateness in terms of content and format. The significant improvements in knowledge measured for most of the e-learning lessons partly reflect their effectiveness. As the use of anti-cancer drugs will only continue to increase in LMICs, this e-learning module provides a free, simple, easily accessed means of addressing the lack of training opportunities on the safe handling of chemotherapies for healthcare workers in these countries. It could be integrated into a multi-modal approach to reducing occupational exposure and increasing patient safety in cancer care centers.

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Data Availability Training material is available on www.Pharm-Ed.net.

Code Availability Not applicable.

Declarations

Conflict of Interest The authors declare no competing interests.

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Conclusion and perspectives

10. Conclusion and perspectives

10.1 Conclusion

This PhD thesis focused on the safe handling of chemotherapies in LMICs. In contrast to high-income countries, this concern is still greatly underestimated in many LMICs, where the access and use of cancer treatments has recently increased, due to the striking rise in cancer cases. Since poor practices have been shown to jeopardize patient safety and can adversely affect worker health, it is imperative to address this issue and implement measures to ensure process safety and worker protection. This thesis resulted in the design of appropriate ready-to-use tools (assessment tools and online training) that can easily be used to evaluate and support the improvement of local practices. In addition, this thesis provided an overview of the level of quality and safety of chemotherapy handling practices in different settings, but also identified gaps and areas where improvements and corrective actions are needed to ensure patient and staff safety.

10.1.1 Self-assessment tool and checklists to assess the safety and quality of chemotherapy handling practices

The first study resulted in the Cyto-SAT (appendix 1), a self-assessment tool designed to assist the personnel at cancer centers in LMICs safely handling cytotoxic medicines. 134 items derived from international recommendations were validated by a strong consensus of international experts through a Delphi survey. The items were categorized in 10 domains and 28 subdomains enabling to cover the entire process of chemotherapy drug handling (management, personnel, logistics, prescription, preparation, administration, cleaning, waste disposal, incident management and patient counseling). Several features characterize Cyto-SAT to make it suitable for its

use in LMICs. Firstly, Cyto-SAT does not include items requiring integrated information technologies, even if the computerization of some processes is always listed as a desirable objective. Unlike other tools designed for use in national or regional facility inspections, it does not contain one context-specific items, allowing its application in multiple settings. Also, Cyto-SAT provides an innovative prioritization of items, which is an important aspect to guide appropriate resource allocation in settings with limited resources. In a second part of this study, the pilot test of Cyto-SAT by 33 cancer centers from 26 LMICs allowed to confirmed its applicability in local contexts, its usefulness and usability by healthcare facilities and its acceptability as an ongoing quality improvement tool.

The 3rd article of this thesis describes the development and proof of concept of a toolkit to facilitate a comprehensive assessment of chemotherapy handling practices in LMIC health care facilities. As a complement to Cyto-SAT, we created three additional checklists focusing on sensitive steps of the cytotoxic process, particularly at risk of errors i.e., the prescription, the preparation and the administration of chemotherapy drugs. These checklists enabled to perform structured observations to assess how different staff applied safety and quality practices during each process. Surface-wipe sampling was also included in the toolkit, as this methodology is recommended for evaluating contamination trends, implementing corrective measures, and increasing workers' awareness about the risks related to handling chemotherapy drugs.(104,105). The toolkit was then successfully applied in three African hospitals. It allowed to easily and quickly benchmark the facilities and practices against international standards and design an action plan. Thus, this 3rd study showed that the toolkit provides valuable support for implementing a continuous quality improvement process, promoting best practices and ultimately ensuring the safety of patients and staff.

10.1.2 Level of quality and safety of chemotherapy handling practices in LMICs

In the 2nd article, we analyzed the results of self-assessments conducted by 53 cancer centers in 34 LMICs that tested the Cyto-SAT to get an overview of the level of the quality and safety of practices in these different settings. Findings revealed wide disparities in practices across institutions for all domains. Many safety deficiencies in chemotherapy handling practices were highlighted, particularly in lower-income countries. Major gaps were observed in the “chemotherapies preparation” domain, which is one of the chemotherapy process’s riskiest steps in term of patient and worker safety. Consequently, improvements in this domain represent a top priority to prevent the risk of medication errors and reduce occupational exposure. Major opportunities for improvement were also identified in essential cross-cutting domains such as proper initial and continuous staff education about safe handling and effective incident management. Similar observations were made during the audits conducted in three African hospitals for the 3rd study. Surface-wipe sampling allowed us to highlight the levels of contamination in the different hospitals' working environments. Compared with the results obtained from samples from European or Swiss hospitals analyzed by Cytoxlab, the amounts of contamination we sampled were much higher, reflecting a higher risk of occupational exposure. Although there are no acceptable or recommended limits, the precautionary principle implies reducing environmental contamination by chemotherapies to a minimum, notably through better working techniques, process reorganization, the use of equipment that limits the risks of contaminating personnel, and the application of adequate cleaning or chemical decontamination procedures.

Findings from these studies also served as valuable information for conducting an in-depth needs assessment as part of the training program development process constituting the final part of this thesis.

