tropEd Masters Programme in International Health

Safe handling of cytotoxic drugs and related waste: Development of a self-assessment tool adapted to resource-constraint settings

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EXECUTIVE SUMMARY

Due to their inherent toxicity, high precautions should be used when handling cytotoxic medicines to ensure patient safety and to prevent occupational exposure and environmental contamination. Safe handling program should be implemented wherever cytotoxic drugs are transported, received, stored, prepared, administered and disposed.
To date, persistent weaknesses exist in international and national cancer control programs regarding aspects related to safe handling of cytotoxic medicines. Unsafe handling practices have been pointed out in several studies, particularly in countries where access and use of those medicines have recently increased. With the rising burden of cancer and the increased use of chemotherapy treatment, raising awareness on the importance of safe handling of cytotoxic drugs in LMIC has therefore become a priority.

This master thesis aimed to develop a self-assessment tool for healthcare services in low and middle-income countries (LMIC) in order to support the implementation of safe handling practices and promote continuous quality improvement regarding cytotoxic drugs management in LMIC. Additionally, a prioritization of the items was intended in order to guide and assist resource-constraint settings in establishing priorities and design their action plan with short, middle and long term objectives.

After pre-selecting quality and safety items from various recognized references on safe handling practices, a two-round online Delphi survey has been conducted to validate our self-assessment tool.

This study resulted in the development of a self-assessment tool covering safe handling practices of the entire cytotoxic medicines process within a healthcare facility (from receiving the drugs to their administration to patients and final disposal of related waste). The validation of 134 items by 28 international pharmaceutical experts in oncology practice from 13 high and low and middle income countries ensures the quality and exhaustiveness of the tool. The high participation rate of the experts underlined their interest and thus the relevance of this project. Even if the prioritization of some items has not reached the expected consensus, we hope that the indicated priority will guide them in defining their action plan and in resource allocation.

A future evaluation of the applicability, appropriateness and usefulness of this assessment tool in various health facilities of resource-constraint settings will complete the validation of this self assessment tool and participate in enhancing future acceptability and use of this tool in LMIC.

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ABBREVIATIONS

ASHP	American Society of Health-System Pharmacists
CMR	Carcinogenic, mutagenic, reprotoxic
DALYs	Disability-adjusted life years
ESOP	European Society of Oncology Pharmacists
GMP	Good Manufacturing Practices
GTF.CCC	Global Task Force on Expanded Access to Cancer and Control
HEPA	High-Efficiency Particulate Air
IARC	International Agency for Research on Cancer
IHI	Institute for Healthcare Improvement
INCTR	International Network for Cancer Treatment and Research
ISMP	Institute for Safe Medication Practices
ISOPP	International Society of Oncology Pharmacy Practitioners
LEM	List of Essential Medicines
LMIC	Low and middle income countries
MoH	Ministry of Health
NCCP	National Cancer Control Programme
NCDs	Non Communicable Diseases
NIOSH	National Institute for Occupational Safety and Health
OECI	Organization of European Cancer Institute
OSHA	Occupational Safety and Health Administration
PDSA	“Plan, Do, Study Act”
PPE	Personal Protective Equipment
SDGs	Sustainable Development Goals
UICC	Union for International Cancer Control
WHO	World Health Organization

PREAMBULE

Safe handling of cytotoxic drugs is an extremely important aspect of cancer management, since these drugs have been identified as hazardous drugs. Safe handling program should be implemented wherever cytotoxic drugs are transported, received, stored, prepared, administered and disposed (1).

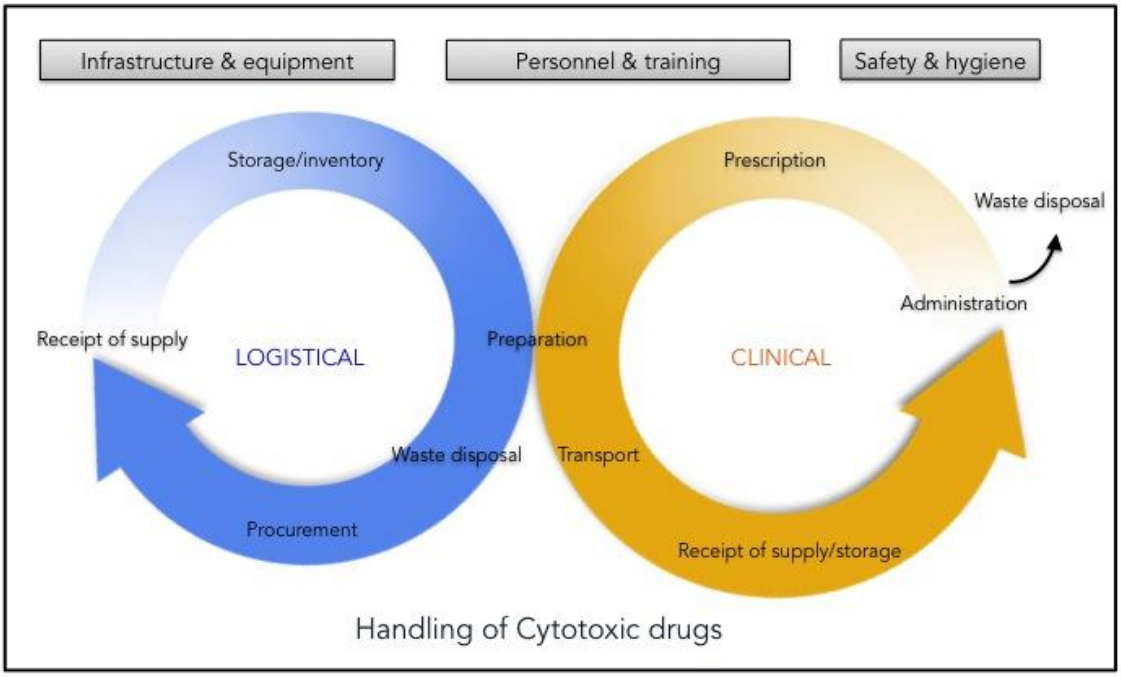

Figure 1: Illustration of cytotoxic drugs process

Due to their inherent toxicity, high precautions should be used to ensure patients and staff safety and to prevent environmental contamination (2). Numerous groups of professional associations have developed guidelines for safe handling based on scientific evidence or best practices (1, 3-5). Some studies conducted in developing countries showed low compliance to safe handling practices guidelines (6-8).

In the last years, with the increasing burden of cancer in low and middle income countries (LMIC), many international organizations or agencies such as the Union for International Cancer Control (UICC), the International Network for Cancer Treatment and Research (INCTR) or the Global Task Force on Expanded Access to Cancer and Control (GTF.CCC), have been active to improve cancer control program in collaboration with the World Health Organization (WHO). Together, they advocate for

making cancer a global health priority that needs to be tackle in the post-2015 development agenda (9-11).

As a part of cancer control programs, substantial efforts are being made for improving diagnosis and access to cancer treatments in developing countries, notably in expanding access to affordable cytotoxic drugs for chemotherapies. Handling and use of those drugs are meant to increase in the coming years and therefore beyond patients' safety, risk of occupational exposure and environmental contamination should become a growing concern for the governments, especially in resource-poor settings where inadequate infrastructures and low capacities are prevailing. However persistent weaknesses in cancer control programs still exist regarding the aspect of safe handling of the cytotoxic drugs (2).

1. INTRODUCTION

1.1 CANCER

1.1.1 Global burden

Cancer is a group of noncommunicable diseases (NCDs) defined as « *the uncontrolled growth and spread of cells that may affect almost any tissue of the body* » (WHO) (12).

Cancer represents a leading cause of mortality and morbidity worldwide after cardiovascular diseases, killing more people than malaria, HIV/AIDS and tuberculosis combined (13-15). The GLOBOCAN project estimated globally 14.1 million new cancer cases, 8.2 million cancer deaths and 32.6 million people living with cancer (within 5 years of diagnosis) in 2012 (16).
Current estimates of global cancer burden report that cancer caused 208.3 million Disability-Adjusted Life Years (DALYs) in 2015, of which 96% came from Years of Life Lost (LLs) and 4% came from Years Lived with Disability (YLDs) (17, 18).

Population growth and ageing are major contributors to this rising burden. More than 20 million new cancer cases and 13 million cancer deaths are expected annually by 2030 (14, 16).
Although cancer can affect anyone, environmental and behavioural risks factors have been identified to relate to the development of certain types of tumors, such as tobacco and alcohol use, lack of physical activity, overweight and obesity, unhealthy diet with low fruit and vegetable intake, chronic infections (e.g., hepatitis B, HIV/AIDS, human papillomavirus, helminthes infections, etc.), radiation, pollution of air, water and soil and occupational exposure (e.g., heavy metals, silica, polycyclic aromatic hydrocarbons). Acting on these key risks could prevent more than 30% of cancer deaths (12-14).

Distribution and burden of cancer varies across world regions and socio-economic groups, showing regional pattern in types of tumors. Variation of the age structure of the population, genetic, prevalence of risks factors, availability and screening use of diagnostic tests as well as access and quality of treatment are some factors participating in these geographical differences. Understanding risks factors

and their relations with cancer pattern is of utmost importance when designing tailored and effective cancer control strategies (13, 14, 16).

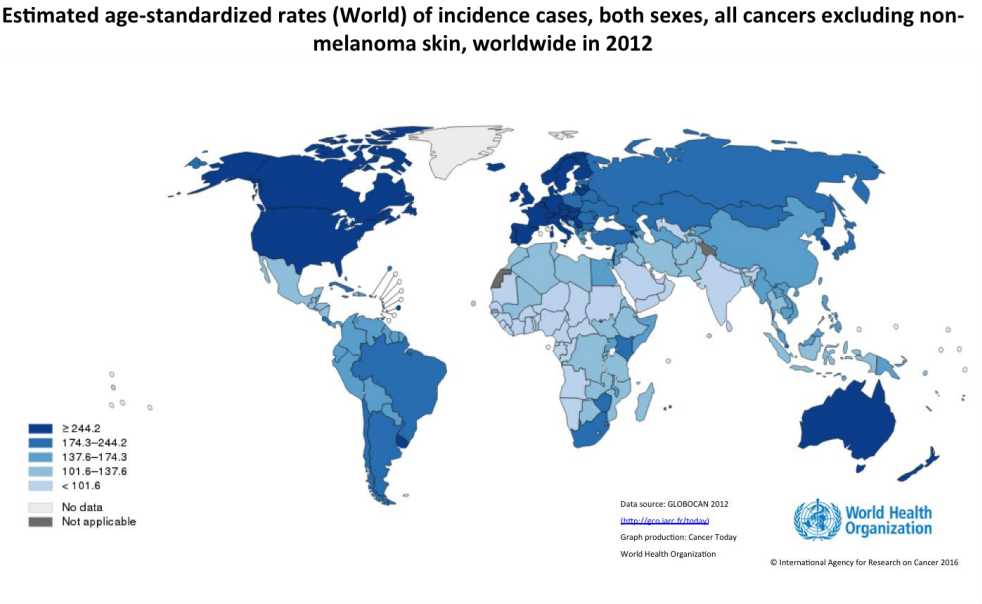

Figure 2: GLOBOCAN estimated age-standardized cancer incidence and mortality rates (per 100 000) worldwide in 2012 for both sexes, excluding non-melanoma skin cancer IARC (19)

For a long time overshadowed by HIV/AIDS, tuberculosis and malaria, cancer has been now recognized as global public health problem in low and middle income countries and not only a concern of wealthy and developed countries anymore (20, 21). With 57% of the new cancers, 65% of the cancer deaths and 48% of the 5-year prevalent cancer cases in 2012, developing countries are facing a new burden that is increasing rapidly. The International Agency for Research on Cancer (IARC) predicted that by 2030, 60-70% of the new cancer cases will occur in LMIC representing about 15 million of new cases (16).

Demographic transition and change in lifestyle in LMIC with the adoption of unhealthy western lifestyles such as smoking, physical inactivity and consumption of calorie-dense food are some of the main contributing factors leading to this rising burden. In addition, LMIC continue to be disproportionately affected by cancers related to infectious agents or exposure to toxic substances (13, 17, 20, 22).

Although, LMIC 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 (2, 23). The long-term disabilities and premature deaths caused by cancer induce a high financial and social burden on families and health system. The World Cancer Report 2014 mentioned, *"noncommunicable diseases are recognized as a barrier to human development"*. Therefore, the economic impact and human development challenge resulting from this newly recognized burden for LMIC stressed the urge to take action and implement appropriate national cancer control programs in LMIC (2, 13, 24).

In 2013, the World Health Organization, other UN agencies and partners collaborated to implement the Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013-2020 aiming at, among others, reducing premature deaths from cancers and implementing action for cancer prevention (12). In 2015, cancer, among others noncommunicable diseases, has been integrated in the development agenda with the 3rd Sustainable Development Goal (SDG) and its target "*By 2030, reduce by one-third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being"* (25).

1.1.2 Cancer control strategies

In response to the 58th World Health Assembly in 2005 and the approval of a resolution on cancer prevention and control by the WHO Member States, WHO developed a practical guide to support and reinforce the implementation of effective cancer programs (26).

WHO guide for comprehensive cancer control encompasses four essential components: prevention, early detection, diagnosis and treatment and palliative care (figure 3) (27).

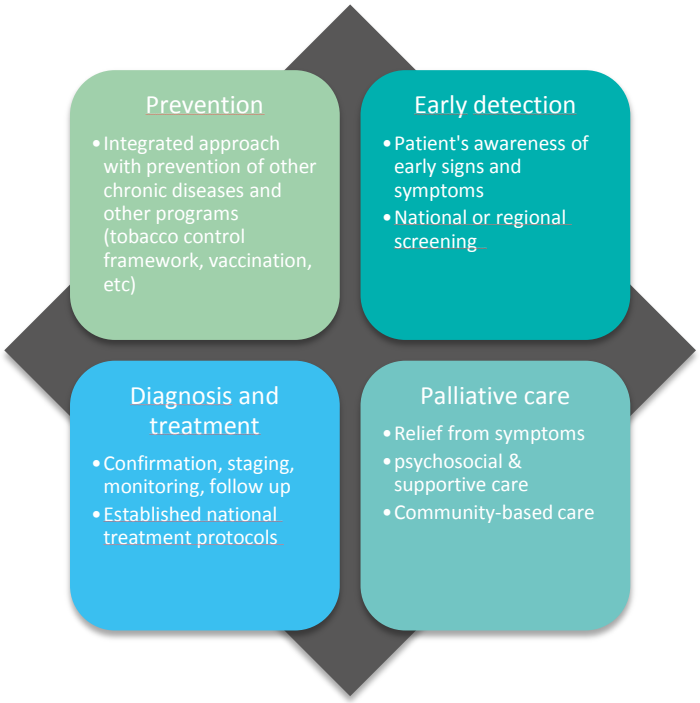

Figure 3: Core components of WHO comprehensive cancer control program[27]

In 2007, the London Declaration gave a new call for action to raise awareness on the importance of delivering comprehensive cancer care in LMIC especially in Africa. The collaboration and synergy among all the partners involved in the fight against cancer, such as research institutions, NGOs, governments, civil society, pharmaceutical industry, etc. was strongly encouraged (24).

Adequate cancer surveillance and establishment of national cancer registries recording relevant data to assess and monitor cancer burden (e.g., incidence, prevalence, mortality, etc.) is a crucial step in order to plan effective and sustainable control programs (24, 28).

Training and research in oncology are transversal and fundamental aspects of implementing cancer control program that should not be underestimated. Lack of trained and competent staff in any component of a comprehensive program is a part of the barriers to effective programs (2, 20). Researches on cost-effectiveness cancer intervention in LMIC are necessary to define sustainable and resource-level-appropriate cancer control (28, 29).

Cancer treatments encompass a variety of interventions, including surgery, radiotherapy, hormonotherapy and chemotherapy. Treatment programs need to be adapted to the context and the priority of LMIC. Human resources,

infrastructures and finances should be considered to ensure feasibility and sustainability (20, 23, 27, 28).

Chemotherapy regimen should be based on cost-effective medicines. These past years, substantial efforts have been made to improve access to affordable chemotherapy treatments to tackle the rising burden of cancer in LMIC.

In 2015, about 16 new cytotoxic medicines have been added in the updated versions of the WHO essential medicines lists (19th edition EML and 5th edition EML for Children) (30).

However, most of these medicines require extreme precautions when handled and used as they have been identified as hazardous (1). Yet, safe handling aspects regarding related to these medicines (storage, preparation, administration, waste disposal, etc.) and medicines safety monitoring are often neglected in national cancer control programs (2).

1.2 RISKS ASSOCIATED WITH CYTOTOXIC DRUGS

1.2.1 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 (31). Although the effectiveness and the benefit of chemotherapy treatment have been acknowledged in numerous cancer types, cytotoxic drugs have been recognized as hazardous substances due to their potential mutagenic, carcinogenic and reproductive toxicity properties (32).

Intrinsic toxic properties differ according to the substances. Several carcinogenic risk classifications of substances exist, that does not only consider therapeutic agents but also chemical agents. Most well-known are the classifications from the International Agency for Research on Cancer (IARC) and the European Union (33, 34).

The IARC classification of substances is based on "*the strength of the evidence of carcinogenicity arising from human and experimental animal data*" (see table 1).

Table 1: IARC carcinogenic risks classification

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 takes into account 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)

Effects / Hazard Class	Categories	Category definitions
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: carcinogenicity, teratogenicity or other developmental toxicity, reproductive toxicity, organ toxicity at low doses, genotoxicity, structure and toxicity profiles of new drugs that mimic existing drugs determined hazardous by the previous criteria (35).

Currently more than 30 medicines are included in the complementary lists of the latest versions of the WHO Model lists of essential medicines (36, 37). 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 19th WHO Model List of Essential Medicines (LEM) and 5th Model list of Essential Medicines for Children (April 2015) (36, 37)

LEM	Cytotoxic medicines		NIOSH list[35]	IARC class[33]	CMR class.
A +C	Asparaginase			n.a	CMR
A	Bendamustine		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	C?MR
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	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	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	Hydroxycarbamide	capsule, 200mg, 250mg, 300mg, 400mg, 500mg; tablet, 1g	yes	3	C ?MR
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	C ?MR
A	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+C	Mercaptopurin	tablets: 50mg	yes	3	CMR
A+C	Mesna	injection, 100mg/mL in 4-mL and 10-mL ampoules; tablet, 400mg, 600mg	no	n.a	
A+C	Methotrexate	tablet, 2.5mg (as sodium salt); powder for injection, 50mg (as sodium salt) in vial	yes	3	CMR
A	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	Paclitaxel	powder for injection 6 mg/mL	yes	n.a	CMR
A	Procarbazine	capsule, 50mg (as hydrochloride)	yes	2A	?
A	Rituximab	Injection 100mg/10mL in 10mL vial ; 500mg/50mL in 50 mL vial	no	n.a	
A+C	Tioguanine	solid oral doage form 40 mg	yes	n.a	CMR
A	Tratuzumab	powder for injection 60mg,150mg, 440 mg in vial	no	n.a	C ?M
A+C	Vinblastine	powder for injection, 10mg (sulfate) in vial	yes	3	CMR
A+C	Vincristine	powder for injection, 1mg, 5mg (sulfate) in vial	yes	3	CMR
A	Vinorelbine	injection 10mg/mL in 1 mL vial, 50mg/5mL in 5 mL vial	yes	n.a	MR

1.2.2 Risks for patients

Cytotoxic drugs are highly beneficial therapeutic medicines but extreme care should be taken due to their narrow therapeutic index and high toxicity. Their activity is often not selective and does not differentiate between cancer cells and normal cells. During chemotherapy, patients should be closely monitored for any side effects or adverse events related to the treatment.