10.1.3 Effectiveness of a training module on safe handling of chemotherapy

In the final part of this thesis, we sought to build a training module on safe chemotherapy handling practices to address the lack of training opportunities in this highly relevant topic and to test its effectiveness with intended users. Thus, the 4th article presents the six-step approach that led to the implementation of a comprehensive e-learning module on safe handling of chemotherapy drugs, tailored to resource-limited settings. The developed training curriculum consists of eleven asynchronous, self-directed e-learning lessons and a variety of supporting materials and resources (e.g., SOPs, checklists, video tutorials, etc.). This training module was made accessible for free on the Pharm-Ed platform (https://pharmed.datapharma.ch/courses/medicaments-cytostatiques-et-chimiotherapie/). Evaluation of these different lessons using a pre-test/post-test system demonstrated significant improvements in participants' theoretical knowledge in all but one lesson (which had insufficient statistical power) and a high degree of participant satisfaction with the content and courseware. The results from the previous part of the thesis and following Kern's systematic approach to curriculum development allowed us to provide a relevant, appropriate and highly appreciated training module. However, because not all of the participants completed the entire e-learning module,

it was impossible to measure its overall effectiveness. In addition, levels 3 and 4 of Kirkpatrick's model—resulting from the transposition of knowledge into professional practice and its impact at the institutional level—were not assessed.

10.2 Perspectives

The work done in this thesis represents a first step in the development of a comprehensive safe cytotoxic handling program. The perspectives that can be envisaged as a direct extension of this thesis concern three important objectives:

- Extending the deployment of these tools
- Ensuring their sustainable use
- Optimizing the training program and its evaluation

10.2.1 Extending the deployment of these tools

Now that these tools to support improved quality and safety of chemotherapy handling practices have been designed and tested in local settings, the next step is to raise awareness on their existence and to promote their use by as many cancer centers as possible in LMICs. For this, several possibilities should be explored. First, the tools should be promoted to national and international professional associations and organizations working in the oncology field. These could then act as a relay to advocate for safe handling practices and the use of existing tools. Secondly, translation of the material in additional languages could help reach other regions. For our research, we developed the majority of our tool in French except for Cyto-SAT that was translated in English. Making Cyto-SAT available in English helped to broaden participation in the survey. Therefore, translating all the materials, including the e-learning program, into

English would allow more people to use them. In addition, Spanish and Portuguese translations would also be beneficial to increase their dissemination in Latin America and other African countries.

10.2.2 Ensuring a sustainable use of the tools

Our ultimate goal would be for the toolkit to be used regularly by LMIC cancer facilities as a continuous quality improvement tool to track their progress in the quality and practice safety over time. To achieve it, several suggestions are presented below.

First of all, the ergonomics of the tools could be optimized to enhance their usability. Creating a user-friendly mobile app could make it easier for the assessment team to enter the data from their mobile phone. A summary page with graphic illustration of the results could help visualize areas for improvement. A grouped presentation of low scored items for each domain could also facilitate the development of the action plan. In addition, the app could provide a direct comparison with the results of past assessments for the same cancer center to observe changes over time. Also, once the app would have gathered a certain amount of data, it could be interesting to have an option for cancer centers to benchmark their practices against other centers in similar settings. Finally, the app could give direct access to guidelines and useful resources.

The self-assessment process is a way to involve the personnel in quality improvement approaches and empower them to advocate for a comprehensive safe handling program. Nevertheless, the implementation of a safe handling program requires a comprehensive and multi-modal approach for which managerial support at the institutional level or even from national authorities seems essential. Indeed, a multi-modal approach should include integration of safety policies and procedures at

national and facility-level, the availability of safety equipment, staff training and supervision, and managerial support for safety programs. Thus, in a more global approach, a collaboration with the ministries of health of the countries with the help of partners seems important to promote our toolkit and ensure its sustainable use.

Besides, conducting a qualitative study to investigate and understand the barriers and facilitators to implementing safe and quality practices in the different settings would help identifying the best strategies and future actions to improve handling practices.

10.2.3 Optimization of the training program and its evaluation

Due to the COVID-19 pandemic, the initial design of the training program and the planned effectiveness evaluation had to be revised so that the study could be conducted entirely at a distance. Initially the program should have been presented as a blended-learning approach. Indeed, the pedagogical strategy could be improved by combining the e-learning part with a face-to-face session in which technical skills (e.g., good preparation practices, chemotherapy spill management) could be taught through simulation, for example. While it was difficult to explore more than the knowledge dimension through MCQs at the end of the e-learning, the simulation would allow the participants to demonstrate the acquired skills and behavior.

To address some of the present study's limitations and better evaluate the effectiveness of our program, it would be interesting to retest the participants' knowledge several months after their training to measure knowledge retention over time. Secondly, to complete the evaluation of the module's effectiveness, a field study involving the participants' healthcare institutions could be conducted to observe actual

changes in behaviors and practices. An increased number of pilot sites compared to our 3rd study would be required to be able to evaluate the third level of the Kirkpatrick's model for training programs. Evaluation of level 4 of the pyramid would necessitate to define measurable indicators that would represent the impact on clinical outcomes.

Finally, discussions with partners and local authorities in LMICs to integrate this training module into a national comprehensive safe handling program should be part of the agenda. It could be used in a dynamic of initial, refresher and continuous training for the different categories of personnel involved in the handling of chemotherapy drugs. In order to sustain the blended learning approach and incorporate regular supervision, training of local trainers should be encouraged too

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Appendix

APPENDIX

11.1 Appendix 1: Cyto-SAT

N°	ITEM	ADDITIONAL INFORMATION
MANAGEMENT AND ORGANIZATION		
1	A risk analysis has been conducted in order to evaluate the working environment and to identify and assess hazards related to the flow of cytotoxic medicines within the facility (from the receipt to the use of the products)	A risk assessment approach is used to determine the containment strategies and/or work practices. This considers: overall working environment; equipment (i.e. ventilated cabinets, closed-system drug transfer devices, needleless systems and personal protective equipment); physical layout of work areas; volume, frequency and form of drugs handled (coated or uncoated tablets, powder or liquid); equipment maintenance; decontamination and cleaning; waste handling; potential workplace exposure; routine operations; spill response; and waste segregation, containment. and disposal, training and level of experience of the staff
2	A comprehensive safety management programme has been put in place to deal with all aspects of the safe handling of cytotoxic drugs	A staff member is responsible for coordinating the implementation of preventive measures and preparing guidelines, in close collaboration with other relevant staff within the facility.
* 3	Policies and procedures ensure that guidelines for the safe handling of medicines are applied to all processes in which cytotoxic drugs are handled.	Policies and procedures are updated regularly. The frequency of update is to be defined by the local institution, according of the context. Any changes must be documented.
* 4	A self-assessment of compliance with safety guidelines regarding the safe handling of cytotoxic medicines is carried out regularly.	Each institution should define its frequency according to local context.
* 5	Material Safety Data Sheets (MSDS) are readily available for all cytotoxic medicines used in the facility.	MSDS can be kept in a file, be available on a computer or be consulted via the internet.
* 6	A list of the cytotoxic medicines used in the facility is available and regularly updated.	The list can be kept in a file or be available on a computer.
* 7	Smoking, drinking and eating are forbidden in areas where cytotoxic medicines are prepared, stored and administered	
* 8	All staff know and understand the facility's policies and approach on quality assurance.	Documents are readily available and written in an easily understandable manner.
*		

9	There is a regularly updated organigram (organizational chart) indicating the roles and responsibilities of all the staff members involved in processes using chemotherapies, as well as their contacts details.	
* 10	There are written job descriptions detailing the responsibilities, skills and tasks of each staff member.	Required national or international qualifications to handle cytotoxic can also be added
* 11	There is a sufficient number of competent staff to ensure that high quality care is carried out safely.	The staff available daily should enable to fulfill the tasks and responsibilities according to this repository and to maintained an acceptable workload.
PERSONNEL		
Eduction and training		
* 12	Based on their tasks and responsibilities, all staff involved in the handling of cytotoxic medicines have received adequate initial training on the type of products they are dealing with, cytotoxic risks, suitable protective measures and proper handling methods.	This includes pharmacy and nursing staff and doctors, plus support staff such as porters, cleaners, stock managers and waste management staff.
13	There is regular continuous education for staff.	Training sessions are specific to the category of staff. An annual training plan should be prepared
14	Both theoretical knowledge and practical skills are validated following training (according to the tasks and responsibilities of the staff)	E.g. oral or written tests; assessment using simulation exercises; or practical audits on the following subjects: - Knowledge of cytotoxic medicines handled and their risks; - Knowledge of SOPs related to their handling; - Proper use of personal protective equipment; - Proper handling and use of equipment and devices; - Managing incidents such as breakages, spills and exposure to cytotoxic medicines.
15	All training and skill validations are documented.	Training records are kept for at least 5 years.
Medical surveillance		
* 16	An occupational health surveillance programme is available for staff members who handle cytotoxic medicines	The occupational health surveillance includes: the evaluation of protective measures for pregnant and breastfeeding women; risk assessments in case of accidental exposure or proven or suspected deficiencies in technical protection systems; and investigations that must be carried out in suspected cases of disorders associated with exposure to cytotoxic medicines

17	No pregnant and breastfeeding women are involved in the handling of cytotoxic medicines.	Pregnant or breastfeeding women must not take part in the preparation, reconstitution, administration, cleaning or disposal of cytotoxic medicines (consult also the stipulations of the national labor law if available)
* 18	Staff involved in the preparation of cytotoxic medicines, with an upper respiratory tract infection or a cutaneous infection informs their superior before any manipulation	The decision to exclude temporarily or not the person from the preparation should be evaluated one by to avoid a risk of microbiological contamination of the preparation. A medical advice can be eventually sought
LOGISTICS		
Receipt of cytotoxic drugs		
* 19	Cytotoxic medicine deliveries are only received and unpacked by trained staff.	The staff responsible for receiving cytotoxic medicines has been trained about the possible surface contamination of primary packaging and vials, the risks of breakages and the appropriate precautions to apply.
* 20	Staff use appropriate personal protective equipment when receiving and unpacking cytotoxic medicines	Protective gloves
* 21	The reception of cytotoxic medicine deliveries is carried out appropriately.	Product deliveries are handled by trained staff who visually check the integrity of the packaging to identify any breakages or fissures. If products seem to be intact, reception and unpacking are carried out immediately, or the boxes are placed in a secure area (adequately labeled and with restricted access) until this can be done. Medicines that must stay in the cold chain are unpacked and refrigerated upon receipt.
22	The staff receiving and unpacking cytotoxic medicines know the procedures to adopt in cases of accidental spills or leakages.	They are also able to apply those procedures in practice
* 23	Staff washes their hands with soap after handling cytotoxic medicines.	Wearing gloves is not a substitute for washing hands.
Storage		
* 24	Cytotoxic medicines are stored separately from the rest of the inventory, in a dedicated storage area (including those requiring storage in a refrigerator).	Product segregation prevents contamination and the risk of exposure. If segregation in a separate room for cytotoxics is impossible, storage of cytotoxics is in a clearly identified area.
* 25	The storage area for cytotoxic medicines is clearly defined and labeled. Access is restricted to authorized personnel only.	Easily recognizable warning labels should be placed to alert staff (e.g. "Danger/caution cytotoxics"), and security measures should limit access (e.g. locks, badges).
*		Temperature is monitored and recorded on a logbook.