Principal reported effects in treated patients include pain, nausea and vomiting, alopecia, cardiotoxicity, immunotoxicity, hematopoietic toxicity, renal and hepatic toxicity, neurotoxicity, dermal toxicity, etc. (38)

Other aggravating factors in chemotherapy context can increase the risk for the patients such as patient aspects (immunocompromized and weak from the disease) or high-risk administration route (intravenous or intrathecal) prone to extravasations and infections (3).

For all these reasons, extreme precautions should be taken when prescribing, preparing or administering the drugs. Overdosage can increase morbidity and in worst cases lead to fatal events. Medication errors with cancer medicines are not rare. For example, an American retrospective study by Philips and colleagues reported in 2001 that cytotoxic drugs were the second cause of death among mortalities caused by medications errors (39).

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, significant training of the staff involved in the chemotherapy treatment should be part of any risk management program (1, 3)

1.2.3 Risks for the personnel

Beyond patients' 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 seventies (3, 40).

Falck and colleagues published first evidences of occupational exposure in 1979, by reporting mutagenic substances in the urine of nurses who handled cytotoxic medicines (41) . 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 (42), some direct adverse health effects, such as skin reaction, hair loss and alteration of normal blood cell counts, have been observed on staffs where insufficient preventions measures have been applied (5).
Reproductive toxicity has also been associated to occupational exposure. Several studies reported increased fetal loss, congenital malformations, low birth weight and stillbirths although statistically significant differences were only found for spontaneous abortion in nurses who handled cytotoxic medicines (42-44).

Occupational exposure can occur through direct skin contact (e.g., splashing, spillage), inhalation of aerosols (e.g., overpressurized vials, cleaning spill), needle stick injuries or ingestion (e.g., contaminated hands-to-mouth contact). Secondary source 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 (38, 45).

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 (1, 3, 46).
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 transport, storage, cleaning or disposal of cytotoxic drugs and related waste (46).

The risks and potential health hazards assessment depend on a combination of factors as presented in table 4.

Table 4: Summary of the risks related to handling cytotoxic medicines (40, 45, 47)

RISKS ASSESSMENT		COMMENTS
Toxicity	Carcinogenicity	Chronic toxicity
	Mutagenicity	
	Reproductive toxicity	
	Irritation	Acute toxicity
	Hypersentivity	
	Others (nausea, light-headedness)	
Route of Exposure	Dermal absorption	
	Inhalation	
	Ingestion	
Galenical form	Liquid	
	Lyophilized powders	
	Tablets, capsules	
	Aerosols	
Handling activities	Handling drug-contaminated vials	Group of workers potentially exposed: Pharmaceutical staff, stock keepers, nursing personnel, housekeeping personnel, transporters, waste disposal personnel, maintenance personnel
	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	
Level of exposure	Duration of contact	
	Frequency of exposure	
	Product chemical and physical properties	
	Applied protective measures	
Protective Measures	Engineering controls	E.g., biosafety cabinet
	Organisational measures/administrative controls	E.g., work practices, training programs
	Personal protective equipment	E.g., gloves, masks, gown

1.2.4 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 (48).

A systematic review revealed that health care waste management remain a major challenge in numerous LMIC (49). Therefore particular attention should be given to cytotoxic wastes 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 required special and very costly incinerator (48).

Handling of cytotoxic medicines is a high-risk procedure with potential dramatic consequences on human and environmental health.

These potential health hazards required to be fully addressed as the number of patient load and use of chemotherapy will increase in the coming years in LMIC. A series of measures tackling these safety issues should be part of every Cancer Control Program. A comprehensive risk assessment should be performed in every setting where cytotoxic medicines are handled in order to design an appropriate risk management strategy including the implementation of adequate safe handling practices (1).

1.3 SAFE PRACTICES FOR HANDLING CYTOTOXIC DRUGS AND RELATED WASTE

1.3.1 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 (50, 51).

Since the eighties, numerous professional organizations or government agencies have published updated documents based on scientific evidences or best practices (40).

The purpose of these documents may differ from one another (e.g., guidelines, national regulations, document from insurance companies) and their orientation and level of details presented vary as well. Although they all share the same principles, i.e., safe handling of cytotoxic/hazardous drugs, some documents (e.g., from insurances companies or Occupational Safety and Health Administration) are exclusively oriented toward workers protection and their recommendations aim to minimize the risk of occupational exposure only (5, 46, 52). On other hands, 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 different aspects related to safe handling including Good Manufacturing Practices (GMP) principles

(especially for parenteral cytotoxic drugs) to ensure the quality of the product for patient safety and to protect the environment from contamination (3, 53, 54). 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 the patients receiving chemotherapy (55).

In 2013, The Pan American Health Organization (PAHO) and their 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 (56). 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 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” (48, 57).
Although the WHO documents did not present new information, they might reinforce the message that safe handling practice should be implemented in any place where cytotoxic medicines were handled and used even in limited-resource settings.

Indeed promoting safe handling to prevent hazards associated to cytotoxic drugs is not only based on expensive engineering solutions but relies a combination of 3 different levels of preventive measures and hazard controls (3, 5, 56):

- Engineering measures:

  Engineering solutions is often considered as the first level of preventive measure to implement in order to reduce the amount of contamination. For instance, preparation of chemotherapy in a separate dedicated area and using special ventilation tools is recommended. A biosafety cabinet with vertical laminar airflow or an isolator, both filtering and extracting the air through High-Efficiency Particulate Air (HEPA) filters, limits or prevents the contact between the operator and the hazardous substance.

Other devices can also be used throughout the cytotoxic process in order to increase safety (e.g., needless systems, closed-system devices, etc.).

However, in limited-resource settings this type of costly equipment might represent a real challenge.

- Administrative and organizational measures:

  The implementation of policies and detailed procedures on every aspect related to safe handling of cytotoxic drugs are essential to reduce the number of person exposed, the duration of exposure and ensure standardized and safe working practices.

  Regular training, supervision and assessment of the different categories of staff involved in the cytotoxic process participate in the respect and the correct application of the procedures.

  Importantly, all established policies and procedure should be regularly revised and updated to be in line with any scientific, regulative or local context evolution.

- Personal protective equipment:

  Personal protective equipment is the last level of preventive measures. The type of personal protective equipment (PPE) recommended will depend on the task performed, the working environment and on the first two levels of preventive measures implemented.

  PPE includes, among others, the appropriate use of protective gloves, gowns respiratory protection, eyes and face protection.

1.3.2 Handling practices in LMIC

While research on safe handling practices in cancer care delivery are still limited in LMIC, published studies highlighted unsafe practices regarding cytotoxic drugs handling (6-8). The main reasons mentioned were inappropriate infrastructure, multitasking and work pressure, insufficient knowledge and improper work practices due to lack of training, lack of awareness and wrong beliefs. (6, 8, 58, 59).

In some resource-constraint settings, handling cytotoxic medicines has not yet been acknowledged to be dissimilar to other drugs. *Strother and colleagues (2012)* reported that in many LMIC, oncology practice environment did no differ from cancer care facilities of high-income countries during the eighties, prior consideration of the risks and the development of safety guidelines and regulations (60).

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 (7, 58, 59). 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 (61).

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 LMIC 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 (58, 60, 62).

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-constraint setting (60).
Based on lessons learnt from high-income countries, the AMPATH-Oncology Pharmacy Service consisted in three main components: training activities, building and reorganization of premises, development and implementation of policies and procedures in order to ensure safe handling practices and increase drug availability and security.
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.

More recently, *Vaz da Conceiçao and colleagues (2015)* described a similar experience in Angola, with the establishment of oncology pharmacy units in three health facilities in collaboration with the Institute of Oncology in Porto, Portugal (62). A preliminary self-assessment of the situation was performed in the three hospitals using a checklist developed by the authors “The Cancer Units Assessment Checklist for low and middle income African Countries”. The usefulness and feasibility of this checklist was previously evaluated and described in a preliminary report (63).
The situation analysis and the development of an action plan were then completed by recommendations of external auditors.

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. The study was conducted in 15 selected wards of a General Hospital in Malaysia treating about 1500 chemotherapy patients annually (58). Ninety-six nurses were enrolled in this prospective interventional study. Before and after the intervention, nurses’ knowledge and attitude were evaluated by a self-administered questionnaire and assessment of practices was conducted by a pharmacist using a self–constructed performance checklist. The pharmacy-based intervention encompassed training sessions, handling workshop, cytotoxic drugs reconstitution in the hospital pharmacy using closed-system transfer device and implementation of a new cytotoxic drugs handling policy in the hospital.

These three low and middle-income countries experiences 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. Support from the hospital authorities and/or the Ministry of Health with policies and procedures that stress on safety measures to handle cytotoxic medicines and related waste was also mentioned as essential.

2. DEVELOPMENT OF A SELF-ASSESSMENT TOOL

2.1 CONTINUOUS QUALITY IMPROVEMENT AND SELF-ASSESSMENT

To ensure patient, workers and environmental safety related to the handling of cytotoxic medicines, continuous improvement of the cytotoxic drugs process should become a permanent objective of any health facility that delivers chemotherapy treatments.

Quality improvement is considered as a continuous managing process that consists of systemic and regular reviews and actions leading to measurable improvement of processes (64).

While several models of quality improvement exist, the “plan, do, study act” (PDSA) cycle, also known as the Deming cycle, has been widely used in quality improvement projects, notably by the Institute for Healthcare Improvement (IHI) (65, 66).

The PDSA cycle is a structured and dynamic approach involving a series of four successive and interrelated steps to be repeated over time for continual improvement (see figure 4).

Figure 4 : The PDSA cycle or Deming cycle (67)

Self-assessment has been demonstrated to be an efficient method to measure quality improvement, especially in resource-constraint settings (68, 69).

Self-assessment allows measuring current practices or processes in regards to a set of standards or recommendations of best practices. It provides an opportunity to identify strengths and weaknesses as well as areas for improvement (70). Different means of data collection can be used to gather evidence, such as interview,

observation, simulation, policies and procedures review. Triangulation of information obtained by the different methods is often recommended for more reliability (71).

In continuous quality improvement, results from self-assessment can then be used as a basis for elaborating an action plan with short-term and long-term objectives considering several factors as (72):

- the importance of the improvement to patient or staff safety
- the impact of the improvement on the process
- the urgency to implement the improvement action
- the resources (financial and human) and abilities required to achieve the change.

A self-assessment tool based on recognized guidelines of safe handling of cytotoxic drugs could assist healthcare facilities in evaluating their level of adherence with best practices and standards over time. The tool should be appropriate for LMIC and prioritization of the different quality criteria could guide appropriate actions in limited resources settings.

2.2 EXISTING TOOLS

After a literature and an Internet-based research, several existing assessment tools, checklists or questionnaires had been found related to cytotoxic medicines.
Local regional, national or international professional associations developed their own assessment tool with a lot of variations regarding their scope, their development process, their purpose of application etc.

The Organization of European Cancer Institute (OECI) launched in 2005 an accreditation program for oncology care centers with the aim to improve the quality of cancer care throughout Europe (73). The OECI working group established standards and criteria representing a comprehensive cancer care. The ensuing Quality Manual addressed the following aspects: prevention (e.g., screening, health education), care, research, education (teaching and continuing education), and networking. A questionnaire was then developed as an assessment tool in 2008 (1st version) and revised in 2015 (2nd version) to measure compliance to these quality standards by using a scoring system. This questionnaire is very comprehensive consisting of 265

items covering 63 topics. However, only 8 items addresses the aspects of cytotoxic medicines, covering prescription, preparation distribution and administration (74).

In 2012 a collaborative partnership between Portuguese and Angolan Cancer centers and oncology Institutes developed the “Cancer Units Checklist for low or middle income African countries” (63). Based on the OECI’s quality standards questionnaire and adapted to the African context by the authors, this tool was used to establish cancer units in Angola. The checklist assessed 10 different domains: policy and cooperation, cancer data registration, accuracy of diagnosis, responsibilities and tasks of the oncology team, good clinical practices, cancer treatment process, safeguarding the quality, patient and family support services, education and research, stakeholders engagement. However, although access to the entire tool was not possible, the items addressing the cytotoxic drug process didn’t seem to cover enough details to assess appropriately safe handling practices. Indeed, *Vaz da Conceiçao and colleagues (2015)* reported only 11 questions that allow assessing the oncology pharmacy - risk management and training (62). In *Miguel and colleagues (2014)* survey, the tool was used in combination with external experienced consultants.

Professional groups developed two others assessment tools focusing only on the compounding process.

In Switzerland, the association of district pharmacists collaborated with the Swiss association of Hospital Pharmacists in order to developed an assessment checklist (75). This questionnaire/checklist aimed to standardize and support the inspections and internal self-assessments related to the compounding process of the cytotoxic drugs in health facilities. The evaluation criteria were mainly based on standards requirements defined in the Swiss Regulations included in the “Pharmacopoea Helvetica” since 2006 (76).

Another tool was developed by the Oncolor network, a group of hospital pharmacies from the Lorraine region in France. This tool was established to improve the activities and processes within a centralized chemotherapy compounding unit according to recommendations of best practices and evaluate the compliance to national regulations (77). Two versions of this tool were developed, a self-assessment tool in 2007 and an audit grid in 2009, differing from each other mainly on their structure and scoring system.

Both of the tools described above contain more than 170 items focusing on the cytotoxic compounding process. While they are very detailed on the compounding aspect, they do not cover the other steps of the cytotoxic process as administration, patient information etc. Moreover, they are adapted to local regulations and include practices involving a lot of informatics technologies, thus not very suitable for lower resource settings.

The last tool was developed in 2012 by the Institute for Safe Medication Practice (ISMP) and an advisory panel of 28 international experts in oncology. The "International Medication Safety Self-assessment for Oncology" aimed at improving oncology medication safety in both inpatients and outpatient settings (78).
The 175 assessment items were elaborated based on international guidelines and standards or on safeguards resulting from analysis of medication errors that were reported in the ISMP database. Institutions around the world had the possibilities to submit their findings from their self-assessment into an online portal to generate a report and/or compare with findings from similar settings when available in the database (79).
The aspects addressed in this tool are mainly oriented towards patient safety. There are very few items and details to evaluate working practices regarding compounding and administration. Cytotoxic waste management is not addressed at all.

In conclusion none of the presented tools covered the whole cytotoxic medicines process with sufficient details on each step (from receiving the drugs to administering them and waste disposal) and seemed to be suitable for use in LMIC.

The main characteristics of the mentioned tools are summarized in table 5.

Table 5: Overview of existing assessment tools

Characteristics of the tool	Questionnaire OECI Quality standards(74)	ISMP International Medication Safety Self-Assessment® for Oncology (79)	Oncolor Audit de Unités centralisées de preparation des chimiothérapies de Lorraine (77)	Fabrication de cytostatiques: Questionnaire-check-liste (75)	The Cancer Units Assessment Checklist for low and middle income African Countries (63)
Country/region of use	Europe	International	Regional -Lorraine (France)	Switzerland	Africa (Angola)
Year of publication	Last version 2015	2012	2009 (audit grid) 2007 (self-assessment grid)	2008	2012
Authors	OECI accreditation working group	Institute for Safe Medication Practices and an International interdisciplinary advisory panel of 28 oncology experts from 11 countries	19 hospital pharmacies, members of the Oncolor network	Working group of 4 Swiss pharmacist-inspectors and 1 hospital pharmacists	Partnership between Angolan and Portuguese Cancer centres and institutes of Oncology
Development	Not described	• Review of standards of practices and guidelines • Analysis of medication errors reported to the ISMP National Medication Errors Reporting Program (ISMP MERP) and the Canadian Medication Incident Reporting and Prevention System	• Review of standards of practices and guidelines • Review of French regulations and laws.	• Review of standards of practices and guidelines • Review of national regulation (Swiss GMP) • Review of recommendations for occupational exposure from Swiss National Accident Insurance Fund	• Based on OECI questionnaire and Association of Community Cancer centres guidelines
Scope and purpose	Comprehensive accreditation tool for cancer care in Europe	Medication safety self assessment	Quality improvement of the centralized chemotherapy compounding unit and evaluate the compliance to national regulations (self assessment and external audit)	Inspection of Chemotherapy Compounding process in Hospitals	Implementation of an Oncology Unit in Africa
Nb of items	265 items covering 63 topics	175 items organized according to ISMP's10 key elements of the medication use system™	173 items	198 questions categorized according to the Swiss GMP chapters	10 different domains evaluated (nb of items unknown)
Comments	The tool is very comprehensive for cancer care center, however the part addressing the cytotoxic drugs process is very limited (only 8 items)	The tool is mainly oriented toward patient safety. Few items and details on working practices regarding preparation and administration. No item on waste management.	Does not cover all steps of the cytotoxic process within the hospital (e.g., no item on administration, patient information) Adapated to local practices, not suitable for LMIC	Specific to fulfil the Swiss regulations (compliance to Swiss GMP standards) regarding hospital compounding of chemotherapies No items regarding the others steps of the medication process within the hospital. Not suitable for LMIC	Not enough details to evaluate all the aspects of safe handling practices

2.3 OBJECTIVES

2.3.1 Overall objective

The study aimed to develop a self-assessment tool for health services in LMIC in order to support the implementation of safe handling practices and promote continuous quality improvement regarding cytotoxic drugs handling and management in LMIC.

2.3.2 Secondary objectives

To prioritize standards and quality indicators in order to guide and assist resource-constraint settings in establishing priorities and design their action plan with short, middle and long term objectives.

3. MATERIAL AND METHODS

3.1 THE DELPHI TECHNIQUE

A Delphi technique has been chosen to validate our self-assessment tool by international experts on safe handling of cytotoxic medicines. This technique has been widely used to elicit expert opinions and agree on quality-indicators in healthcare (80).

The Delphi technique is a structured process that collects expert opinion through questionnaire and multiple iterations in order to build consensus on a particular topic. Online survey enables to gather opinions from a panel of selected experts geographically dispersed (80, 81). Although the different Delphi surveys can differ in their objectives and procedure, they share common characteristics (82).

Anonymity of the answers is one of the main characteristics of this method, avoiding influence or domination by some experts. Therefore, individual opinion of each expert is anonymous to the other panelists through the entire process except to the investigator (80-83).

Delphi surveys are usually conducted over two or more iterations until reaching consensus. However there is no universal definition of consensus or agreement on the number of rounds (80, 84). A systematic review by *Diamonds and colleagues (2014)* reported that “percent of agreement” was the most commonly used definition for consensus, with a median threshold for consensus defined as 75% of agreement. However, they observed that a lot of studies did not consider consensus as the primary criteria for terminating the process but that they were conducted for a predefined numbers of iterations (84).

Controlled feedback of information between the rounds is an important part of the process. It provides the panelists summary information of the results of the previous questionnaire. Individual feedback enables to confront the opinion of one’s individual respondent with the statistical group response and encourage him/her (e.g., group results versus individual results) to reassess his/her judgment (82, 83).

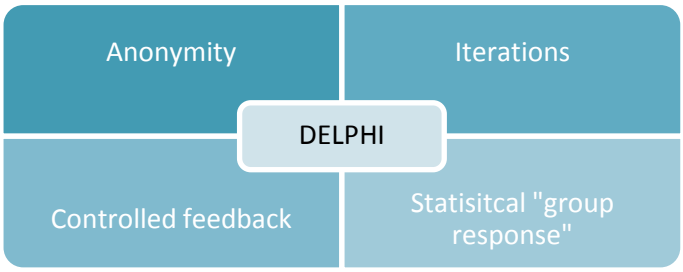

Figure 5: Main Characteristics of Delphi technique (82)

Selection of the panel is a crucial step in Delphi process as it will directly influence the relevance and the quality of the findings (81). Although there is no consensus on the exact optimal number of participants, eligible criteria should allow selecting experts with backgrounds and experience useful to contribute with relevant inputs and that are willing to reach consensus (83).