26	Storage areas contain equipment and monitoring system in order to ensure the correct storage conditions (temperature, light, humidity, exhaust air ventilation) and fulfill safety precautions.	
* 27	The storage area has sufficient general exhaust ventilation	
* 28	Only trained staff have access to the storage area for cytotoxic medicines, and they wear appropriate personal protective equipment when resupplying or stocktaking	Gloves should be worn when handling cytotoxic medicines, even in primary packaging and vials. Numerous studies have reported surface contamination of vials and primary packaging.
* 29	Staff wash their hands with soap after handling cytotoxic medicines when resupplying or stocktaking	Wearing gloves is not a substitute for washing hands.
Transport		
30	Cytotoxic medicines are transported in a manner that will prevent damage to and contamination of the environment, and maintain the integrity of the medicines themselves and the safety of the transporter.	This includes all in-house or inter-facility transport.
* 31	Cytotoxic medicines are transported in exclusively dedicated containers/boxes.	
* 32	Transport containers/boxes for cytotoxic medicines are easily recognizable for any person who might handle them.	Easily recognizable warning labels must be attached to the containers and provide specific instructions regarding storage and measures to be taken in case of breakage.
* 33	Cytotoxic medicines are transported in very tough, leak proof containers that can be sealed and are made of a material that can easily be cleaned and decontaminated.	Vials must also be securely positioned within their containers in order to minimize impacts and risks of breakage. Ready-to-use preparations must first be placed in leak-proof bags
* 34	Personnel transporting cytotoxic medicines know the procedures to carry out in case of an accidental spill.	Staff knows who to contact in case of an emergency.
PRESCRITPION		
35	Only authorized healthcare practitioners can prescribe chemotherapy treatment.	The facility has a readily available, up to date list of authorized prescribers.
*		

36	Prescriptions are based on standard pre-prepared chemotherapy treatment protocols dependent on the diagnosis, available in the facility (these have either been developed in-house or with reference to external review board or nationally approved clinical research protocols or guidelines).	Standard treatment protocols are regularly revised and updated. They are readily available to all the staff involved in prescribing and validating the prescription. Any prescriptions that are off-protocol must be accompanied by the physician in charge of the chemotherapy's written justifications
* 37	Prescriptions are done in a structured way, with the use of standardized, formatted (pre-printed or electronic) prescription forms. They are nominative, readable, contain no abbreviations and clearly identify the prescriber, the department giving care and the facility.	No prescription (or prescription modification) that was only communicated orally should be validated
38	Prescriptions include the following information: patient identity (name, sex, date of birth) weight, height, body surface area, diagnosis, relevant laboratory results (e.g. clearance), name of the protocol, product INN, dosage regimen, dates and times of administration, start and duration of the treatment, pharmaceutical formulation and route of administration, solvent and infusion volume, premedications.	Use of standardized, pre-printed or electronic prescription forms for chemotherapy treatment protocols is recommended.
39	Before preparation, all prescription/orders are analyzed, cross-checked using the standard agreed chemotherapy protocol and then validated by the signature of a qualified person (e.g. a pharmacist).	Independently verify each order for chemotherapy before preparation, including confirming: that the prescription corresponds with standards protocols; drug names, regimen and volume; route and rate of administration; product/solvent and product/product compatibilities; dose calculations (including the variables used in this calculation), treatment cycle and day of cycle and cumulative doses.
PREPARATION		
Management and organization		
40	Only trained, qualified personnel prepare cytotoxic medicines.	Each operator should be individually validated for both aseptic working methods and proper compounding techniques. (see Chapter on "Personnel")
41	Preparation of oral or parenteral cytotoxic medicines takes place in a controlled area dedicated to this activity. Signs designating the hazard must be prominently displayed at the entrance.	It is recommended that the preparation of cytotoxic medicines should be centralized in order to minimize the risks of contamination and limit the number of people exposed. The preparation area should be located away from breakrooms and refreshment areas.

42	Access to preparation areas is restricted to authorized personnel involved in preparation of cytotoxic medicines and wearing appropriate personal protective equipment.	
* 43	The quality, safety and aseptic conditions (if cleanroom) of the entire preparation process for parenteral/sterile cytotoxic medicines have been validated.	The objective of validation is to demonstrate that the processes used ensure to reproducibly obtain a cytotoxic preparation, with the correct products, within acceptable concentration limits, and that chemical and microbiological integrity of the product will be maintained for the established conservation period.
Preparation area of parenteral drugs		
44	An administrative area is available for examining prescriptions, preparing production sheets and storing documentation and patient files.	This area is outside the preparation room, but close to it.
* 45	The preparation room only contains the necessary materials for the preparation	The objective is to limit the risk of confusion and to minimize the contamination in case of cleanroom
* 46	The preparation of sterile cytotoxic (parenteral) medicines takes place in a cleanroom	The preparation of sterile cytotoxic drugs can be defined as an aseptic preparation and should follow GMP and PIC/S guidelines for aseptic procedures. Preparations realized in non-aseptic conditions (without a cleanroom) even with a BSC must not be kept more than 24h.
* 47	The preparation room surfaces are designed to minimize particle shedding and prevent the build-up of particulate matter as per Good Manufacturing Practices.	Work surfaces and all other surfaces in the preparation room should be smooth and facilitate effective cleaning and disinfection.
* 48	Ergonomic guidelines for the workspace are closely followed.	Notably, these include guidelines on air conditioning, lighting and the workspace, essential for the well-being of the staff and risk minimization of incidents
* 49	The preparation of cytotoxic medicines is performed in a class II b or class III (vertical laminar-airflow hood) biosafety cabinet (BSC) or in an isolator with system externally vented through HEPA filters (high-efficiency particulate air).	A continuous monitoring device ensures confirmation of adequate airflow and/or cabinet performance. If the preparation is not done in a BSC or an isolator, it is only extemporaneous
* 50	Access to the preparation room is through airlocks only, with adequate procedures to prevent simultaneous door opening (doors to the cytotoxic preparation room and to the external environment).	The airlock should provide facilities for gowning prior to personnel entering the preparation room.
*		Ideally distinct from the staff airlock.

51	A pass-through hatch enables the transfer of cytotoxic preparations between the cytotoxic preparation room and the external environment.	
* 52	Pressure gradients are maintained between the different rooms in the preparation zone and monitored continuously.	The compounding room has negative pressure compared to the adjacent positive pressure airlock, thus providing inward airflow to contain any contamination in the compounding room. The positive pressure of the airlock also protects the preparation room from the outside environment.
* 53	Preparation rooms are ventilated effectively.	Air exchanges should be frequent enough to prevent room contamination and an accumulation of toxic products (at least 12 air exchanges/hour).
Hygiene and protective equipment		
54	The personnel follow the general hygiene procedures related to medicine preparation.	Staff pay attention to hand hygiene (washing and disinfection) before and after drug preparation activity; they wear no jewelry, wrist-watches or makeup.
* 55	Operators and assistants wear appropriate personal protective equipment during the preparation or reconstitution of cytotoxic medicines according to the working environment and collective protective equipment	
56	During compounding, gloves in contact with cytotoxic vials are regularly changed or are immediately replaced when torn, punctured or directly contaminated.	According to recommendations, gloves should be changed every 30 minutes.
* 57	Personal protective equipment is removed (either discarded or laundered according to the appropriate procedure) before exiting the preparation area (in the airlock's "dirty area")	
* 58	Appropriate measures are used to avoid insects or other animals entering preparation areas.	
59	The storage and use of leftover cytostatic solutions, i.e. vials containing solution residues, is carried out according to a validated procedure that takes into account chemicophysical stability and the risk of microbiological contamination	The conservation and use of leftover cytotoxics more than 24 hours is only possible if the preparation is performed under strict aseptic conditions (cleanroom).
Preparation process set up		
* 60	Doors and windows are closed during compounding.	In an aseptic area, windows should be sealed anyway

61	Before and after compounding, all unnecessary items are removed from the work surface and it is cleaned and/or disinfected	Cleaning with an alcohol -soaked wipe should be done before and after each work session. Periodic cleaning with a detergent solution and rinse with water and then disinfecting with alcohol should be done according to the local context (e.g. daily, weekly, monthly). Ventilation should be switched on at least 30 minutes before drug preparation starts and not stopped earlier than 30 minutes after work ends.
* 62	All the materials and products required for the preparation are assembled and checked by a certified person before work starts.	Production materials are prepared based on protocol. The drug and its strength, dosage, quantity, reconstitution fluid, as well as equipment and cleanliness, the expiry dates of all component materials, the accuracy of the labels generated and worksheets must all be verified. This verification must be documented.
63	All equipment is sterile or disinfected before use.	All items of equipment are sprayed or wiped down with alcohol or another appropriate disinfectant immediately before being placed in the BSC or the isolator pass-through. Materials with secondary sterile packaging should be "peeled off" (not applicable if isolators) and placed in the BSC without coming into contact with hands or other non-sterile objects.
Preparation Techniques		
* 64	The preparation of cytotoxic medicines takes place on a impermeable-plastic-backed absorbent preparation mat in order to avoid contamination of the workbench.	Mats should be changed immediately a spill occurs and regularly during use; they should be discarded at the end of production.
65	During preparation, adequate precautions are applied to avoid confusion or mix-up of patients' treatment.	Only one patient's treatment is prepared at a time, and only one particular drug is on the workbench at a time. Preparation of a series of doses, i.e. a batch of the same drug at the same dose (fixed dose), can be performed simultaneously.
66	The operator compounds preparations by strictly following the operating instructions.	
67	The operator uses proper working techniques under a BSC to maintain product asepsis.	There should be no disturbances or interruptions in airflow, minimum work distances from the grills must be respected, benches should be tidy, clean/dirty areas must be separate, vial septums must be disinfected using an alcohol swab, exiting and entering the work area during compounding should be avoided.
*		

68	The operator uses proper working techniques to reduce the risks of chemical contamination or needle stick injuries or cuts.	The operator should for example: either use Luer-lock connections on needles and syringes to minimize the risk of separation in case of over pressurization or use a needless system or closed-system transfer devices; possibility to use a sterile swab when opening an ampoule, or at the injection port of a vial or infusion bag. A safety box should be available for needles and sharp waste. Evacuating residual air from syringes should be carried out carefully using a sterile swab to limit the risks of contamination.
* 69	The operator uses proper working techniques to prevent the build-up of pressure differentials between the inside and outside of cytotoxic vials.	E.g: air venting device fitted with a 0.2 micron hydrophobic filter; wide bore needles (18G/1.2 mm).
70	The operator uses a syringe size appropriate to the sample volume.	The syringe should not be less than one-third full, in order to ensure the precision of the volume measured.
71	I.V tubing is primed prior to adding the cytotoxic product in the infusion bag.	
72	Once filled, chemotherapy infusion bags are ready for immediate use, that is, with the infusion set or administration system already connected and the tubes primed with the dilution solvent. The air has already been evacuated from syringes.	The aim is to avoid risk of exposure to the cytotoxic for the nurse when starting the administration
Packaging and labeling		
* 73	There are packaging instructions for each different preparation	Primary packaging must be suitable for the dosage form and volume that it is intended to contain. Container/content interactions must be avoided.
* 74	The preparation is packed in adequate, sealed secondary packaging.	The use and characteristics of secondary packaging should be determined according to the risks of deterioration of the primary packaging until use, especially where there is a risk of breakage or leakage and is essential during transport of the preparation
*		