3.2 PHASING AND TIMELINE OF THE PROJECT

The project was conducted throughout 2015-2016 and consisted in three main phases as presented in figure 6.

The first phase was dedicated to the preparation of the Delphi study with the formation of a steering committee, the literature review and the elaboration of the questionnaire that would be submitted to the experts.

The second phase corresponded to the two-round Delphi survey and the third phase consisted in the finalization of the self-assessment tool.

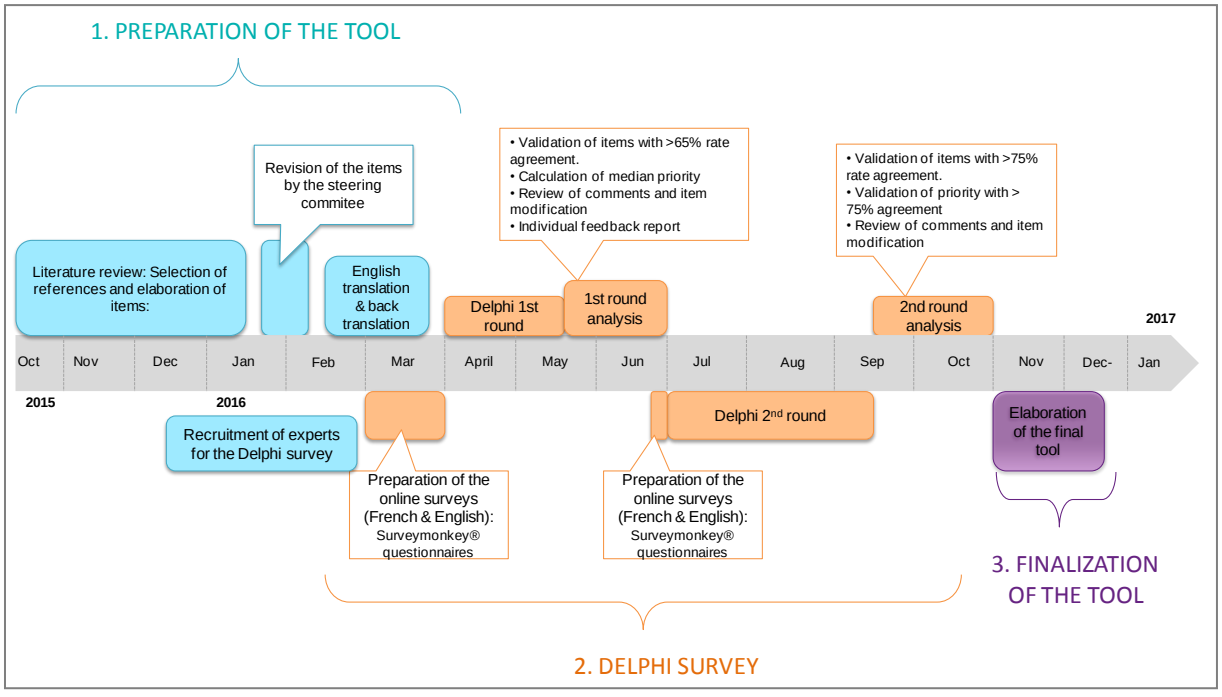

Figure 6: Phasing and timeline of the project

3.3 DELPHI STEERING COMMITTEE

A steering committee, internal to the pharmacy department of Geneva University Hospitals (HUG), was formed to elaborate the strategy and the design of the project. It was comprised of the Head of the Pharmacy, the pharmacist in charge of the quality assurance, the pharmacist in charge of the cytotoxic drugs preparation unit and the principal investigator of the study (see appendix 1). The steering committee was responsible for taking decisions on major steps of each phase, such as: the definition of the scope of the self-assessment tool, the revision of the items submitted to the expert panel, the recruitment process of the experts (e.g eligibility criteria, identification of experts), and the definition of consensus and exclusion criteria. Furthermore the steering committee undertook the review and discussion of the comments provided by the experts at each round to decide whether or not an item should be modified, completed or rephrased.
Members of the steering committee didn't take part as panel members in the Delphi survey.

3.4 LITERATURE REVIEW AND ELABORATION OF THE QUESTIONNAIRE

Major national and international references in the domain of safe handling cytotoxic medicines were reviewed to derive items addressing safety and quality aspects at every stage of the cytotoxic process.

Different types of documents (in English and French) were selected by the steering committee such as recommendations from scientific societies, guidelines and regulations from organ of workers' protection and regulatory framework (see table 6).
To be in line with the philosophy of the project, the "sine qua non" condition to select a reference was also that the document should be available online on free access.

The preliminary questionnaire was sent to the steering committee for comments on the items before beginning the study.

The survey was conducted in French and English to enable international experts to participate. Therefore each item was translated in English and a back translation in French was then performed to ensure that the two versions were matching.

Table 6: References used for the elaboration of the items

DOCUMENTS	AUTHORS	YEAR	REGION/COUNTRIES	TYPE DE DOCUMENTS
Standards ISOPP [3]	International Society of Oncology Pharmacy Practitioners	2007	International	Recommendations from scientific societies
QuapoS 4:Quality Standard for the Oncology Pharmacy Service with Commentary [54]	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 [1]	American Society of health system pharmacists	2006	USA	Recommendations from scientific societies
USP (United States Pharmacopeia) Chapter 800: Hazardous Drugs-Handling in Healthcare settings [53]	The Compounding Expert Committee	2015 (draft)	USA	Regulatory framework
Bonnes Pratiques de Préparation [85]	Afssaps (Agence française de sécurité sanitaire de produits de santé)	2007	France	Regulatory framework
Suvapro: sécurité dans l'emploi des cytostatiques [5]	Swiss Accident Insurance Fund	2004	Switzerland	Recommendations for occupational safety
WHO-Good Manufacturing Practices Annex 3 [57]	WHO Expert Committee on Specifications for Pharmaceutical Preparations	2010	International	Regulatory framework
Chemotherapy Administration Safety Standards [86]	American society of clinical Oncology (ASCO)/Oncology Nursing society (ONS)	2013	USA	Quality standards from scientific societies
OSHA technical Manual: Controlling Occupational Exposure to Hazardous Drugs Section IV, chapter 2 [52]	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 [46]	National Institute for Occupational Safety and Health	2004	USA	Recommendations for occupational safety
Safe Handling of Hazardous Chemotherapy Drugs in Limited-Resource Settings [87]	Pan American Health Organization (PAHO)	2013	PAHO	Recommendations

3.5 DELPHI PANEL RECRUITMENT

In order to develop a “generic” self-assessment tool that can be used in various settings, we aimed to include a panel of international experts to represent both high and low and middle income countries.

Considering the area of expertise needed, only pharmaceutical experts with strong experience in the area of cytotoxic medicines and oncology pharmacy were approached.

Different methods were used to identify experts that could potentially participate in the survey. First, we looked into the existing network of the steering committee.

Secondly, we contacted country delegate members from professional society’s website as The International Society of Oncology Pharmacy Practitioners (ISOPP)

and the European Society of Oncology Pharmacists (ESOP). Thirdly, we contacted authors from relevant publications in the field of oncology pharmacy in low and middle-income countries. We also asked experts if they could recommend us some other potential eligible participants.
An information letter was sent by email to the identified experts asking them to confirm their willingness and agreement to participate in the survey (Appendix 2). Experts who didn't respond were reminded twice.
Each expert having agreed to participate was asked to fill in a declaration of interest form. The template and declaration results are presented in Appendix 6.
Experts of the panel remained anonymous to each other throughout the study. As there is no clear number on appropriate Delphi panel size (83), the objective was to have a sufficient amount of experts (about 30) with a large representation of countries and settings to perform statistical analysis (81).

3.6 THE DELPHI STRUCTURE

As previously mentioned, there is no universally requirement on neither number of rounds nor consensual definition of "expert consensus" (80, 84, 88). As we already pre-selected standards and formulated the items, we decided to conduct a two-round Delphi survey to avoid participant fatigue and risk of dropout.

The second round enabled the experts to modify their opinion or remain with their initial decision after reading the first round report indicating the group answers.
Criteria and cut-off for defining consensus were also decided before the beginning of the survey and are described later in the document.

The survey was submitted to the panel of experts as an online self-administered questionnaire through Surveymonkey® software. An email was sent to each expert with survey instructions, a tutorial on how to fill in the survey (appendices 3 and 4) and an individual hyperlink to access the questionnaire.
Each item was completed with links to references and with some additional information (see figure 7 as an example).

As the purpose of the tool was on one hand to enable health facilities to identify gaps in quality and safety with a scoring system and on the other hand to establish an

action plan to improve their processes, experts were asked, for each item, to give their opinion on:

- Their **level of agreement** with the content and formulation of the items according to a 1-5 Likert scale: (1= strongly disagree, 2= disagree; 3**=** don't agree nor disagree, 4=agree; 5= totally agree).

- The **level of priority** of the item. Experts were asked to prioritize the items while considering the probability of occurrence of the prevented risks, the criticality of the risk, the effectiveness of the measure, how easy it is to implement, etc.

  A ranking scale from 1 to 3 was used in the first round (1= indispensable, absolutely required even for occasional handling of cytotoxic medicines, 2= essential, required for regular use of cytotoxic medicines, 3= desirable, if regular use and/or resources sufficient).

  In analogy with the VEN[1] (Vital-Essential-Non essential) classification for medicines (89), this latter criterion aimed at providing guidance to health facilities in term of priority of action and resources allocation for implementing or improving safe handling practices of cytotoxic drugs.

For both criteria, a "no opinion" option was given to the experts to let them the opportunity not to take position with an item.

A free text field allowed experts to add comments or references to clarify their position and/or suggest modification (+/- addition of items with references) to any item.

[1] "VEN analysis is a method setting priorities, in which medicines are classified according to their health impact"

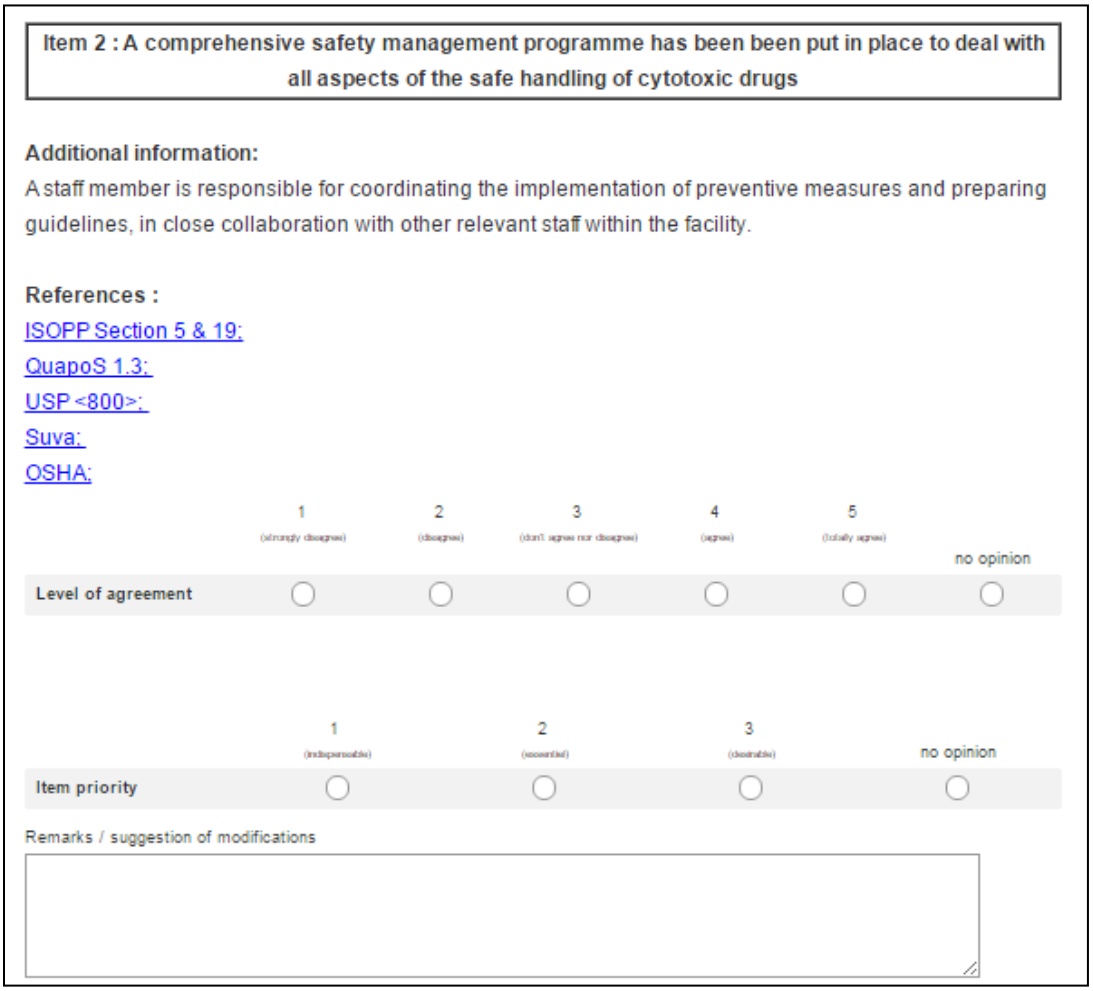

Figure 7: Example of an item's presentation in the online questionnaire

3.6.1 First round

The duration of the first round was planned to be approximately one month. Several email reminders were sent to those having not completed the questionnaire: A first reminder was sent two weeks after the beginning of the survey and then one reminder per week until completion of the deadline

Criteria and cut-off to drop an item and define consensus were decided by the steering committee prior to the beginning of the survey.
At the end of the first round, only the items that were rated between 4 and 5 (agree or totally agree) by more than 65% of experts and have obtained a median ≥ 4 were submitted to the second round.

After this first round, comments made by the experts on the different items were discussed by the steering committee to decide whether or not an item should be modified.

Before the second round, an individual feedback report was sent to every expert with the following information:

- Summary results of the first round (characteristics of the experts, participation rate, global level of agreement, etc.)
- The statistical group response for each item with median level of agreement, interquartile range, proportion of expert with a high level of agreement (4 or 5) and the expert's own response to illustrate their position compared to the group.
- Distribution of response regarding prioritization categories and the expert's own response to illustrate their position compared to the group.
- Included or excluded items between the 2 rounds,
- Any modification of the items

An extract of an individual feedback report is presented in Appendix 6 .

3.6.2 Second round

The second round was conducted as the first one, with one-month duration and several email reminders for the experts who didn't answer.

At the end of the Delphi, final consensus was reached if an item obtained a median of agreement ≥ 4 and if proportion of experts agreeing with the item (4 or 5 on the Likert scale) was ≥ 75%. Thus, any item with < 75% of agreement would not be included in the final tool.

Regarding prioritization, the median priority score calculated after the first round was suggested as priority level in the second round. If the calculated median score was between 2 levels (e.g., 1.5) the priority having received most of the votes was chosen. Thus in the second round, experts were asked to indicate their level of agreement with the suggested priority level on a Likert-type scale (1= strongly disagree, 2= disagree; 3= don't agree nor disagree, 4=agree; 5= totally agree). In case of disagreement, they were encouraged to indicate their preferred priority by adding a comment in a free text field.

Final consensus on priority was then reached if > 75% of expert agrees with the median priority.

New comments obtained from experts on the different items were discussed among the steering committee as in the first round. Only small modifications were

eventually done to clarify some items. Extra caution was taken to avoid major change in the content of the items that would have required a new validation by the panel.

3.6.3 Statistical analysis

Participant responses were exported from Surveymonkey® software into a Microsoft Excel spreadsheet to perform descriptive statistics. Proportions, median (as measure of central tendency), interquartile range (as level of dispersion) were calculated with Microsoft® Office Excel® 2007.

3.6.4 Elaboration of the final tool

Items that have reached agreement consensus (>75% rate of agreement) were included in the final tool.

Prioritization of the items was indicated for every item with a distinction whether or not the priority had reached consensus.

The final tool, presented in appendix 8, was sent to the experts.

4. RESULTS

4.1 ELABORATION OF THE TOOL

Based on the literature review, 138 items were described and classified in 10 different categories and further subdivided in 28 subcategories reflecting the cytotoxic medicines process through a health care facility (table 7).

After revision by the steering committee members, 137 items were submitted for validation to the experts (1 item deleted).

The content of the items focused on safe practices and processes specific to cytotoxic medicines in order to ensure safe handling, safe care and decrease environment contamination.

Table 7: Categories and subcategories classification with number of items

CATEGORIES	SUB-CATEGORIES	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 organisation	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 organisation	2
	• Cleaning practices	6
	• Laundry	2
10. **Patients counselling**		**4**
	TOTAL	**137**

4.2 OBTAINING AN EXPERTS' CONSENSUS THROUGH A DELPHI METHOD

4.2.1 Chronology of the Delphi survey

Figure 8 represents the chronology of the Delphi survey.

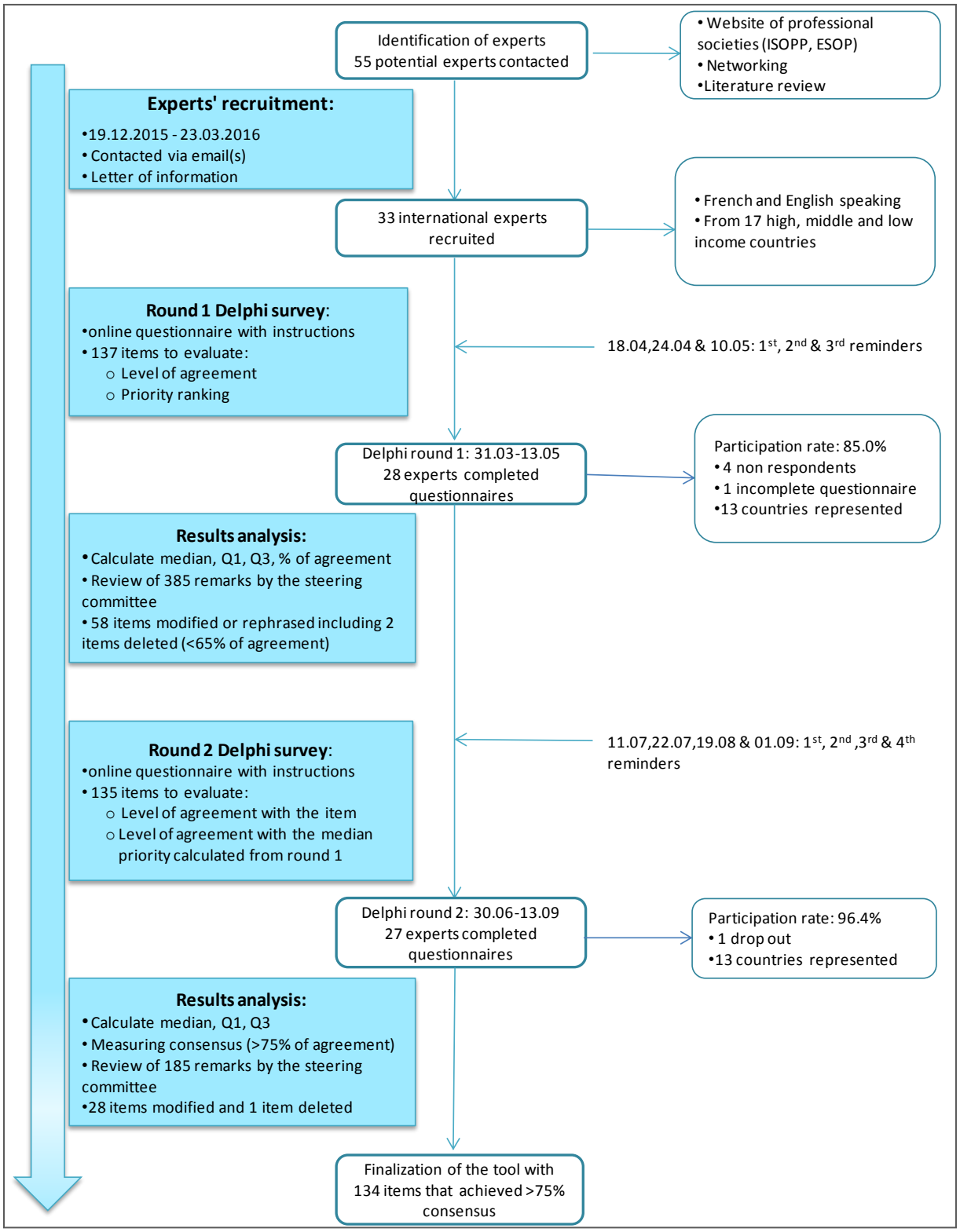

Figure 8: Chronology and sequence of the Delphi

4.2.2 The experts'panel

From December 2015 to March 2016, 55 pharmaceutical experts in oncology pharmacy representing both high and low and middle income countries were contacted to participate in the Delphi survey.

33 (60%) international English and French-speaking experts from 17 countries answered positively (figure 9).
28 (85%) of them from 13 countries from high and LMIC finally completed the first round questionnaire. Four experts didn't respond at all and one expert never finished completing the questionnaire.
27/28 (96%) experts participated in the second round.

The complete list of experts that have participated in the Delphi survey is presented in Appendix 3 and their main characteristics are summarized in table 8.

Figure 9: Geographical distribution of the expert's panel

Table 8: Characteristics of the pharmaceutical experts involved in the Delphi survey (1st round)

Characteristics of the experts		
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)

4.3 DELPHI FIRST AND SECOND ROUNDs

4.3.1 First round

The first round lasted six weeks, from 31st of March 2016 to 13th of May 2016. An individual link to the questionnaire was sent by email to the experts who had agreed to participate. After three reminders, 28 (85%) experts completed the questionnaire. (figure 7)

The mean participation rate regarding level of agreement for the items was 98.5% ± 2.7% and 96.9% ± 4.8% regarding the priority.

135/137 items (98.5%) obtained the sufficient level of agreement to pass the first round (i.e > 65% of expert that have agreed or totally agreed with the item). Aggregate results of the level of agreement for the items are presented in figure 9.

The experts formulated 385 comments. After revision and discussion of their relevance by the steering committee, 56 items (standard and/or additional information) were modified or rephrased.
According to our cut-off criteria, two items were deleted as they did not reach >65% of agreement.

Regarding prioritization of the items, only 19/137 (14%) items were ranked the same priority by > 65% of the experts and among them only 12 reached a consensus with >75%.
The distribution of the median priority calculated for the different items is presented in figure 11.

4.3.2 Second round

The individual report with the results of the first round was sent to each expert in attachment to the email announcing the beginning of the second round. This later took place from the 30th of June to the 13th of September 2016.
After four reminders, 27/28 (96%) experts responded to this questionnaire.

The mean participation rate regarding the level of agreement with the content and wording of the items was 99.7% ± 1.0%. A slightly lowest mean participation rate regarding the level of agreement with the median priority was observed (95.8% ± 1.4%).

In this second round, the experts formulated 185 comments. Few clarifications or rewording were added to 28 items (mostly in the “additional information”).

According to our definition, all the items (135) submitted in the second round reached consensus regarding their content and formulation (figure 10).
However one additional item was finally deleted after discussion with the steering committee (item 68) although more than 75% of experts agree with the item. Indeed, this item has generated a lot of comments and questions. The steering committee decided that this item was not providing any added value to the tool and chose to remove it.

Only 52/135 (38.5%) obtained a consensus regarding their priority rank (figure 11), i.e. where ≥75% of the experts “agree” or “totally agree” with the median score of the priority obtained in the first round.
45 items (86.5%) concern items of priority rank 1 and 7 items (13.5%) of priority rank 2.

Regarding the items that didn't reached consensus, very comments mentioning the reasons for disagreement and the suggested priority were provided by the experts.

Results of the two rounds are presented in table 9. The red color represents modifications made after the first round end the green color represents modifications made after the second round.

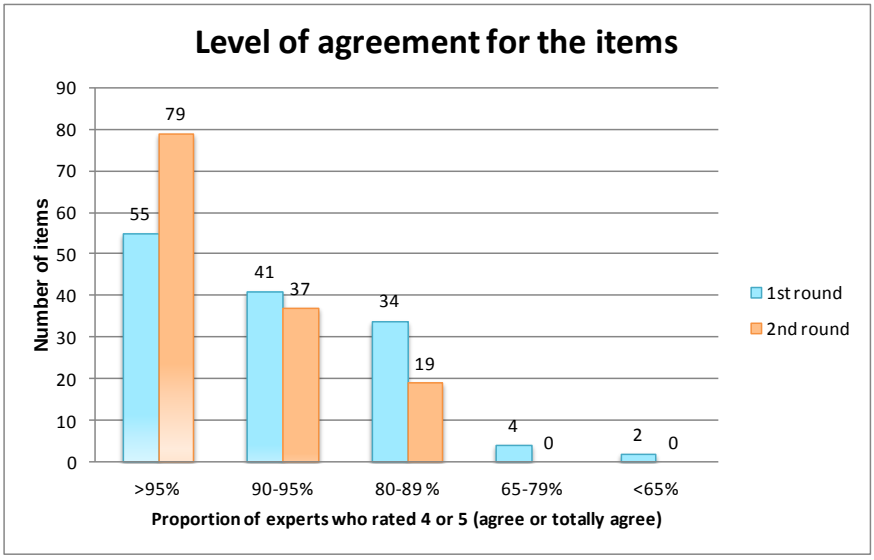

Figure 10: Aggregate results of the level of agreement with the items after the first and second rounds

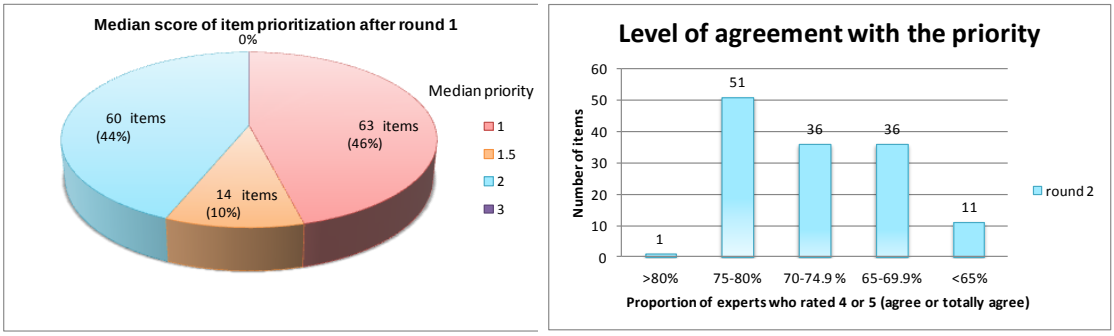

Figure 11: Median score of item prioritization after round 1 and aggregate level of agreement with the median priority in round 2.

Table 9: Results of the two rounds and descriptive statistics

N°	Item	Additional information	Delphi 1st round			Delphi 2nd round		
			Median (Q1-Q3) Level of agreement	% of 4 & 5 for level of agreement	Status	Median of agreement (Q1-Q3) for content and formulation of item	% of 4 & 5 for level of agreement with the item	Status
			Priority	Prioritization rate		for level of Priority	With the median priority	
MANAGEMENT AND ORGANISATION								
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	5 (4.5-5)	92.6%	modified	5 (5-5)	100.0%	validated
			1 (1-2)	1: 64.3% 2: 32.1% 3: 3.6%	1	5 (4-5)	76.9%	consensus
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.	4 (4-5)	92.9%	agreement	5 (4-5)	100.0%	validated
			1 (1-2)	1: 53.6% 2: 32.1% 3: 14.3%	1	5 (4-5)	76.9%	consensus
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 ~~at least annually~~ regularly. The frequency of update is to be defined by the local institution, according of the context. Any changes must be documented.	4 (4-5)	89.3%	modified	5 (4-5)	96.3%	validated
			2 (1-3)	1: 42.9% 2: 21.4% 3: 35.7%	2	4 (2-4.75)	65.4%	no consensus on priority
4	A self-assessment of compliance with safety guidelines regarding the safe handling of cytotoxic medicines is carried out regularly ~~annually~~.	Each institution should define its frequency according to local context.	4 (3-5)	71.4%	modified	4 (4-5)	92.6%	validated
			2 (1-3)	1: 28.6% 2: 35.7% 3: 35.7%	2	4 (2.5-5)	73.1%	no consensus on priority
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.	4 (4-5)	82.1%	agreement	4 (4-5)	85.2%	validated
			2 (1-3)	1: 30.8% 2: 34.6% 3: 34.6%	2	4 (3-4)	64.0%	no consensus on priority
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.	5 (4-5)	92.6%	agreement	5 (4-5)	92.6%	validated
			2 (1-2)	1: 48.1% 2: 33.3% 3: 18.5%	2	4 (2-5)	55.6%	no consensus on priority
7	Smoking, drinking and eating are forbidden in areas where cytotoxic medicines are prepared, stored and administered		5 (5-5)	100%	agreement	5 (5-5)	100.0%	validated
			1 (1-1)	1: 89.3% 2: 10.7% 3: 0.0%	1	5 (2.5-5)	73.1%	no consensus on priority

N°	Item	Additional information	Delphi 1st round			Delphi 2nd round		
			Median (Q1-Q3) Level of agreement	% of 4 & 5 for level of agreement	Status	Median of agreement (Q1-Q3) for content and formulation of item	% of 4 & 5 for level of agreement with the item	Status
			Priority	Prioritization rate		for level of Priority	With the median priority	
8	All staff know and understand the facility's policies and ~~procedures~~ approach on quality assurance.	Documents are readily available and written in an easily understandable manner.	5 (4-5)	92.9%	modified	5 (4-5)	100.0%	validated
			1 (1-2)	1: 59.3% 2: 25.9% 3: 14.8%	1	4 (2.25-5)	69.2%	no consensus on priority
9	There is a regularly updated organigram (organisational chart) indicating the roles and responsibilities of all the staff members involved in processes using chemotherapies, as well as their contacts details.		4 (4-5)	85.7%	agreement	4 (4-5)	92.6%	validated
			2 (1-2)	1: 32.1% 2: 46.4% 3: 21.4%	2	4 (3.25-5)	73.1%	no consensus on priority
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	4 (4-5)	82.1%	agreement	4 (4-5)	88.9%	validated & completed
			2 (1-3)	1: 32.1% 2: 39.3% 3: 28.6%	2	4 (2.5-5)	73.1%	no consensus on priority
11	There is a sufficient number of ~~qualified~~ 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.	5 (4-5)	92.9%	agreement	5 (5-5)	88.9%	validated & completed
			1 (1-2)	1: 64.3% 2: 28.6% 3: 7.1%	1	5 (3.25-5)	73.1%	no consensus on priority
PERSONNEL								
Education 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.	5 (5-5)	96.3%	agreement	5 (5-5)	100.0%	validated
			1 (1-1)	1: 81.5% 2: 18.5% 3: 0%	1	5 (3.25-5)	73.1%	no consensus on priority
13	There is regular continuous education for staff.	Training sessions are specific to the category of staff. An annual training plan should be prepared	5 (4-5)	96.4%	agreement	5 (4-5)	96.3%	validated & completed
			2 (1-2)	1: 39.3% 2: 46.4% 3: 14.3%	2	4 (2-5)	69.2%	no consensus on priority

N°	Item	Additional information	Delphi 1st round			Delphi 2nd round		
			Median (Q1-Q3) Level of agreement	% of 4 & 5 for level of agreement	Status	Median of agreement (Q1-Q3) for content and formulation of item	% of 4 & 5 for level of agreement with the item	Status
			Priority	Prioritization rate		for level of Priority	With the median priority	
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.	4 (4-5)	92.6%	modified	4 (4-5)	96.3%	validated
			2 (1-3)	1: 48.1% 2: 18.5% 3: 33.3%	2	4 (2-5)	69.2%	no consensus on priority
15	All training and skill validations are documented.	Training records are kept for at least 5 years.	4 (4-5)	92.9%	agreement	4 (4-5)	88.9%	validated
			2 (1-3)	1: 26.8% 2: 46.4% 3: 25.0%	2	4 (2.25-5)	69.2%	no consensus on priority
Medical surveillance								
16	An occupational health surveillance programme is available for staff members who handle cytotoxic medicines ~~participate in a medical surveillance programme.~~	The occupational health surveillance includes: ~~examinations by an occupational physician;~~ 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	4.5 (4-5)	96.4%	modified	5 (4-5)	96.3%	validated
			1.5 (1-3)	1: 50.0% 2: 17.9% 3: 32.1%	1	4.5 (2.25-5)	69.2%	no consensus on priority
17	No pregnant and breastfeeding women are involved in the handling of cytotoxic medicines.	Pregnant or breastfeeding women ~~should be given the option to not take part in~~ must not take part in the preparation, reconstitution, administration, cleaning or disposal of cytotoxic medicines (consult also ~~see~~ the stipulations of the national labour law if available)	5 (5-5)	92.9%	modified	5 (5-5)	85.2%	validated & completed
			1 (1-1)	1: 85.7% 2: 10.7% 3: 3.6%	1	5 (4.75-5)	79.2%	consensus
18	~~No~~ Staff involved in the preparation of cytotoxic medicines, with an upper respiratory tract infection or a cutaneous infection ~~informs their superior before any manipulation are involved in the preparation of cytotoxic medicines.~~	The decision to exclude temporarily or not the person from the preparation should be evaluated one by one to avoid a risk of microbiological contamination of the preparation. A medical advice can be eventually sought	4 (4-5)	81.5%	modified	5 (4-5)	88.9%	validated & completed
			2 (1-2)	1: 42.3% 2: 38.5% 3: 19.2%	2	5 (3.25-5)	73.1%	no consensus on priority
19	~~No personnel receiving immunosuppressive therapy are involved in the preparation of cytotoxic medicines~~		4 (2-4)	58.3%	deleted	[redacted]		
			2 (1-3)	1: 30.0% 2: 25.0% 3: 45.0%				

N°	Item	Additional information	Delphi 1st round			Delphi 2nd round		
			Median (Q1-Q3) Level of agreement	% of 4 & 5 for level of agreement	Status	Median of agreement (Q1-Q3) for content and formulation of item	% of 4 & 5 for level of agreement with the item	Status
			Priority	Prioritization rate		for level of Priority	With the median priority	
LOGISTICS								
Receipt								
20	Cytotoxic medicine deliveries are only received and unpacked by trained, ~~qualified~~ 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.	4 (4-5)	85.7%	modified	4 (4-5)	96.3%	validated
			2 (2-3)	1: 21.4% 2: 42.9% 3: 35.7%	2	4 (2-5)	69.2%	no consensus on priority
21	Staff use approriate personal protective equipment when receiving and unpacking cytotoxic medicines	Protective gloves ~~and gown.~~	4 (4-5)	82.1%	modified	4 (4-5)	92.6%	validated
			2 (1-2.25)	1: 35.7% 2: 39.3% 3: 25.0%	2	4 (2-4.75)	69.2%	no consensus on priority
22	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.	4 (4-5)	96.4%	agreement	4 (4-5)	100.0%	validated
			2 (1-2)	1: 32.1% 2: 57.1% 3: 10.7%	2	4 (3.25-5)	73.1%	no consensus on priority
23	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	5 (4-5)	96.4%	agreement	5 (4.5-5)	96.3%	validated
			1 (1-2.25)	1: 57.1% 2: 17.9% 3: 25.0%	1	5 (4-5)	76.9%	consensus
24	~~Work surfaces are properly cleaned after the receipt of each delivery.~~		4 (3-5)	63.0%	deleted			
			2 (1-3)	1: 39.1% 2: 30.4% 3: 30.4%				
25	Staff washes their hands with soap after handling cytotoxic medicines.	Wearing gloves is not a substitute for washing hands.	5 (4-5)	85.7%	agreement	5 (5-5)	92.6%	validated & completed
			1 (1-2)	1: 59.3% 2: 22.2% 3: 18.5%	1	5 (2.5-5)	73.1%	no consensus on priority

N°	Item	Additional information	Delphi 1st round			Delphi 2nd round		
			Median (Q1-Q3) Level of agreement	% of 4 & 5 for level of agreement	Status	Median of agreement (Q1-Q3) for content and formulation of item	% of 4 & 5 for level of agreement with the item	Status
			Priority	Prioritization rate		for level of Priority	With the median priority	
Storage								
26	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.	5 (4-5)	100.0%	agreement	5 (4-5)	92.6%	validated
			2 (1-2)	1: 35.7% 2: 42.9% 3: 21.4%	2	4 (2-5)	69.2%	no consensus on priority
27	The storage area for cytotoxic medicines is clearly defined and labeled. Access is restricted to authorised 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).	4.5 (4-5)	89.3%	agreement	4 (4-5)	96.3%	validated
			2 (1-3)	1: 35.7% 2: 32.1% 3: 32.1%	2	4 (2-4.75)	69.2%	no consensus on priority
28	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.	5 (4-5)	96.3%	agreement	4 (4-5)	88.9%	validated
			2 (1-3)	1: 37.0% 2: 33.3% 3: 29.6%	2	4 (2-5)	61.5%	no consensus on priority
29	The storage area has sufficient general exhaust ventilation		4 (4-5)	77.8%	agreement	4 (4-4.5)	100.0%	validated
			2 (2-3)	1: 18.5% 2: 44.4% 3: 37.0%	2	4 (2-4.75)	65.4%	no consensus on priority
30	Only trained staff have access to the storage area for cytotoxic medicines, and they wear appropriate personal protective equipment when resupplying or stocktaking	~~Protective gown and~~ 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.	4 (4-5)	89.3%	modified	4 (4-5)	88.9%	validated
			2 (1-2.25)	1: 32.1% 2: 42.9% 3: 25.0%	2	4 (2-5)	64.0%	no consensus on priority
31	Staff wash their hands with soap after handling cytotoxic medicines when resupplying or stocktaking	Wearing gloves is not a substitute for washing hands.	4 (4-5)	82.1%	agreement	4 (4-5)	88.9%	validated & completed
			2 (1-2)	1: 33.3% 2: 44.4% 3: 22.2%	2	4 (2-5)	61.5%	no consensus on priority
Transport								
32	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. ~~Pneumatic tubes should not be used due to mechnical stress and contamination risks~~	5 (4-5)	100.0%	modified	5 (4-5)	81.5%	validated & completed
			1.5 (1-2)	1: 50.0% 2: 35.7% 3: 14.3%	1	4.5 (4-5)	76.0%	consensus