75	The final product's primary packaging is adequately and unambiguously labelled according to Best Practices and local regulation	For example the label should include: name and address of the pharmacy that produced the preparation; the patient's family name, given name, date of birth; name of ward, department or therapeutic facility ordering the product; names, quantities and qualities of all the cytostatics and other active substances; type and volume of carrier solution; method of administration; day of administration in the course of treatment; instructions for use; instructions for storage; time and date of production; expiry date; and other quality control information such as transport information (cold chain), batch number (or logbook register number).
Checking procedure		
		Checks should be performed either by visual inspection by another qualified person during the preparation; or using appropriate technology that directly, automatically records volumes on the container; or using weighing procedures with integrated balances and software that produce weighing tickets during the preparation process and for the final product; or by an analytical control on the final product. Whichever method is used, proof of the check must be recorded and attached to the production worksheet.
76	Identity and volume of the drugs used are double-checked by the operator and using a reconciliation method	
		The following factors should be cross-checked: patient information on the label must match the medical prescription (if nominative prescription); the medicine information on the label must match the medical prescription and the preparation protocol; the dilution solvent must be appropriate (nature, quantity and compatibility); the container must be adequate for its content; the completeness of labelling; the product's organoleptic properties (e.g. color, clarity, particle free); and finished pack integrity via a visual inspection.
77	No preparations are released and dispensed before the person in charge has reconciled and validated the final product in order to certify that the product fulfills the established specifications.	
*		Protocol specifications must include the following information: the cytotoxic medicine's name, pharmaceutical form and dosage; the types and names of the products to be used; types and names of the medical devices and equipment to be used; the proper preparation procedure; maximum permissible deviation from the value specified in the prescription; packaging and labelling types; information to appear on the label; information on shelf life; and information about special precautions to apply when handling the finished preparation.
78	Specific production protocols exist for each different cytotoxic medicine.	
*		

79	Production worksheets (describing the work done) are completed for each product prepared. This allows complete traceability at every step in preparation. Worksheets are stored for at least 1 year after the preparation's expiry date (or according to national regulations)	A standardized worksheet should be developed and it should record at least the following information: the preparation's name and, where appropriate, the name of the person who cross-checked its production; the batch number being manufactured; the date and time of the preparation; the operator's name; the names, batch numbers and expiry dates of the different products used (solvents and cytotoxic medicines); the theoretical and actual quantities of each starting product used; the in-process checking performed and the results obtained; the final quantity of product obtained; the type of packaging and number of units packaged, a specimen product label; the expiry date of the final product; notes on any special problems or deviations from normal preparation, including details; a signed authorization for any deviation from the master formula; and signature of the person responsible of production.
* 80	Each preparation is recorded on a preparation logbook	The logbook can also be electronically available
Maintenance		
* 81	Equipment used to prepare cytotoxic medicines and air-treatment systems are serviced according to a planned maintenance schedule.	Each intervention during a service must be recorded on a maintenance log, e.g. replacement of HEPA filters, equipment calibration, etc.
* 82	Surrounding conditions (microbiological contamination, particulate contamination) are regularly monitored according to a planned monitoring programme.	if cleanroom
Non sterile preparation		
* 83	All activities likely to result in particle generation, for example, crushing tablets, mixing or filling capsules, should be performed in a Biological Safety Cabinet (BSC)	Whenever possible, sterile and non-sterile preparation activities should not be performed within the same BSC.
ADMINISTRATION		
Management and organisation		
* 84	Written administration and surveillance protocols exist and are updated for every chemotherapy available in the facility.	Protocols should include: products' generic names and their different dosages; administration route (if necessary precision of medical device to be used) with the duration and chronology of administration of cytotoxic products and supporting medication; surveillance instructions; and what actions to take in case of complications.
85	Only trained, entitled personnel are permitted to administer cytotoxic medicines to patients.	See chapter on "Personnel".

Hygiene and safety measures		
* 86	Access to the chemotherapy administration area is limited to healthcare personnel, patients and a limited number of relatives, if essential; the latter are informed of the potential risks.	Children and pregnant and breastfeeding women should avoid the chemotherapy administration area.
87	Healthcare personnel correctly apply hand hygiene measures during treatments and respect the rules for ensuring asepsis.	Hand hygiene (washing and disinfection) should be compliant with WHO recommendations, including no jewelry.
* 88	When administering parenteral cytotoxic medicines, staff wears appropriate personal protective equipment (PPE) and removes them before leaving the chemotherapy administration area.	PPE should include trousers, a long-sleeved gown and gloves. If there is a risk of splashing or an aerosol, protective googles and a mask are also recommended.
89	If a direct contact occurs between a cytotoxic product and gloves or a gown, they are immediately changed and hands are thoroughly rinse with water washed.	Some experts recommend that soap or disinfectant should not be used as they can alter the skin's protective barrier. Gloves should also be changed between treating each patient.
90	After administration of the chemotherapy, staff wash their hands with soap and water.	
Documentation		
* 91	Traceability of chemotherapy administrations is ensured by treatment administration sheets developed based on protocols. All the fields on the sheet are completed and signed by the personnel who administer treatment.	The use of standardized/pre-printed or electronic forms are recommended. These documents should include the products administered (generic name), their dosage, the time, chronology and duration of administration, surveillance and clinical parameters monitored and the signature of the administering personnel.
92	Before administering chemotherapy, the personnel verify the accuracy of information on the prepared product against the administration protocol. The verification is documented.	A check-list should be used to verify: the patient's identity; the drug name, dosage and volume; route of administration; date of administration; information regarding product conservation; expiry date until end of administration; and the medicine's appearance and physical integrity.
93	The personnel question the patient to verify that his/her identity (given name, family name, date of birth) matches the administration plan and the information written on the product.	A checklist should be used to verify and document the control.
Work practices		