N°	Item	Additional information	Delphi 1st round			Delphi 2nd round		
			Median (Q1-Q3) Level of agreement	% of 4 & 5 for level of agreement	Status	Median of agreement (Q1-Q3) for content and formulation of item	% of 4 & 5 for level of agreement with the item	Status
			Priority	Prioritization rate		for level of Priority	With the median priority	
33	Cytotoxic medicines are transported in exclusively dedicated containers/boxes.		5 (4-5)	100.0%	agreement	5 (4-5)	96.3%	validated
			1.5 (1-3)	1: 50.0% 2: 21.4% 3: 28.6%	1	4 (2-5)	68.0%	no consensus on priority
34	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.	5 (4-5)	85.7%	agreement	5 (4-5)	96.3%	validated
			2 (1-3)	1: 42.9% 2: 28.6% 3: 28.6%	2	4 (2-5)	60.0%	no consensus on priority
35	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 minimise impacts and risks of breakage. Ready-to-use preparations must first be placed in leak-proof bags	5 (4-5)	92.9%	agreement	5 (4-59	92.6%	validated
			2 (1.5-2.5)	1: 25.9% 2: 48.1% 3: 25.9%	2	4 (2-5)	65.4%	no consensus on priority
36	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.	4 (4-5)	92.9%	agreement	5 (4-5)	92.6%	validated
			1 (1-2)	1: 51.9% 2: 37.0% 3: 11.1%	1	5 (3.25-5)	73.1%	no consensus on priority
PRESCRIPTION								
37	Only ~~trained, qualified medical~~ authorised ~~staff~~ healthcare practitioners can prescribe chemotherapy treatment.	The facility has a readily available, up to date list of authorised prescribers.	5 (4.75-5)	92.9%	modified	5 (4-5)	92.6%	validated
			1 (1-1.25)	1: 75.0% 2: 21.4% 3: 3.6%	1	5 (4-5)	76.9%	consensus
38	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.	5 (4.75-5)	92.9%	agreement	5 (4-5)	100.0%	validated
			1 (1-2)	1: 63.0% 2: 25.9% 3: 11.1%	1	4.5 (2.5-5)	73.1%	no consensus on priority
39	Prescriptions are done in a structured way, ~~with the use of of standardized, formatted (preprinted or electronic) prescription forms.~~ They are nominative, readable, contain no abbreviations and clearly identify the prescriber, the department giving care and the facility.	~~The use of standardized, formatted (preprinted or electronic) prescription forms for chemotherapy treatment is recommended.~~ No prescription (or prescription modification) that was only communicated orally should be validated	5 (5-5)	96.4%	modified	5 (5-5)	92.6%	validated
			1 (1-1)	1: 78.6% 2: 21.4% 3: 0.0%	1	5 (1.75-5)	73.1%	no consensus on priority

N°	Item	Additional information	Delphi 1st round			Delphi 2nd round		
			Median (Q1-Q3) Level of agreement	% of 4 & 5 for level of agreement	Status	Median of agreement (Q1-Q3) for content and formulation of item	% of 4 & 5 for level of agreement with the item	Status
			Priority	Prioritization rate		for level of Priority	With the median priority	
40	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, preprinted or electronic prescription forms for chemotherapy treatment protocols is recommended.	4 (4-5)	92.3%	agreement	5 (4-5)	88.9%	validated
			1 (1-2)	1: 52.0% 2: 48.0% 3: 0.0%	1	5 (4-5)	76.9%	consensus
41	Before preparation, all prescription/orders are analysed, 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.	5 (4-5)	96.4%	agreement	5 (4-5)	92.6%	validated & completed
			1 (1-2)	1: 64.3% 2: 28.6% 3: 7.1%	1	5 (4-5)	76.0%	consensus
PREPARATION								
Management and organisation								
42	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")	5 (5-5)	100.0%	agreement	5 (5-5)	100.0%	validated
			1 (1-1)	1: 89.3% 2: 7.1% 3: 3.6%	1	5 (4-5)	76.9%	consensus
43	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 centralised in order to minimise the risks of contamination and limit the number of people exposed. The preparation area should be located away from breakrooms and refreshment areas.	5 (5-5)	100.0%	agreement	5 (5-5)	92.6%	validated
			1 (1-1)	1: 81.5% 2: 14.8% 3: 3.7%	1	5 (4-5)	76.9%	consensus
44	Access to preparation areas is restricted to authorised personnel involved in preparation of cytotoxic medicines and wearing appropriate personal protective equipment.		5 (4.75-5)	100.0%	agreement	5 (5-5)	96.3%	validated
			1 (1-2)	1: 67.9% 2: 25.0% 3: 7.1%	1	5 (4-5)	80.0%	consensus
45	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 microbiolgical integrity of the product will be maintained for the established conservation period	5 (4.75-5)	92.9%	modified	5 (4.5-5)	92.6%	validated
			1 (1-2)	1: 56% 2: 36.0% 3: 8.0%	1	5 (3.25-5)	73.1%	no consensus on priority

N°	Item	Additional information	Delphi 1st round			Delphi 2nd round		
			Median (Q1-Q3) Level of agreement	% of 4 & 5 for level of agreement	Status	Median of agreement (Q1-Q3) for content and formulation of item	% of 4 & 5 for level of agreement with the item	Status
			Priority	Prioritization rate		for level of Priority	With the median priority	
Preparation area of parenteral medicines								
46	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.	5 (4-5)	92.9%	agreement	5 (4-5)	92.6%	validated
			2 (1-3)	1: 35.7% 2: 28.6% 3: 35.7%	2	4 (4-5)	76.9%	consensus
47	~~Materials and medicines are stored outside the preparation room~~ The preparation room only contains the necessary materials for the preparation	~~The preparation room should 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	4 (4-5)	89.3%	modified	4 (4-5)	92.6%	validated
			2 (1.75-3)	1: 25.0% 2: 42.9% 3: 32.1%	2	4 (2-5)	61.5%	no consensus on priority
48	The preparation of sterile cytotoxic (parenteral) medicines takes place in a cleanroom ~~if conserved >24h.~~	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.	5 (4-5)	92.9%	modified	5 (4.5-5)	85.2%	validated
			1 (1-2)	1: 63.0% 2: 25.9% 3: 11.1%	1	5 (2.5-5)	73.1%	no consensus on priority
49	The preparation room surfaces are designed to minimise 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.	5 (4-5)	96.4%	agreement	5 (5-5)	92.6%	validated
			1 (1-2)	1: 67.9% 2: 21.4% 3: 10.7%	1	5 (2-5)	69.2%	no consensus on priority
50	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 ~~potential errors.~~	4.5 (4-5)	96.2%	modified	5 (4-5)	96.3%	validated
			2 (1-2)	1: 38.5% 2: 42.3% 3: 19.2%	2	4 (3.25-5)	73.1%	no consensus on priority
51	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 ~~that vents to the outside of the building~~ 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	5 (5-5)	96.4%	modified	5 (5-5)	92.6%	validated & completed
			1 (1-1)	1: 82.1% 2: 17.9% 3: 0.0%	1	5 (2.25-5)	69.2%	no consensus on priority
52	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. ~~Step-over barriers are used to separate the different stages of gowning.~~	5 (4-5)	92.9%	modified	5 (4-5)	96.3%	validated
			2 (1-2.5)	1: 40.7% 2: 33.3% 3: 25.9%	2	4 (2.25-5)	73.1%	no consensus on priority

N°	Item	Additional information	Delphi 1st round			Delphi 2nd round		
			Median (Q1-Q3) Level of agreement	% of 4 & 5 for level of agreement	Status	Median of agreement (Q1-Q3) for content and formulation of item	% of 4 & 5 for level of agreement with the item	Status
			Priority	Prioritization rate		for level of Priority	With the median priority	
53	A pass-through hatch ~~(distinct from the staff airlock)~~ enables the transfer of cytotoxic preparations between the cytotoxic prepration room and the external environment.	Ideally distinct from the staff airlock. ~~A system should be in place to prevent the simultaneous airlock door opening.~~	5 (4-5)	92.9%	modified	5 (4-5)	96.3%	validated
			2 (1-3)	1: 37.0% 2: 33.3% 3: 29.6%	2	4 (3.25-5)	73.1%	no consensus on priority
54	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.	5 (4-5)	88.9%	agreement	5 (4-5)	92.6%	validated
			2 (1-2)	1: 48.0% 2: 28.0% 3: 24.0%	2	4 (2-5)	69.2%	no consensus on priority
55	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).	5 (4-5)	100.0%		5 (4-5)	96.3%	
			1 (1-2)	1: 59.3% 2: 33.3% 3: 7.4%	1	4 (1.25-5)	69.2%	no consensus on priority
Hygiene and protective equipments								
56	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 jewelery, wrist-watches or makeup.	5 (4-5)	89.3%	agreement	5 (5-5)	100.0%	validated
			1 (1-2)	1: 64.3% 2: 28.6% 3: 7.1%	1	5 (4-5)	76.9%	consensus
57	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 ~~(2 pairs of gloves, gown or overall, mask, goggles, hair cover, and shoes and shoes covers).~~	~~Staff should wear lint-free, preferably disposable, low permeability fabric, long sleeved, rear entry gowns with elastic or knitted cuffs. Double-gloving should imply 1 pair of powder-free latex (minimum thickness 0.2 mm) or nitrile gloves worn under the gown cuff and 1 pair of sterile gloves placed over the gown cuff. They should also wear type P2 (N95) or P3 masks and goggles with lateral protection.Shoes dedicated to this activity should be sterilisable.~~	4 (4-5)	84.6%	modified	5 (4-5)	96.3%	validated
			2 (1-2)	1: 40.0% 2: 56.0% 3: 4.0%	2	4 (2-5)	57.7%	no consensus on priority
58	During compounding, gloves are regularly changed or are immediately replaced when torn, punctured or directly contaminated.	According to recommendations, gloves should be changed every 30 minutes.	5 (4-5)	96.4%	modified	5 (4-5)	100.0%	validated
			1 (1-2)	1: 66.7% 2: 22.2% 3: 11.1%	1	4 (2-5)	72.0%	consensus
59	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")		5 (4-5)	92.9%	agreement	5 (4-5)	92.6%	validated
			2 (1-2)	1: 42.9% 2: 39.3% 3: 14.3%	2	4 (3.25-4)	73.1%	no consensus on priority

N°	Item	Additional information	Delphi 1st round			Delphi 2nd round		
			Median (Q1-Q3) Level of agreement	% of 4 & 5 for level of agreement	Status	Median of agreement (Q1-Q3) for content and formulation of item	% of 4 & 5 for level of agreement with the item	Status
			Priority	Prioritization rate		for level of Priority	With the median priority	
60	Appropriate measures are used to avoid insects or other animals entering preparation areas.		5 (4-5)	96.3%	agreement	5 (5-5)	100.0%	validated
			1 (1-2)	1: 63.0% 2: 29.6% 3: 7.4%	1	5 (3.25-5)	73.1%	no consensus on priority
61	The storage and use of leftover cytostatics 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).	5 (5-5)	92.9%	modified	5 (5-5)	100.0%	validated
			1 (1-1)	1: 89.3% 2: 7.1% 3: 3.6%	1	5 (4-5)	76.9%	consensus
Preparation process set up								
62	Doors and windows are closed during compounding.	In an aseptic area, windows should be sealed anyway	5 (5-5)	92.9%	agreement	5 (5-5)	96.3%	validated
			1 (1-2)	1: 63.0% 2: 33.3% 3: 3.7%	1	5 (3.25-5)	73.1%	no consensus on priority
63	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). ~~Work surfaces should be cleaned with a detergent and then disinfected with alcohol~~. Ventilation should be switched on at least 30 minutes before drug preparation starts and not stopped earlier than 30 minutes after work ends.	5 (4-5)	92.9%	modified	5 (4-5)	92.6%	validated
			1 (1-2)	1: 53.6% 2: 46.4% 3: 0.0%	1	5 (4-5)	76.9%	consensus
64	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. ~~signed off by the certified person.~~	5 (4-5)	100.0%	agreement	5 (4-5)	92.6%	validated & completed
			1.5 (1-2)	1: 50.0% 2: 39.3% 3: 10.7%	1	5 (2.5-5)	73.1%	no consensus on priority
65	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.	5 (5-5)	89.3%	modified	5 (5-5)	92.6%	validated
			1 (1-2)	1: 66.7% 2: 25.9% 3: 7.4%	1	4 (4-5)	76.0%	consensus
Preparation techniques								

N°	Item	Additional information	Delphi 1st round			Delphi 2nd round		
			Median (Q1-Q3) Level of agreement	% of 4 & 5 for level of agreement	Status	Median of agreement (Q1-Q3) for content and formulation of item	% of 4 & 5 for level of agreement with the item	Status
			Priority	Prioritization rate		for level of Priority	With the median priority	
66	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.	5 (4-5)	92.9%	agreement	5 (4-5)	92.6%	validated
			2 (1-2)	1: 48.1% 2: 37.0% 3: 14.8%	2	4 (2-5)	61.5%	no consensus on priority
67	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.~~	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.	5 (4-5)	88.9%	modified	5 (4.5-5)	96.3%	validated
			1 (1-2)	1: 53.8% 2: 23.1% 3: 23.1%	1	5 (4-5)	76.9%	consensus
68	~~The vial size closest to the dose prescribed is selected.~~	~~This approach should minimise the risk of errors and leftovers.~~	4 (3-5)	66.7%	agreement	4 (4-5)	81.5%	Deleted
			3 (1.25-3)	1: 27.3% 2: 27.3% 3: 45.5%	3	4 (3-4.75)	68.0%	no consensus on priority
69	The operator compounds preparations by strictly following the operating instructions.		5 (5-5)	100.0%	agreement	5 (4.5-5)	100.0%	validated
			1 (1-2)	1: 71.4% 2: 28.6% 3: 0.0%	1	5 (4-5)	76.9%	consensus
70	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.	5 (5-5)	100.0%	agreement	5 (4.5-5)	96.3%	validated
			1 (1-2)	1: 64.3% 2: 35.7% 3: 0.0%	1	5 (4-5)	69.2%	no consensus on priority
71	The operator uses proper working techniques to reduce the risks of chemical contamination or needlestick injuries or cuts.	The operator should for example: either use Luer-lock connections on needles and syringes to minimise the risk of separation in case of overpressurisation 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.	5 (4-5)	96.4%	modified	5 (4.5-5)	96.3%	validated
			1 (1-2)	1: 57.1% 2: 32.1% 3: 10.7%	1	4.5 (2.25-5)	69.2%	no consensus on priority
72	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).	5 (4-5)	96.4%	agreement	5 (4-5)	92.3%	validated
			2 (1-2)	1: 35.7% 2: 46.4% 3: 17.9%	2	4 (2.5-5)	73.1%	no consensus on priority
73	The operator uses a syringe size appropriate to the sample volume.	The syringe ~~should be no more than three-quarters full when filled with the required volume of solution, in order to minimise the risk of the plunger separating from the syringe barrel, and~~ should not be less than one-third full, in order to ensure the precision of the volume measured.	5 (4-5)	82.1%	modified	5 (4-5)	92.6%	validated
			2 (1-2)	1: 33.3% 2: 55.6% 3: 11.1%	2	4 (2-5)	65.4%	no consensus on priority

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			Median (Q1-Q3) Level of agreement	% of 4 & 5 for level of agreement	Status	Median of agreement (Q1-Q3) for content and formulation of item	% of 4 & 5 for level of agreement with the item	Status
			Priority	Prioritization rate		for level of Priority	With the median priority	
74	I.V tubing is primed prior to adding the cytotoxic product in the infusion bag.		5 (4-5)	89.3%	modified	5 (4-5)	92.6%	validated
			2 (1-2.25)	1: 32.1% 2: 42.9% 3: 25.0%	2	4 (2.25-4.75)	69.2%	no consensus on priority
75	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	5 (4-5)	96.3%	modified	5 (4-5)	96.3%	validated
			2 (1-3)	1: 37.0% 2: 33.3% 3: 29.6%	2	4 (2.25-5)	69.2%	no consensus on priority
Packaging and labeling								
76	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.	5 (4-5)	92.9%	agreement	5 (4.5-5)	100.0%	validated
			1.5 (1-2)	1: 50.0% 2: 32.1% 3: 17.9%	1	5 (4-5)	76.9%	consensus
77	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	5 (4-5)	92.9%	agreement	5 (4-5)	96.3%	validated & completed
			2 (1-2)	1: 50.0% 2: 39.3% 3: 10.7%	2	4 (3.25-5)	73.1%	no consensus on priority
78	The final product's primary packaging is adequately and unambiguously labelled according to Best Practices and local regulation	For example the label should ~~must~~ 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).	5 (4.75-5)	92.9%	modified	5 (4.5-5)	96.3%	validated
			1 (1-1)	1: 77.8% 2: 18.5% 3: 3.7%	1	5 (1.75-5)	73.1%	no consensus on priority
Checking procedure								
79	~~During the preparation,~~ Identity and volume of the drugs used are double-checked by the operator and using a reconciliation method ~~during the preparation (no 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	5 (4-5)	89.3%	modified	5 (4.5-5)	88.9%	validated & completed

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			Priority	Prioritization rate		for level of Priority	With the median priority	
	~~checking a posteriori)~~	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.	1.5 (1-2.25)	1: 50.0% 2: 25.0% 3: 25.0%	1	5 (4-5)	76.9%	consensus
80	No preparations are released and dispensed before the ~~pharmacist~~ 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. colour, clarity, particle free); and finished pack integrity via a visual inspection.	5 (4-5)	82.1%	modified	5 (4.5-5)	92.6%	validated & completed
			1 (1-2)	1: 55.6% 2: 33.3% 3: 11.1%	1	5 (4-5)	76.9%	consensus
Documentation								
81	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.	5 (4-5)	96.4%	agreement	5 (4.5-5)	100.0%	validated
			1 (1-2)	1: 53.6% 2: 42.9% 3: 3.6%	1	5 (2.5-5)	73.1%	no consensus on priority
82	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, ~~in accordance with GMP~~, it ~~must~~ 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 authorisation for any deviation from the master formula; and signature of the person responsible of production.	4 (4-5)	85.7%	agreement	4 (4-5)	92.3%	validated & completed
			2 (1.75-3)	1: 25.0% 2: 32.1% 3: 42.9%	2	4 (2-4)	68.0%	no consensus on priority
83	Each preparation is recorded on a preparation logbook	The logbook can also be electronically available	5 (4-5)	82.1%	modified	5 (4-5)	92.6%	validated
			2 (1-2)	1: 28.6% 2: 50.0% 3: 21.4%	2	4 (2-4)	61.5%	no consensus on priority

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			Priority	Prioritization rate		for level of Priority	With the median priority	
Maintenance								
84	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.	5 (4-5)	96.4%	agreement	5 (4-5)	96.3%	validated
			1.5 (1-2)	1: 50.0% 2: 39.3% 3: 10.7%	1	4.5 (2.5-5)	73.1%	no consensus on priority
85	Surrounding conditions (microbiological contamination, particulate contamination) are regularly monitored according to a planned monitoring programme.	if cleanroom	5 (4.5-5)	92.6%	modified	5 (4-5)	88.9%	validated
			1 (1-2)	1: 63.0% 2: 25.9% 3: 11.1%	1	5 (1.25-5)	69.2%	no consensus on priority
Non sterile preparation								
86	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)	~~Generally speaking~~ Whenever possible, sterile and non-sterile preparation activities should not be performed within the same BSC. ~~For occasional non-sterile compounding (creams, liquid mixtures) of cytotoxic medicines, equipment usually for sterile preparations may be used but must be decontaminated, cleaned and disinfected before resuming sterile compounding in that BSC.~~	4 (4-5)	78.6%	modified	4 (4-5)	96.3%	validated
			2 (1-3)	1: 28.0% 2: 40.0% 3: 32.0%	2	4 (2.5-5)	73.1%	no consensus on priority
ADMINISTRATION								
Management and organisation								
87	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.	4 (4-5)	100.0%	agreement	4 (4-5)	96.3%	validated & completed
			2 (1.25-2)	1: 26.9% 2: 57.7% 3: 15.4%	2	4 (3.25-5)	73.1%	no consensus on priority
88	Only trained, entitled personnel are permitted to administer cytotoxic medicines to patients.	See chapter on "Personnel".	5 (4-5)	96.4%	agreement	5 (4-5)	100.0%	validated
			1 (1-2)	1: 60.7% 2: 35.7% 3: 3.6%	1	4.5 (4-5)	76.9%	consensus
Hygiene and safety measures								
89	Access to the chemotherapy administration area is limited to healthcare personnel,	Children and pregnant and breastfeeding women should avoid the chemotherapy administration area.	4 (4-5)	85.2%	agreement	4 (4-5)	92.6%	validated & completed

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			Priority	Prioritization rate		for level of Priority	With the median priority	
	patients and a limited number of relatives, if essential; the latter are informed of the potential risks.		2 (1.25-3)	1: 26.9% 2: 34.6% 3: 38.5%	2	4 (3-5)	65.4%	no consensus on priority
90	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 jewellery.	5 (4-5)	96.4%	agreement	5 (5-5)	96.3%	validated
			1 (1-2)	1: 53.6% 2: 35.7% 3: 10.7%	1	5 (4-5)	76.9%	consensus
91	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, ~~2 pairs of~~ gloves ~~(one pair worn under the cuff, one pair worn over the cuff). For oral adminsitration, 1 pair of gloves is recommended; for topical adminstration (i.e. creams) 2 pairs are recommended~~. If there is a risk of splashing or an aerosol, protective googles and a mask ~~(FFP2 or N95)~~ are also recommended.	4 (4-5)	81.5%	modified	4 (4-5)	84.6%	validated
			2 (2-3)	1: 24.0% 2: 40.0% 3: 36.0%	2	4 (2-5)	64.0%	no consensus on priority
92	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.	5 (4.75-5)	96.4%	modified	5 (5-5)	92.6%	validated & completed
			1 (1-2)	1: 60.7% 2: 25.0% 3: 14.3%	1	5 (4-5)	76.9%	consensus
93	After administration of the chemotherapy, staff wash their hands with soap and water.		5 (4-5)	92.9%	agreement	5 (4.5-5)	92.6%	validated
			1 (1-2)	1: 59.3% 2: 37.0% 3: 3.7%	1	4.5 (4-5)	76.9%	consensus
Documentation								
94	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 standardised/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.	5 (4-5)	96.3%	modified	5 (4-5)	96.3%	validated & completed
			2 (1-2)	1: 33.3% 2: 59.3% 3: 7.4%	2	4 (2-5)	65.4%	no consensus on priority
95	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.	5 (5-5)	100.0%	agreement	5 (5-5)	100.0%	validated
			1 (1-2)	1: 66.7% 2: 29.6% 3: 3.7%	1	5 (4-5)	76.9%	consensus
96	The personnel question the patient to verify that his/her identity (given name, family name, date of birth) matches the	A checklist should be used to verify and document the control.	5 (4.5-5)	100.0%	agreement	5 (5-5)	100.0%	validated

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			Priority	Prioritization rate		for level of Priority	With the median priority	
	administration plan and the information written on the product.		1 (1-2)	1: 70.4% 2: 18.5% 3: 11.1%	1	5 (4-5)	76.9%	consensus
				Work practices				
97	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 ~~IV line or needle~~ removal in order to contain any possible leakage.	5 (4-5)	96.2%	modified	5 (4-5)	100.0%	validated
			2 (1-2.75)	1: 30.8% 2: 42.3% 3: 26.9%	2	4 (4-5)	76.0%	consensus
98	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 retropriming) are possible as far as the risk of exposure of the healthcare personnel is minimized during the administration	5 (4-5)	92.3%	modified	5 (4-5)	92.6%	validated
			2 (1-2)	1: 48.0% 2: 36.0% 3: 16.0%	2	4 (2.5-5)	73.1%	no consensus on priority
99	The ~~tubing~~ infusion is safely ~~disconnected~~ 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 aerolization	5 (4-5)	96.4%	modified	5 (5-5)	96.3%	validated
			1 (1-2)	1: 66.7% 2: 25.9% 3: 7.4%	1	5 (2.5-5)	73.1%	no consensus on priority
100	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 collective protective equipment. ~~under the same conditions as for parenteral cytotoxic drugs.(see chapter on "Preparation")~~	5 (4-5)	89.3%	modified	5 (5-5)	96.3%	validated & completed
			1 (1-2)	1: 59.3% 2: 33.3% 3: 7.4%	1	5 (4-5)	76.9%	consensus
	INCIDENT MANAGEMENT							
				Surface contamination				
101	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. ~~This is printed out and displayed in areas where cytotoxic medicines are handled.~~	Any accidental leak or spillages must be contained (the zone must be identified and marked out) and cleaned up immediately by ~~qualified~~ trained staff wearing appropriate personal protective equipment.	5 (4-5)	96.4%	modified	5 (4-5)	100.0%	validated
			1 (1-1.25)	1: 75.0% 2: 17.9% 3: 7.1%	1	5 (4-5)	76.9%	consensus
102	All staff members who might be involved in handling cytotoxic medicines have received	Staff should undergo training and simulation exercises.	5 (5-5)	92.9%	agreement	5 (4.5-5)	100.0%	validated

N°	Item	Additional information	Delphi 1st round			Delphi 2nd round		
			Median (Q1-Q3) Level of agreement	% of 4 & 5 for level of agreement	Status	Median of agreement (Q1-Q3) for content and formulation of item	% of 4 & 5 for level of agreement with the item	Status
			Priority	Prioritization rate		for level of Priority	With the median priority	
	training appropriate to their roles regarding the procedures and measures to be taken in case of a spill or a breakage.		1 (1-2)	1: 60.7% 2: 25.0% 3: 14.3%	1	4.5 (3.25-5)	73.1%	no consensus on priority
103	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.	5 (4-5)	85.7%	agreement	5 (4-5)	96.3%	validated
			1 (1-2)	1: 55.6% 2: 29.6% 3: 14.8%	1	4 (4-5)	76.9%	consensus
104	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.	5 (4.75-5)	89.3%	agreement	5 (4-5)	96.3%	validated & completed
			1 (1-2)	1: 59.3% 2: 37.0% 3: 3.7%	1	5 (4-5)	76.9%	consensus
105	Used materials are directly discarded according to the waste management procedure ~~or cleaned and decontaminated according to established procedures.~~	If economic issues, some objects could be cleaned and decontaminated according to an adequate procedure (e.g. safety glasses , shovel etc.)	5 (4.75-5)	92.9%	modified	5 (4-5)	100.0%	validated
			1 (1-2)	1: 60.7% 2: 28.6% 3: 10.7%	1	5 (4-5)	76.9%	consensus
106	Spill kits are replaced as soon as possible in case of future incidents.	~~in less than 48 hours.~~ Ideally, a replacement kit should be available in advance.	5 (4-5)	96.4%	modified	5 (4-5)	92.6%	validated
			1.5 (1-2)	1: 50.0% 2: 46.4% 3: 3.6%	1	4 (3.25-5)	73.1%	no consensus on priority
Staff contamination								
107	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.	5 (4-5)	92.6%	agreement	5 (4.5-5)	100.0%	validated & completed
			1 (1-2)	1: 53.6% 2: 32.1% 3: 14.3%	1	5 (4-5)	76.9%	consensus
108	The equipment and materials for managing the emergency treatment for chemical contaminated staff are located in areas where cytotoxic medicines are preprared, administered, ~~transported~~	Close proximity of an emergency shower or water supply. For eyes, a sterile isotonic solution (0.9% sodium chloride) is recommended	5 (4-5)	92.9%	modified	5 (4-5)	96.3%	validated & completed
			1 (1-2)	1: 51.9% 2: 25.9% 3: 22.2%	1	5 (4-5)	76.0%	consensus
109	All staff members involved in handling cytotoxic medicines have received		5 (4-5)	92.9%	agreement	5 (4.5-5)	92.6%	validated

N°	Item	Additional information	Delphi 1st round			Delphi 2nd round		
			Median (Q1-Q3) Level of agreement	% of 4 & 5 for level of agreement	Status	Median of agreement (Q1-Q3) for content and formulation of item	% of 4 & 5 for level of agreement with the item	Status
			Priority	Prioritization rate		for level of Priority	With the median priority	
	appropriate training according to their tasks. They know the procedures and measures to take in case of staff contamination.		1 (1-2)	1: 52.6% 2: 36.8% 3: 10.5%	1	4.5 (4-5)	76.9%	consensus
	Extravasations							
110	There is an established standard operating procedure for managing extravasation of cytotoxic medicines ~~administered in the facility.~~	Treatment protocols for managing extravasations ~~should differentiate~~ might differ ~~between~~ depending on the agents~~:~~ "non vesicant", "irritant" and "vesicant" agents.	5 (4-5)	92.9%	modified	5 (4-5)	100.0%	validated
			1 (1-2)	1: 60.7% 2: 32.1% 3: 7.1%	1	4.5 (4-5)	76.9%	consensus
111	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.	5 (4-5)	92.6%	agreement	5 (4-5)	100.0%	validated
			2 (1-2)	1: 48.1% 2: 37.0% 3: 14.8%	2	4.5 (2.25-5)	69.2%	no consensus on priority
112	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.	5 (4-5)	92.6%	agreement	5 (4-5)	96.3%	validated
			1.5 (1-2)	1: 50.0% 2: 21.4% 3: 28.6%	1	4 (2.25-5)	73.1%	no consensus on priority
	Quality assurance							
113	All incidents involving cytotoxic medicines are reported, monitored, analysed, recorded and any corrective measures applied are followed up on and evaluated.	All incidents must be reported on a incident report form. Its causes should be analysed in order to avoid future repetition.	4 (4-5)	92.9%	agreement	4 (4-5)	96.3%	validated
			2 (2-3)	1: 21.4% 2: 35.7% 3: 42.9%	2	4 (2.25-5)	69.2%	no consensus on priority
	WASTE MANAGEMENT							
	Waste disposal							
114	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.	5 (4-5)	96.4%	agreement	5 (4-5)	96.3%	validated
			1 (1-2)	1: 60.7% 2: 35.7% 3: 3.6%	1	5 (4-5)	76.9%	consensus
115	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	5 (4-5)	96.3%	modified	5 (4.5-5)	96.3%	validated

N°	Item	Additional information	Delphi 1st round			Delphi 2nd round		
			Median (Q1-Q3) Level of agreement	% of 4 & 5 for level of agreement	Status	Median of agreement (Q1-Q3) for content and formulation of item	% of 4 & 5 for level of agreement with the item	Status
			Priority	Prioritization rate		for level of Priority	With the median priority	
		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 differenciate between slightly contaminated (traces of cytotoxics) and heavily contaminated (leftovers, expired vials, etc) waste	1 (1-2)	1: 55.6% 2: 33.3% 3: 11.1%	1	4.5 (2.5-5)	73.1%	no consensus on priority
116	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, exept when disposing waste.	5 (4-5)	100.0%	agreement	5 (4.5-5)	100.0%	validated
			1.5 (1-2)	1: 50.0% 2: 35.7% 3: 14.3%	1	5 (4-5)	76.9%	consensus
117	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	5 (5-5)	96.4%	agreement	5 (5-5)	100.0%	validated
			1 (1-2)	1: 57.1% 2: 42.9% 3: 0.0%	1	5 (4-5)	76.9%	consensus
118	Only trained~~, qualified~~ personnel handle cytotoxic waste containers; they wear approriate personal protective equipment.	a minima :Gloves~~, gown.~~	4 (4-5)	88.9%	modified	4 (4-5)	96.3%	validated & completed
			2 (1.5-3)	1: 25.9% 2: 37.0% 3: 37.0%	2	4 (2.25-4)	69.2%	no consensus on priority
119	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.	4 (4-5)	96.4%	agreement	4 (4-5)	96.3%	validated & completed
			2 (1.75-3)	1: 25.0% 2: 32.1% 3: 42.9%	2	4 (4-5)	76.9%	consensus
120	Cytotoxic waste is incinerated at 1200°C	~~Under certain regulations, slightly contaminated waste can be disposed of together with household waste.~~ Depending on national regulations, waste with low levels of chemical contamination can follow different types of disposal	5 (4-5)	96.2%	modified	5 (4-5)	84.6%	validated & completed
			1.5 (1-2)	1: 50.0% 2: 26.9% 3: 23.1%	1	4 (2-5)	68.0%	no consensus on priority
Patients'excreta								
121	Trained personnel handle the excreta (vomit, urine, faeces, blood, or puncture liquid) of patients undergoing chemotherapy	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	4 (4-5)	96.4%	modified	4 (4-5)	92.6%	validated

N°	Item	Additional information	Delphi 1st round			Delphi 2nd round		
			Median (Q1-Q3) Level of agreement	% of 4 & 5 for level of agreement	Status	Median of agreement (Q1-Q3) for content and formulation of item	% of 4 & 5 for level of agreement with the item	Status
			Priority	Prioritization rate		for level of Priority	With the median priority	
	(for at least 7 days after treatment), they wear the appropriate personal protective equipment, including for cleaning toilets.	patient information)	2 (1-3)	1: 32.1% 2: 39.3% 3: 28.6%	2	4 (2-5)	76.9%	consensus
122	Contaminated linen should be placed in a bag clearly identified ~~labelled "Hazardous Contamination"~~ and forwarded to the laundry	See chapter on "Cleaning".	4 (4-5)	85.2%	modified	4 (4-5)	96.3%	validated
			2 (1-3)	1: 28.0% 2: 40.0% 3: 32.0%	2	4 (4-5)	76.9%	consensus
123	Mattresses and pillows are protected with plastic covers and wiped-down between patients.		5 (4-5)	100.0%	agreement	5 (4-5)	96.3%	validated
			2 (1-3)	1: 35.7% 2: 28.6% 3: 35.7%	2	4 (4-5)	69.2%	no consensus on priority
CLEANING								
Management and organisation								
124	Cleaning and maintenance tasks are only carried out by ~~qualified~~ trained personnel.	Cleaning staff have received appropriate training on cytotoxic medicines and safety measures they should apply.	4.5 (4-5)	96.4%	modified	5 (4-5)	96.3%	validated
			2 (1-2.25)	1: 32.1% 2: 42.9% 3: 25.0%	2	4 (2-4.75)	69.2%	no consensus on priority
125	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 ~~annually~~ regularly and updated when required.	4 (4-5)	100.0%	modified	4 (4-5)	96.3%	validated
			2 (1-2.25)	1: 39.3% 2: 35.7% 3: 25.0%	2	4 (3-4)	72.0%	no consensus on priority
Cleaning practices								
126	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 splashproof gown. (note: for cleaning up accidental spills, see chapter on "Incidents")	5 (4-5)	96.4%	agreement	4 (4-5)	96.3%	validated
			2 (1-2)	1: 35.7% 2: 53.6% 3: 10.7%	2	4 (2-4.75)	69.2%	no consensus on priority
127	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.	5 (4-5)	92.9%	agreement	5 (4-5)	96.2%	validated
			2 (1-3)	1: 44.4% 2: 22.2% 3: 33.3%	2	4 (4-5)	76.9%	consensus

N°	Item	Additional information	Delphi 1st round			Delphi 2nd round		
			Median (Q1-Q3) Level of agreement	% of 4 & 5 for level of agreement	Status	Median of agreement (Q1-Q3) for content and formulation of item	% of 4 & 5 for level of agreement with the item	Status
			Priority	Prioritization rate		for level of Priority	With the median priority	
128	Cleaning is only carried out using moistened materials.	No vacuum cleaners, no dry sweeping.	5 (4-5)	92.0%	agreement	5 (4-5)	96.2%	validated
			1 (1-2)	1: 56.0% 2: 24.0% 3: 20.0%	1	4 (4-5)	76.9%	consensus
129	Staff washes their hands thoroughly with soap immediately after cleaning activities.		5 (4-5)	96.4%	agreement	5 (4.5-5)	96.3%	validated & completed
			1 (1-2)	1: 57.1% 2: 39.3% 3: 3.6%	1	5 (4-5)	76.9%	consensus
130	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.	5 (4-5)	92.9%	agreement	5 (4-5)	92.6%	validated
			1 (1-2)	1: 57.7% 2: 34.6% 3: 7.7%	1	5 (4-5)	76.9%	consensus
131	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, ~~those should be emptied and sterilized once a month~~ 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	5 (5-5)	100.0%	modified	5 (5-5)	100.0%	validated & completed
			1 (1-2)	1: 64.3% 2: 32.1% 3: 3.6%	1	5 (4-5)	76.9%	consensus
Laundry								
132	Contaminated, reusable protective clothing (gowns) and linen soiled with patient excreta are placed in clearly labelled laundry bags and are washed separetely from other clothing.	Laundry should start with a cold prewash cycle and then continue using the normal washing process	5 (4-5)	88.5%	agreement	5 (4-5)	100.0%	validated
			2 (1-3)	1: 41.7% 2: 29.2% 3: 29.2%	2	4 (4-5)	76.0%	consensus
133	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	resitant gloves, gown with long sleeves	4 (4-5)	84.6%	agreement	4 (4-5)	88.9%	validated
			2 (1.75-3)	1: 25.0% 2: 33.3% 3: 41.7%	2	4 (3-5)	68.0%	no consensus on priority

N°	Item	Additional information	Delphi 1st round			Delphi 2nd round		
			Median (Q1-Q3) Level of agreement	% of 4 & 5 for level of agreement	Status	Median of agreement (Q1-Q3) for content and formulation of item	% of 4 & 5 for level of agreement with the item	Status
			Priority	Prioritization rate		for level of Priority	With the median priority	
PATIENT COUNSELLING								
134	The patient's informed consent for chemotherapy treatment is ~~documented.~~ 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.	5 (4-5)	76.9%	modified	5 (4-5)	92.6%	validated
			1 (1-2.25)	1: 56.5% 2: 21.7% 3: 21.7%	1	4.5 (3.25-5)	73.1%	no consensus on priority
135	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.	5 (4-5)	96.4%	agreement	5 (5-5)	96.3%	validated
			1.5 (1-2)	1: 50.0% 2: 39.3% 3: 10.7%	1	4.5 (4-5)	76.9%	consensus
136	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.		5 (4-5)	96.4%	agreement	5 (5-5)	96.3%	validated
			1.5 (1-2)	1: 50.0% 2: 42.9% 3: 7.1%	1	5 (4-5)	76.9%	consensus
137	Any patient counseling session is documented and added to the patient's file.		4 (4-5)	80.8%	agreement	4 (4-5)	85.2%	validated
			2 (2-3)	1: 24.0% 2: 36.0% 3: 40.0%	2	4 (3-5)	69.2%	no consensus on priority

4.3.3 Finalization of the tool

The final tool consists in 134 items classified in 10 different categories and further subdivided in 28 subcategories reflecting the flow of the cytotoxic medicines process throughout a health care facility.

The median score of the priority obtained in the first round was indicated for each item with a differentiation if a consensus had been obtained or not at the end of the second round. The following coding system was chosen:

- **I or i**: Indispensable (absolutely required even for occasional handling of cytotoxic medicines)
- **E or e**: Essential (required for regular use of cytotoxic medicines)
- **D or d**: Desirable (desirable if regular use and/or resources sufficient)

The capital letter indicated that an experts' consensus had been reached while the lowercase letter indicated no consensus.

Each assessment item has a scoring system ranging from 1 (no activity) to 4 (full implementation) to be filled by the evaluation team.

An option of non applicable is offered for item that could not be considered in the evaluated setting (table 10).

Table 10: scoring system for the self assessment (79)

Score	Definition
1	There has been **no activity** to implement this item
2	The item has been **discussed and considered, but it is has not been implemented yet**. There may be a document and no implementation and some staff awareness.
3	The item is **partially implemented** in the facility or implemented only in some areas, for some patients, drugs and/or staff.
4	The item is **fully implemented** throughout the facility for all patients, drugs and/or staff
N/A	Not applicable; It is not possible to consider the item in the local context

The complete tool is presented in Appendix 8.