94	Personnel administer cytotoxic medicines safely by using work practices that reduce the risk of exposure and contamination dependent on the different routes of administration: intravenous (infusion or direct injection), subcutaneous, intramuscular, vesical, intraperitoneal, intrathecal, aerosolization, oral or topical.	Administration techniques should use infusion sets and pumps with Luer-lock fittings, or needleless administration system. A disposable plastic-backed absorbent pad should be placed on the work surface or the patient's arm during administration to absorb any leakage. Sterile gauze should be placed around any IV push or connection sites before injection and during removal in order to contain any possible leakage.
* 95	Priming IV sets or evacuating air from syringes containing cytotoxic medicines is not carried out in the chemotherapy administration area but in the preparation room.	Alternative methods (e.g retro priming) are possible as far as the risk of exposure of the healthcare personnel is minimized during the administration
* 96	The infusion is safely removed from the patient and the entire infusion line discarded intact into the cytotoxic waste container. Needles are never disconnected from syringes; they are disposed of together in a sharp container for cytotoxic medicines.	This is done to avoid the risk of aerosolization
97	Crushing cytotoxic tablets or opening capsules in an open mortar should be avoided.	This is done to avoid the risk of generating airborne particles of the products. The extemporaneous preparation of oral cytotoxic drugs should be performed with appropriate personal protective equipment associated with containment measures and under a collective protective equipment.
INCIDENT MANAGEMENT		
Surface contamination		
98	There is a standard operating procedure in place in the facility regarding cleaning up spills or breakages involving cytotoxic medicines that is known by every staff who handle cytotoxics.	Any accidental leak or spillages must be contained (the zone must be identified and marked out) and cleaned up immediately by trained staff wearing appropriate personal protective equipment.
* 99	All staff members who might be involved in handling cytotoxic medicines have received training appropriate to their roles regarding the procedures and measures to be taken in case of a spill or a breakage.	Staff should undergo training and simulation exercises.
100	Fully equipped spill kits are readily available wherever cytotoxic medicines are handled (in receipt, storage, transport, production and reconstitution, and administration zones).	The spill kits' locations are known, signposted and easily accessible if needed.

101	Clearly signposted spill kits contain all the materials needed to clean up cytotoxic medicine spills.	Content: instructions for use of the kit, warning material for identifying and marking out the contaminated area, an impermeable protective gown, boots or overshoes, goggles, P3-type respirator mask, at least 2 pairs of appropriate gloves, plastic dustpan and broom or squeegees, cotton wool and absorbent swabs, liquid soap and alcohol, absorbent granules for liquids, containers for sharp waste, clearly labeled cytotoxic waste containers, spill report form.
102	Used materials are directly discarded according to the waste management procedure.	If economic issues, some objects could be cleaned and decontaminated according to an adequate procedure (e.g. safety glasses, shovel etc.)
* 103	Spill kits are replaced as soon as possible in case of future incidents.	Ideally, a replacement kit should be available in advance.
Staff contamination		
104	There is an established standard operating procedure for managing accidental staff chemical contamination. It is displayed in areas where cytotoxic medicines are compounded or administered.	All contaminated clothing should be immediately removed and appropriately discarded or laundered. Contaminated areas of skin should be immediately thoroughly rinsed with water. Medical attention should be sought rapidly.
105	The equipment and materials for managing the emergency treatment for chemical contaminated staff are located in areas where cytotoxic medicines are prepared, administered	Close proximity of an emergency shower or water supply. For eyes, a sterile isotonic solution (0.9% sodium chloride) is recommended
106	All staff members involved in handling cytotoxic medicines have received appropriate training according to their tasks. They know the procedures and measures to take in case of staff contamination.	
Extravasation		
107	There is an established standard operating procedure for managing extravasation of cytotoxic medicines	Treatment protocols for managing extravasations might differ depending on the agents: "non vesicant", "irritant" and "vesicant" agents.
* 108	Nursing, medical and pharmacy staff are trained to apply preventive measures and to manage and follow-up after extravasation.	Any extravasation must be documented on a monitoring form.
* 109	An emergency kit for dealing with extravasation is readily available in areas where chemotherapies are administered.	The kit must contain written instructions on how to treat affected areas and how to use the specific antidotes contained in it.
Quality assurance		
*		