5. DISCUSSION

This study enabled the validation of 134 assessment criteria regarding safe handling of cytotoxic medicines by an international pharmaceutical expert panel in oncology.
To our knowledge, it is the first assessment tool that addresses the different steps of the cytotoxic medicines handling process within a health facility, especially targeting LMIC and validated through a Delphi process involving experts from resource-replete and resource-constraint settings.
The final tool contained 134 items organized in 10 categories representing the handling processes of cytotoxic drugs (from receiving medicines to disposal of waste and supportive process as management, training etc.) and 28 sub-categories.

Although our tool shares similar items as the tools previously described under 2.2, the following differences can be pointed out.
Compared to the Swiss and Oncolor grids (75, 77), we broadened the scope of the tool and included activities related to cytotoxic drugs handling process outside of the centralized preparation unit (e.g., administration, patient information). However we didn't intend to cover all other aspects of a comprehensive cancer care center as the assessment tool developed by OECI (74). While covering more activities, our tool contains fewer items than the Swiss and Oncolor grids. Our objective was to obtain a transposable tool that could be use in various settings and enable rapid appraisal of the whole handling process. Therefore the tool doesn't include context-specific items compared to the other grids that were designed for inspection purpose of national or regional facilities using specific equipment or infrastructure and working according to internal procedures and local regulations.

Unlike existing tools, our work doesn't include items requiring integrated informatics technology (IT), and is therefore appropriate for LMIC. However, computerization of some processes is always listed as a desirable objective.

Finally, none of the existing tool has attempted to prioritize the quality indicators and safety measures, which constitutes an innovation of our tool.

5.1 EXPERT PANEL

60% (33/55) of the experts contacted accepted to participate in the study. Among them, we obtained a participation rate of 85% (28) in the 1st round and only one of the experts couldn't participate in the 2nd round. This high participation rate and the low number of dropout emphasize the interest of the experts in the study.

Although there is no consensus on the ideal number of experts to include in a Delphi panel, our results seem to correspond to other surveys described in the literature. In a systematic review (2011) of Delphi study developing Health Care Quality Indicators, *Boulkedid and colleagues* reported a median number (Q1; Q3) of 17 experts (11; 31) (80). In his book "*Méthodes quantitative de consultation d'experts"*, Maleki mentioned that a sufficient number of experts should be recruited to take into account the non-response and dropout during the survey. He added that in general it is indicated to invite twice more experts than the expected number and that at least 30 panelists are recommended to have a certain statistical significance (81).

Most importantly, the literature insists that the composition of the panel directly influences the quality of results generated and that relevant backgrounds, experience, time and willingness to participate are important criteria to consider (83).

The heterogeneity of the group is also mentioned to increase performance of the results (80, 81).

In our study, we chose to include only experts with pharmaceutical background that were highly experienced in oncology (median years of experience was 10 years (Q1=4: Q3=18)) instead of different categories of staff involved in the cytotoxic process. It would have been too difficult to identify and recruit a sufficient amount of experts of each category with the same geographical repartition to ensure an optimal balance in the representativeness of the different categories.

A pharmaceutical background with expertise in oncology and cytotoxic medicines enables to understand the risks and safety measures at all the different steps of the cytotoxics handling process. In contrary, other categories of staff may not have had the expertise to give their opinion and relevant inputs on certain practices not directly related to their activities. Obtaining a satisfactory level of response rate for each item would have been therefore more challenging with several categories of staff, while our results showed a very high average response rate in both rounds, respectively 98.5% (± 2.7%) and 99.7% (± 1.0%) for the level of agreement with the item and 96.9% (± 4.8%) and 95.8% (± 1.4%) for the prioritization.

Nevertheless, our panelists show certain heterogeneity in their characteristics, which strengthens the credibility and acceptance of the tool.
A large geographical repartition of the experts has been achieved with 13 countries represented from both high-income and low and middle-income countries.
The availability of the survey in English and in French languages allowed the involvement of experts from various regions of the world, which enriched the results with different cultures and experiences. However, it was difficult to identify pharmaceutical experts in oncology from least developed countries, as this specialty is hardly developing in those countries.
Most of the experts (75%) were working in an University Teaching Hospital as in many countries, oncology care centers are mostly found in an academic setting. Moreover, experts highly active and involved in the development of the oncology pharmacy field are more to be found in academic settings as well.

The expert panel consisted of a majority of women (64%). Ensuring gender balance in the experts' opinions was also an important aspect to consider; yet not much reported in Delphi literature.

5.2 LEVEL OF AGREEMENT

The level of agreement of the panelists was high since the first round, with more than 98,5% of items for which the median score was > 4 and more than 65% of the experts agreeing or totally agreeing with.
The low number of items added or eliminated between the rounds and the fact that at the end of the second round 100% of the items reached consensus emphasize the upstream work of pre-selection and elaboration of the items. The use of internationally well-recognized guidelines, standards and best practices as references participated in the high level of agreement obtained since the first round.

Furthermore, the comments made by the experts during the first round were reviewed during a steering committee meeting. The ensuing amendments suggested for some items increased globally the level of agreement at the end of the second round, with 100% of the items that reached consensus regarding their content and formulation.

5.3 PRIORIZATION OF THE ITEMS

One of the main difficulties was to obtain a consensus on the prioritization of the items. In the first round, only 14% items were ranked the same priority by > 65% of the experts. After submitting the median score obtained in the first round for the priority of each item, only 38.5% reached the expected consensus of agreement (>75% of agreement according to our definition) at the end of the second round. The threshold of 75% was chosen, as it was often mentioned to be a median threshold in the literature according to the systematic review on Delphi studies from *Diamond and colleagues* (2014) (84). Although the median score was 75%, studies reported also the use of lower thresholds (82, 84). Thus, if we had chosen a threshold at 70%, we would have obtained a consensus on the priority median score for more than two-third of the items, which somehow put in perspective our results.

Our findings show that consensus was more likely to be obtained for items of highest priority, with 45/52 (87%) ranked as a priority 1 (“indispensable”), while 7 (13%) were of priority 2 (“essential”). However we didn’t observed a general trend regarding the type of activities that reached a priority consensus as our results show that each category of the tool contained items that have reached consensus.

Experts were asked to prioritize the items while considering factors such as the probability of occurrence of the prevented risks, the criticality of the risk, the effectiveness of the measure, the feasibility. No systematic evaluation matrix was provided and prioritization of the items was left to the subjectivity of the expert. Consensus on prioritization was therefore much more difficult to obtain than consensus on the content of the items, for which recognized guidelines exist.
In its review, *Boulkedid and colleagues* reported that some studies benefit from a physical meeting with the panelists in order to discuss and clarify the reasons for disagreement when consensus was difficult (80). A physical meeting would have been hardly feasible in our study considering the geographical spread of the experts and the language barrier. Moreover, some studies stated the risks of introducing bias with physical meeting due to dominance of some experts and the lost of anonymity (80, 83).

In order to increase the level of consensus, the opportunity of realizing a third round has been considered. Indeed, between the two rounds, the feedback provided on prioritization of each item was only quantitative, i.e only statistical measures including the median score and percentage of vote for each priority rank were presented to the experts.
However, providing feedback with additional experts' qualitative comments and arguments could further help the panelists to revise potentially their judgment in a third round (80). Unfortunately, although it was asked in the instructions of the second round, very few experts gave their arguments and their preferred priority rank in case of disagreement with the median priority score. Therefore a third round would probably not result in a significant increase in the degree of consensus and might even lead to expert fatigue and dropout.

Despite the relatively low proportion of consensus on prioritization, we think that indicating in the final tool the median priority rank obtained with a distinction if the consensus was achieved or not during the Delphi might add value to the tool and provide guidance to health facilities to set priorities and objectives.

5.4 OUTLOOK

The development of this self-assessment tool represents a first step to build a continuous quality improvement approach of safe handling of cytotoxic medicines in LMIC.
In order to complete its validation, this tool will first need to be pilot-tested in various resource-constraint settings regarding its applicability by local health facilities, its appropriateness to the local context, and its usefulness, i.e. to identify strengths and weaknesses, to highlight opportunities for improvement, to raise awareness on the existing gaps in safety measures and to design an action plan.
The findings of this pilot study might participate in enhancing future acceptability and use of this tool by constraint-resource settings.

The evaluation of the tool could be conducted as an online survey, with the participation of several pilot sites. Besides the strict evaluation of the tool by local users, the collected data could serve additional purposes. Indeed, it could provide a baseline assessment of practices in the different settings and give information on the

variability of safety level that is implemented. It might also help identifying needs for development of additional tools or educational resources to further support the improvement of safe practices.
It could also be interesting to evaluate the variability of the results between several assessors for the same setting.

The validated tool will be launched and accessible on the Pharm-Ed online platform (www.Pharm-Ed.net) on a free access.
The Pharm-Ed project started in 2013 as an initiative from the Pharmacy Department of the University Hospitals of Geneva. It aims at strengthening knowledge and competences on rational use of medicines as well as promoting exchanges of experiences on Good Hospital Pharmacy practices in LMIC (90). An online platform has been launched in 2014 providing free resources and e-learning courses in the field of Hospital Pharmacy. A specific module dedicated to the management and safe handling of cytotoxic medicines is already under development, thus this self-assessment tool will complete the resources of this module.
Considering the variety of settings and the various levels of resources, it is likely that this tool would not fit perfectly all settings in all its details. This tool was elaborated as a generic tool that could be adapted by the local users to evaluate specific process of the health facilities. Therefore the tool will be available in a version that can easily be modified by the users (e.g., Microsoft® .doc or .xls version).

In the near future, the Pharm-Ed project plans to use this tool to monitor the changes in practices and evaluate the impact of its educational module on cytotoxic medicines and their safe handling in a before-after design study in collaboration with several pilots sites.

6. CONCLUSION

With the rising burden of cancer and the increased use of chemotherapy treatments, raising awareness on the importance of safe handling of cytotoxic drugs in LMIC has become a priority. Evidence of unsafe handling practices in many resource-constraint settings stressed the need to develop and implement strategies to prevent and limit direct and indirect risks related to these medicines. Limited resources should not compromise implementation of quality measures and jeopardize the safety of both patients and health workers or lead to harmful environmental consequences.
Quality and safety of handling practices should be set as a permanent objective in any health facilities dealing with chemotherapies.

This master thesis resulted in the development of a self-assessment tool covering safe handling practices of the entire cytotoxic medicines process within a health facility (from receiving the drugs to their administration to patients and final disposal of related waste).
The validation of 134 items by a large international panel of pharmaceutical experts in oncology practice from high and low and middle income countries through a Delphi method ensures the quality and exhaustiveness of the tool. The high participation rate of the experts underlined their interest and thus the relevance of this project.

To complete the validation of this self-assessment tool, an evaluation of its applicability, appropriateness and usefulness in several pilot sites is planned.

We hope that this tool will contribute in implementing continual quality improvement of safe handling of cytotoxic medicines in health facilities in LMIC. Indeed, using this self-assessment tool could support them to monitor progress and identify their strengths, weaknesses and area for improvement regarding best practices and recommendations. Even if the prioritization of some items has not reached the expected consensus, we hope that the indicated priority will guide them in defining their action plan and in resource allocation.

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9. APPENDICES

Appendix 1: Members of the steering committee and translators

Steering committee

	NAME		RESPONSABILITY
1	Pascal Bonnabry	Associate professor at the School of Pharmaceutical Sciences, University of Geneva, University of Lausanne	Head of Pharmacy HUG
2	Ludivine Falaschi (temporary replaced by Lucie Bouchoud)	Pharmacist HUG	In charge of the cytotoxic production unit
3	Laurence Cingria	Pharmacist HUG	In charge of the Quality assurance programme at the Pharmacy
4	Sandrine von Grünigen	Pharmacist HUG	Principal investigator, Pharm-Ed project manager

Translators

	NAME		RESPONSABILITY
1	www.publish-or-perish.ch	Professional translator	French-English translation
2	Pauline Le Pape	Pharmacist HUG	Back translation (English-French)

Appendix 2: Expert recruitment letter

Dear Sir or Dear Madam,

We are looking for international pharmacists (oncology experts) to participate in a research project. The aim of the research is to develop a self-assessment tool for safe handling of cytotoxic medicines and related waste in low and middle income countries (LMIC).

Unsafe practices regarding cytotoxic drugs handling have been highlighted in several studies, particularly in countries where access and use of those medicines have recently increased.

These past years, substantial efforts have been made to improve access to affordable chemotherapy treatments to tackle the rising burden of cancer in LMIC. In 2015, more than 20 cytotoxic medicines have been added in the updated version of the WHO essential medicines list. However persistent weaknesses in international and national cancer control programs regarding aspects related to their safe handling (storage, preparation, administration, waste disposal, etc.) emphasize the need of implementing improvement quality strategies in LMIC.

Our project aims at developing a self assessment tool for safe handling of cytotoxic medicines adapted to the context of LMIC. Based on existing recommendations and guidelines, we intend to select and prioritize quality and safety standards through a modified two-round online Delphi survey.
This Delphi method will gather the opinion of experts on specific topics in two rounds; the first one, with independent rating (blinded to others' answers); the second, with possible adjustments of the initial rating in order to reach convergence of opinions and build consensus. The validated tool will be tested in several pilot sites in LMIC.

We, hereby, invite you to take part in an international working group, as an expert, in the evaluation and validation of this tool. We aim to include a panel of international experts, 15 from resource-replete and 15 from resource-constrained countries.

The first round should start in April 2016 and the second round in June 2016. The time needed for each round should not exceed 1 hour.

This project has no financial nor commercial interest. The finalized tool will be available online in open access. There is no incentive to join the survey; however your participation will be mentioned.
If you agree to be take part in the project, please confirm by email **until January 15th**. In case of a positive answer you will be then contacted in March 2016.

Make sure to forward this email to any of your colleagues who might be willing to participate.

Hopefully this project will spark your interest and we remain at your disposal for any question you may have.

Sincerely,

Ms Sandrine von Grünigen Pharmacist in charge of Pharm-Ed project Pharmacie des Hôpitaux Universitaires de Genève Rue Gabrielle Perret Gentil 4 CH-1211 Genève 14, Suisse Phone : +41 22 37 23 996 Email : sandrine.vongrunigen@hcuge.ch www.Pharm-Ed.net http://pharmacie.hug-ge.ch	Prof. Pascal Bonnabry Chief Pharmacist Pharmacie des Hôpitaux Universitaires de Genève Rue Gabrielle Perret Gentil 4 CH-1211 Genève 14, Suisse Phone +41 22 37 23 974 Email : pascal.bonnabry@hcuge.ch www.Pharm-Ed.net http://pharmacie.hug-ge.ch

Appendix 3: List of the experts involved in the Delphi survey

	Name	Surname	City	Country	Type of facilities	Year(s) of experience in cytotoxic medicines
1	KESSAL	Reda	Alger	Algeria	University Hospital	8
2	DJERMOUNE	Salima	Blida	Algeria	University Hospital	3
3	GUERFI	Bahdja	Blida	Algeria	University Hospital	3
4	MEZAOUR	Yacine	Alger	Algeria	University Hospital	18
5	ROLAND*	Isabelle	Liège	Belgium	University Hospital	15
6	CRAUSTE-MANCIET	Sylvie	Bordeaux	France	University Hospital	20
7	VIGNERON	Jean	Nancy	France	University Hospital	28
8	NOIRET	Véronique	Metz	France	University Hospital	18
9	ESCALUP	Laurence	Paris	France	Private Hospital	23
10	MEDDAH	Bouchra	Rabat	Maroc	University Hospital	5
11	ACKERMANN	Monique	Morges	Switzerland	Regional Hospital	16
12	EVEQUOZ	Stéphanie	Sion	Switzerland	Regional Hospital	4
13	CONSTANTIN	Isabelle	Bern	Switzerland	University Hospital	10
14	BROGGINI	Claudia	Lugano	Switzerland	Private Facility	2
15	SENHAJI	Salim	Geneva	Switzerland	University Hospital	2
16	GUERFALI	Myriam	Tunis	Tunisia	University Hospital	15
17	LIMAYEM	Imen	Tunis	Tunisia	University Hospital	5
18	HAMDI	Adel	Tunis	Tunisia	University Hospital	3
19	BEN SAID	Azza	Tunis	Tunisia	University Hospital	1
20	SCHÖNING	Tilman	Heidelberg	Germany	University Hospital	16
21	MÜLLER RAMÍREZ	Claudio Felipe	Concepcion	Chile	University Hospital	4
22	KAMAL	Sherif	Cairo	Egypt	Regional Hospital	18
23	SWANEPOEL	Carolina	Pretoria	South Africa	University Hospital	15
24	KEETILE	Nicholas	Gezina	South Africa	University Hospital	5
25	STROTHER **	Matthew	Christchurch	New Zeland	Regional Hospital	10*
26	SAAR	Marika	Tartu	Estonia	University Hospital	6
27	VANDENBROUCKE	Johan	Gent	Belgium	University Hospital	39
28	CHAMBERS	Carole	Calgary	Canada	Cancer Control Alberta	31

* This expert didn't participate in the second round

**Medical Doctor, fellowship in Medical Oncology and Clinical Pharmacology with several years' worth of experience across several Sub-Saharan African countries (Kenya, Uganda, etc.) and Fiji, helping to establish cancer care infrastructure, including on-site evaluations of chemotherapy pharmacy practices

Appendix 4: Information about the survey sent to the experts

Hôpitaux Universitaires Genève — Pharm-Ed

Guide for validating the self-assessment tool on safe handling of cytotoxic medicines

How were criteria preselected?

The initial criteria that are submitted to you were preselected based on various references.

The objective was to refer to different types of documents published in English or French such as recommendations from scientific societies, guidelines and regulations from organ of workers'protection and regulatory framework.

In accordance with the philosophy of the project, the "sine qua non" condition was also that these documents could be consulted online with free access.

Table 1 : References used for selection of the criteria

DOCUMENTS	AUTHORS	YEAR	REGION/COUNTRIES	TYPE DE DOCUMENTS
Standards ISOPP	International Society of Oncology Pharmacy Practitioners	2007	International	Recommendations from scientific societies
QuapoS 4:Quality Standard for the Oncology Pharmacy Service with Commentary	DGOP e.V (German Society of Oncology Pharmacy) /ESOP (European Society of Oncology Pharmacy)	2008	Europe	Quality standards from scientific societies
ASHP Guidelines on Handling of Hazardous Drugs	American Society of health system pharmacists	2006	USA	Recommendations from scientific societies
USP (United States Pharmacopeia) Chapter 800: Hazardous Drugs-Handling in Healthcare settings	The Compounding Expert Committee	2015 (draft)	USA	Regulatory framework
Bonnes Pratiques de Préparation	Afssaps (Agence française de sécurité sanitaire de produits de santé)	2007	France	Regulatory framework
Suvapro: sécurité dans l'emploi des cytostatiques	Swiss Accident Insurance Fund	2004	Switzerland	Recommendations for occupational safety
WHO-Good Manufacturing Practices Annex 3	WHO Expert Committee on Specifications for Pharmaceutical Preparations	2010	International	Regulatory framework
Chemotherapy Adminsitration Safety Standards	American society of clinical Oncology (ASCO)/Oncology Nursing society (ONS)	2013	USA	Quality standards from scientific societies
OSHA technical Manual: Controlling Occupational Exposure to Hazardous Drugs Section IV, chapter 2	Occupational Safety & Health Administration (OSHA) (US Departement of Labor)	Consulté 2016	USA	Recommendations for occupational safety
NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings	National Institute for Occupational Safety and Health	2004	USA	Recommendations for occupational safety

Mars 2016 1/3

How was this tool elaborated?