110	All incidents involving cytotoxic medicines are reported, monitored, analyzed, recorded and any corrective measures applied are followed up on and evaluated.	All incidents must be reported on an incident report form. Its causes should be analyzed in order to avoid future repetition.
WASTE MANAGEMENT		
Waste disposal		
111	The facility's cytotoxic waste disposal is compliant with current local regulations and is described in a written procedure.	Some countries differentiate between slightly contaminated and heavily contaminated waste.
* 112	Cytotoxic waste disposal is handled separately. Specific segregation, packaging, collection, transport, storage exist to protect staff, patients and the environment from contamination.	Cytotoxic waste is considered to be all those materials which have come into contact with cytotoxic drugs during the processes of reconstitution and administration. This should include syringes, needles, empty or partially used vials, gloves, single-use personal protective equipment and materials used to clean-up of cytotoxic spills. In addition, cytotoxic drugs which have expired, or which must be destroyed for any other reason, are also treated as cytotoxic waste. Some regulations differentiate between slightly contaminated (traces of cytotoxics) and heavily contaminated (leftovers, expired vials, etc) waste
113	Suitable, clearly labelled cytotoxic waste containers are available in all areas of the facility where cytotoxic medicines are handled.	Cytotoxic waste containers should be of a specific colour and labelled with a danger symbol at all times. Thick, leak-proof plastic bags placed inside a covered waste container should be used for collection of cytotoxic waste solely. The lid should always be closed, except when disposing waste.
114	Needles and syringes are disposed in puncture-resistant containers. Syringes and needles are not separated after the injection but discarded together	Needles and syringes are disposed in puncture-resistant containers. Syringes and needles are not separated after the injection but discarded together
* 115	Only trained personnel handle cytotoxic waste containers; they wear appropriate personal protective equipment.	a minima :gloves
116	The facility's storage areas for containers of cytotoxic waste awaiting destruction remain locked and are clearly identified. Storage areas are sheltered, protected from bad weather, cool, have adequate ventilation and are far away from patients and personnel areas in order to minimize the risk of exposure	Cytotoxic waste should only be stored at the facility for a short duration before being transferred for final destruction.
* 117	Cytotoxic waste is incinerated at 1200°C	Depending on national regulations, waste with low levels of chemical contamination can follow different types of disposal
Patients'excreta		

* 118	Trained personnel handle the excreta (vomit, urine, feces, blood, or puncture liquid) of patients undergoing chemotherapy (for at least 7 days after treatment), they wear the appropriate personal protective equipment, including for cleaning toilets.	Gown and gloves and if necessary a mask and protective boots. For the management of excreta at home, information should be provided to the patients' family and caregivers (see chapter patient information)
* 119	Contaminated linen should be placed in a bag clearly identified and forwarded to the laundry	See chapter on "Cleaning".
120	Mattresses and pillows are protected with plastic covers and wiped-down between patients.	
CLEANING		
Management and organization		
* 121	Cleaning and maintenance tasks are only carried out by trained personnel.	Cleaning staff have received appropriate training on cytotoxic medicines and safety measures they should apply.
* 122	Cleaning activities are conducted in accordance with the established procedure and documented in cleaning logs.	Cleaning and disinfection procedures provide detailed information on which areas require cleaning (logistics, preparation and administration rooms) cleaning frequency (e.g. daily, weekly), and the products and cleaning techniques to be used. They should be reviewed regularly and updated when required.
Cleaning practices		
* 123	Cleaning staff wears the personal protective equipment appropriate to the various tasks to be performed.	The level of personal protection differs according to the type of area to be cleaned. For instance, cleaning of the preparation room requires the same PPE as for the preparation activities. For other areas, staff should at least wear gloves that are chemically resistant to cleaning agents, as well as a splash proof gown. (note: for cleaning up accidental spills, see chapter on "Incidents")
124	Single-use, disposable cleaning equipment is used preferably. Should this be impossible, the equipment used must be used exclusively for cleaning and disinfecting of cytotoxic areas.	Cleaning materials (e.g. wipes, mops and disinfectants) for use in the clean room should be made of materials that generate low amounts of particles.
125	Cleaning is only carried out using moistened materials.	No vacuum cleaners, no dry sweeping.
126	Staff washes their hands thoroughly with soap immediately after cleaning activities.	

127	The cleanroom is cleaned in an appropriate manner.	Cleaning should proceed from the cleanest area in the room to the dirtiest. This should imply a cleaning workflow from the ceiling to the floor, moving outwards from the ventilation tool to the exit.
128	The inside of the biosafety cabinet or the isolator is cleaned by the preparation operators	In addition to daily cleaning of the workbench before and after a work session, a comprehensive cleaning process (included the lower part of the BSC, under the workbench) is performed weekly. Inside the BSC, cleaning should start from the top (upstream), close to the HEPA filter, to move down, starting with the rear wall of the BSC, its sides and lastly, the work surface (downstream). The cleaner should be very careful not to wet HEPA filters. If working with isolators, independently of the cleaning at each working session, they should be thoroughly cleaned and regularly sterilized according to a validated frequency (daily, weekly or monthly) depending on the level of activity and the microbiological monitoring of the environment
Laundry		
129	Contaminated, reusable protective clothing (gowns) and linen soiled with patient excreta are placed in clearly labelled laundry bags and are washed separately from other clothing.	Laundry should start with a cold prewash cycle and then continue using the normal washing process
* 130	Laundry staff and patient relatives have received instructions and know the procedure on how to handle contaminated linen and clothing and wear adequate personal protective equipment	resistant gloves, gown with long sleeves
PATIENT COUNSELING		
* 131	The patient's informed consent for chemotherapy treatment is obtained	Before the initiation of a chemotherapy treatment, patient is given information about the diagnosis, the treatment and its goals, as well as the potential risks and necessary follow-up. The consent process follows appropriate professional and legal regulations.

132	Patients and/or caregivers are taught about the treatment including possible side effects and how to manage them, the risks of possible drug interactions and the precautionary measures to take with regard to a patient's excreta. For oral chemotherapy at home, information related to storage, handling, administration, and planning for missed doses and disposal are also provided.	Patient information materials are appropriate for the patient's and the caregiver's levels of understanding and literacy.
133	Patients and/or their caregivers are informed about warning signs and know who to contact and how in case of an emergency or other specific circumstances.	
* 134	Any patient counseling session is documented and added to the patient's file.	

essential Very important Desirable * =No consensus (<75% of agreement on the level of priority)