137 criteria were preselected and organized in categories and sub-categories (table2).

A preliminary review of the set of criteria was done by the steering committee.

The tool was then translated into English (orginial version was in French) and a back-translation into French was performed to ensure that the two version are identical.

Table 2 : Overview of the tool structure

CATEGORIES/ SUB-CATEGORIES	ITEMS NB
1. Management	**11**
2. Personnel	**8**
• Education and training	4
• Medical surveillance	4
3. Logistics	**17**
• Receipt	6
• Storage	6
• Transport	5
4. Prescription	**5**
5. Preparation	**45**
• Management and organisation	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	**14**
• Management	2
• Hygiene and safety measures	5
• Documentation	3
• Work practices	4
7. Incidents management	**13**
• Surface contamination	6
• Staff contamination	3
• Extravasations	3
• Quality assurance	1
8. Cytotoxic waste management	**10**
• Waste disposal	7
• Patients' excreta	3
9. Cleaning	**10**
• Management and organisation	2
• Cleaning practices	6
• Laundry	2
10. Patients counselling	**4**
TOTAL	**137**

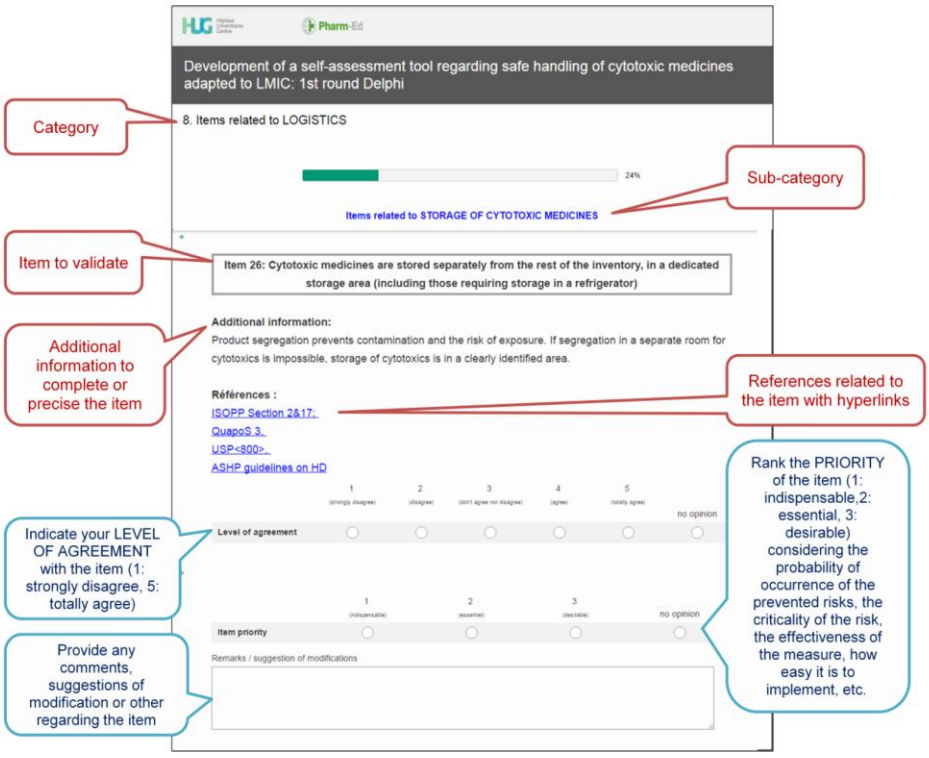
What does the Delphi survey questionnaire look like?

The survey questionnaire is administered via Surveymonkey® software and is organized as follows:

- The set of criteria are grouped into categories and subcategories
- Each sub-category is presented on a new page
- At the top of each page validation instructions are repeated

Each criterion is organized as follows:

- The criterion itself (box)
- Additional information to clarify/complete the criterion
- References (with hyperlink) on which the criterion and additional information are based.
- The rating scale of your level of agreement with the criterion and the additional information from 1 to 5 (1 = strongly disagree, 5 = totally agree)
- The ranking scale to set the priority of the item on 1 to 3. [1 = essential (absolutely required even for occasional handling of cytotoxic medicines), 2 = essential (required for regular use of cytotoxic medicines) 3 = desirable (desirable if regular use and / or sufficient resources)]
- A text box for your remarks, proposals for amendments, comments or additions of criteria (with reference).



Appendix 5: Survey instructions

Dear Sir/Madam,

Thanks a lot for participating in this survey!

In the coming days, you will get a link to start the electronic survey. The latter aims at developing a self-assessment tool for safe handling of cytotoxic medicines, adapted to resource-constraint settings, by means of a two-round Delphi method[2].

In this survey, you will have to **rate your level of agreement** with the different items (content and formulation), according to a 1-5 likert scale:
1: strongly disagree
2: disagree
3: don't agree nor disagree
4: agree
5: totally agree.

On one hand, this tool should enable health facilities to identify gaps with a scoring system and on the other hand to establish an action plan to improve their processes
Therefore, in order to guide them in decision making, we will ask you to **prioritize the different items** while considering the probability of occurrence of the prevented risks, the criticality of the risk, the effectiveness of the measure, how easy it is to implement, etc.

Prioritization will rank the items on a 1 to 3 scale[3]:
1: indispensable (absolutely required even for occasional handling of cytotoxic medicines)
2: essential (required for regular use of cytotoxic medicines)
3: desirable (desirable if regular use and/or resources sufficient)

An answer to all the items in the survey is required. Each item is completed with references and sometimes additional information. A free text field will allow you to add comments, references, suggest modification (+/- addition of items with references) to any item.

After analysing anonymously the answers from the expert panel, we will submit next May-June the items selected in the first round (those rated between 4 and 5 by more than 60 % of experts and having obtained a median ≥ 4). **Your participation to the 2 rounds is required in order to consider your final results.**

For information, we advise you to plan 1-hour slot over the next two weeks in order to fill in the questionnaire. If you want to do it in several times, the system allow you to leave the survey and come back later. For that you can reconnect at any time by following the personal URL received in response to the survey. Finally you can read the attached pdf document to prepare the survey (note: all answers must be provided through the electronic survey).

For any problems or questions, please contact:
Sandrine von Grünigen:

sandrine.vongrunigen@hcuge.ch

tél: +41 22 372 39 96

[2] The Delphi method builds a consensus of experts, independently interviewed, using questionnaires.

[3] In analogy, for example, to VEN classification (vital-essential-non essential) for medicines

Appendix 6: Extract of an individual feedback report

Development of a self-assessment tool regarding safe handling of cytotoxic medicines adapted to LMIC: 1st round Delphi

Item 3 : Policies and procedures ensure that guidelines for the safe handling of medicines are applied to all processes in which cytotoxic drugs are handled

Additional information:

Policies and procedures are updated ~~at least annually~~ regularly. The frequency of uptdate is to be defined by the local institution, according of the context. Any changes must be documented.

3	% of answers	Median	% of 4 and 5	Your vote
Agreement	100%	4	92.9%	4
Priority	100%	1	[redacted]	3

Item 4 : A self-assessment of compliance with safety guidelines regarding the safe handling of cytotoxic medicines is carried out regularly ~~annually~~

Additional information:

Each intitution should define its frequency according to local context.

4	% of answers	Median	% of 4 and 5	Your vote
Agreement	100%	4	82.1%	4
Priority	92.9%	2	[redacted]	3

Item 5 : Material Safety Data Sheets (MSDS) are readily available for all cytotoxic medicines used in the facility

Additional information:

MSDS can be kept in a file, be available on a computer or be consulted via the internet.

5	% of answers	Median	% of 4 and 5	Your vote
Agreement	100%	4	82.1%	4
Priority	94.6%	2	[redacted]	3

Appendix 7: conflict of interest declaration form

Development of a self-assessment tool regarding safe handling of cytotoxic medicines adapted to LMIC: 1st round Delphi

3. Conflict of interest declaration

9%

Please complete this conflict of interest form

* Date

Date DD / MM / YYYY

I, undersigned

Name :

Surname :

Address:

Country :

Email :

Agree to participate in the expert group for the elaboration of the development of a self-assessment tool for safe handling of cytotoxic medicines for countries with limited resources .
By accepting , I commit myself to explicitly declare any potential or real conflict of interest related to the design of the tool.
As: relationships (financial or personal) with the pharmaceutical industry , biomedical equipment manufacturers , as well as companies whose products or services are related to the topic, any participation in the financing of a study and / or the belonging to one or more of these institutions.

* I declare

- ◯ I have no conflicts of interest to declare;
- ◯ We have a competing interest to declare (please fill in box below):

The purpose of this statement is to determine if either statements or conclusions of the authors can be biased by any interest.

In case of doubt, I will contact : Sandrine von Grünigen
(sandrine.vongrunigen@hcuge.ch, Phone : 0041 22 372 39 96)

* Please validate this statement

- ◯ I certify that I have fully read and fully understood this form, and that the information that I have presented here is accurate and complete to the best of my knowledge.

Appendix 8: Presentation of the final self-assessment tool

Hôpitaux Universitaires Genève

Pharm-Ed

SAFE HANDLING OF CYTOTOXIC MEDICINES: A SELF ASSESSMENT TOOL ADAPTED TO RESOURCE-CONSTRAINT SETTINGS

Cyto-SAT

Version 01 (JANUARY 2017)

This tool was developed under the initiative of Pharm-Ed program at the Pharmacy of the University Hospital of Geneva

www.Pharm-Ed.net http://pharmacie.hug-ge.ch/

Safe handling of cytotoxic medicines: a self assessment tool adapted to resource-constraint settings

Cyto-SAT

INTRODUCTION

Handling of cytotoxic medicines is a high risk process for the patients, the personnel and the environment. To reduce the risk of incidents and contamination, preventive measures must be implemented wherever cytotoxic drugs are transported, received, stored, prepared, administered and disposed.
This self-assessment tool was developed to help resource-constraint settings to identify their gaps and raise awareness on the risks related to cytotoxic medicines and to improve handling measures. Cyto-SAT is meant to be used as part of ongoing quality improvement activities.

Elaboration of the tool

Existing national and international recommendations for safe handling of cytotoxic drugs have been consulted by a working group of the University Hospitals of Geneva (Switzerland) to preselect 137 quality and safety standards. Finally 134 standards were validated and prioritized by a consensus of 28 international pharmaceutical experts (through a Delphi method) .
Participation of experts from both developed countries and developing countries aimed to make the tool applicable in settings with limited resources while respecting the quality and safety of the process.

Members of the steering commitee

Prof. Pascal BONNABRY, Chief-Pharmacist, Geneva University Hospitals, School of pharmaceutical Sciences, University of Geneva, University of Lausanne, Switzerland
Sandrine VON GRUENIGEN, Pharmacist, Geneva University Hospitals, Switzerland
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Members of the panel of international experts

We would like to thank all the experts for their volontary participation in the elaboration of the tool

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Vandoeuvre
France

References

The objective was to refer to different types of documents published in English or French such as recommendations from scientific societies, guidelines and regulations from organ of workers'protection and regulatory framework.

All the references below are available online on a free access.

ISOPP Standards of practice, International Society of Oncology Pharmacy Practitioners, 2007

QuapoS 4: Quality Standard for the Oncology Pharmacy Service with Commentary, DGOP e.V (German Society of Oncology Pharmacy) /ESOP

ASHP Guidelines on Handling of Hazardous Drugs, American Society of Health System Pharmacists, 2006

USP (United States Pharmacopeia) Chapter 800: Hazardous Drugs-Handling in Healthcare settings, The Compounding Expert Committee, 2015

Suvapro: sécurité dans l'emploi des cytostatiques, Swiss Accident Insurance Fund, 2004

Chemotherapy Administration Safety Standards, American society of clinical Oncology (ASCO)/Oncology Nursing society (ONS), 2013,

OSHA technical Manual: Controlling Occupational Exposure to Hazardous Drugs, Occupational Safety & Health Administration (OSHA)

NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings, National Institute for

Bonnes Pratiques de préparation (BPP), Agence française de sécurité sanitaire de produits de santé (Afssaps),2007

ISMP International Medication Safety Self assessment for Oncology, Institute for Safe Medication Practices, 2012

Safe Handling of Hazardous Chemotherapy Drugs in Limited-Resource Settings, Pan American Health Organization (PAHO), 2013

Structure and content

The tool covers the different steps of the cytotoxic medicines circuit.
The quality and safety criteria have been organised in categories and sub categories as shown in the table opposite

CATEGORIES	SUB-CATEGORIES	Number of items submitted to 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 organisation	4
	• Preparation area of parenteral medicines	10
	• Hygiene and personal protective equipment	6
	• Preparation process set up	4
	• Preparation technique	9
	• 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 organisation	2
	• Cleaning practices	6
	• Laundry	2
10. Patients counselling		4
	TOTAL	134

Hôpitaux Universitaires Genève

Pharm-Ed

INSTRUCTIONS

This assessment tool aims at assisting health facilities with ongoing quality and safety improvement of handling of cytotoxic medicines in resource-contraint settings.The tool is designed to be used in different contexts, however some adaptations or addition of items may be considered by some facilities to evaluate some internal procedures.

Before starting the assessment, please read carefully the instructions and go through all the items.
The standard is outlined in the first column and is completed by additional information in the second column

The item priority reflects the experts' consensus on the importance to fullfill the standards, considering the probability of occurrence of the prevented risks, the criticality of the risk, the effectiveness of the measure, how easy it is to implement, etc. the proritiy was classified as follow:

I or i*	: Indispensable (absolutely required even for occasional handling of cytotoxic medicines)
E or e*	: Essential (required for regular use of cytotoxic medicines)
D or d*	: Desirable (desirable if regular use and/or resources sufficient)

Prioritization is indicated in order to guide you in the elaboration of an action plan to improve the cytotoxic medicines flow and management.
**A differentiation is made if a consensus had been obtained or not among the experts at the end of the Delphi survey. The capital letter indicated that an experts'consensus had been reached while the lowercase letter indicated no consensus. Consensus was defined as more than 75% of the experts agreeing with the prirotiy.*

Please evaluate each item according to the scoring system below. As necessary, investigate and verify the level of implementation with other healthcare practitioners and staff.

Scoring system

1	There has been **no activity** to implement this item
2	The item has been **discussed and considered, but it is has not been implemented** yet. There may be a document and no implementation and some staff awareness.
3	The item is **partially implemented** in the facility or implemented only in some areas, for some patients, drugs and/or staff.
4	The item is **fully implemented** throughout the facility for all patients, drugs and/or staff
N.A	**Not applicable**; It is not possible to consider the item in the local context

*** 3 and 4 scores can be used only if there is a real implementation. Procedures or guidelines that are not applied are nor not enough.*

The last column allows to write some comments in order to justify the score or point out some ambiguity.

Hôpitaux Universitaires Genève

Pharm-Ed

CYTO-SAT

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

I. MANAGEMENT

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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	I	ISOPP Section 5 & 19; QuapoS 1.3; USP <800>; Suva; OSHA; NIOSH						
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.	I	ISOPP Section 5 & 19; QuapoS 1.3; USP <800>; Suva; OSHA;						
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 uptdate is to be defined by the local institution, according of the context. Any changes must be documented.	e	ASHP ISOPP Section 9 & 20; QuapoS 1.3; USP <800>; Suva; OSHA;						
4	A self-assessment of compliance with safety guidelines regarding the safe handling of cytotoxic medicines is carried out regularly.	Each intitution should define its frequency according to local context.	e	BPP						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

I. MANAGEMENT (continue)

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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.	e	ISOPP Section 2 & 21; ASHP ; OSHA						
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.	e	ISOPP Section 1; USP <800>; OSHA; QuapoS 1.3						
7	Smoking, drinking and eating are forbidden in areas where cytotoxic medicines are prepared, stored and administered		i	ISOPP section 9; ASHP ; OSHA; Suva						
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.	i							
9	There is a regularly updated organigram (organisational chart) indicating the roles and responsibilities of all the staff members involved in processes using chemotherapies, as well as their contacts details.		e	QuapoS appendix 2						
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	e							
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.	i	ISOPP Section 3						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

II. PERSONNEL

II.1 Education and training

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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.	i	BPP 7.2; ISOPP Section 3&4; Suva; QuapoS 1.6; USP<800>;OSHA Section VI;						
13	There is regular continuous education for staff.	Training sessions are specific to the category of staff. An annual training plan should be prepared	e	BPP 7.2; ISOPP Section 3&4; Suva, QuapoS						
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.	e	BPP 7.2; ISOPP Section 3&4; QuapoS 1.6;USP<800>						
15	All training and skill validations are documented.	Training records are kept for at least 5 years.	e	BPP 7.2; ISOPP Section 3&4; QuapoS 1.6, Suva, USP<800>; OSHA						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

II. PERSONNEL (continue)

II.2 Medical surveillance

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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	i	ISOPP Section 3&19; Suva; ASHP ; QuapoS 1.5;USP<800>; BPP 7.2						
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 labour law if available)	I	ISOPP Section 3; Suva; ASHP ; QuapoS 1.5;USP<800>; BPP 7.2						
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	e	ISOPP Section 3						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

III. LOGISTICS

III.1 Receipt

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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.	e	ISOPP Section 2; QuapoS 3.1						
20	Staff use approriate personal protective equipment when receiving and unpacking cytotoxic medicines	Protective gloves	e	ISOPP Section 2; QuapoS 3.1						
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.	e	ISOPP Section 2; QuapoS 3.1						
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	I	ISOPP Section 2; QuapoS 3.1						
23	Staff washes their hands with soap after handling cytotoxic medicines.	Wearing gloves is not a substitute for washing hands.	i	ISOPP section 2						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

III. LOGISTICS (continue)

III.2 Storage

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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.	e	ISOPP Section 2&17; QuapoS 3, USP<800>, ASHP						
25	The storage area for cytotoxic medicines is clearly defined and labeled. Access is restricted to authorised 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).	e	ISOPP Section 2&17; QuapoS 3, USP<800>, ASHP						
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.	e	ISOPP Section 2&17; QuapoS 3.1, USP<800>, ASHP						
27	The storage area has sufficient general exhaust ventilation		e	ISOPP Section 6; USP <800>						
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.	e	ISOPP section 2; ASHP ; QuapoS 3;Suva						
29	Staff wash their hands with soap after handling cytotoxic medicines when resupplying or stocktaking	Wearing gloves is not a substitute for washing hands.	e	ISOPP section 2						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

III. LOGISTICS (continue)

III.3 Transport

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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.	I	ISOPP Section 2; QuapoS 3.7,						
31	Cytotoxic medicines are transported in exclusively dedicated containers/boxes.		i	ISOPP Section 2; QuapoS 3.7, USP<800>, ASHP						
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.	e	ISOPP Section 2&17;QuapoS 3.7, USP<800>, ASHP, Suva						
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 minimise impacts and risks of breakage. Ready-to-use preparations must first be placed in leak-proof bags	e	ISOPP Section 2;QuapoS 3.7, USP<800>, ASHP guidelines on HD, Suva						
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.	i	ISOPP Section 2; QuapoS 3.7, USP<800>, ASHP						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

IV.PRESCRIPTION

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
35	Only authorised healthcare practitioners can prescribe chemotherapy treatment.	The facility has a readily available, up to date list of authorised prescribers.	I	ASCO/ONS						
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.	i	ISOPP section 11;QuapoS 3.5; ASCO/ONS						
37	Prescriptions are done in a structured way, with the use of of standardized, formatted (preprinted 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	i	ISOPP section 11; QuapoS 3.5; ASCO/ONS						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

IV.PRESCRIPTION (Continue)

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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, preprinted or electronic prescription forms for chemotherapy treatment protocols is recommended.	I	QuapoS 3.5; ASCO/ONS						
39	Before preparation, all prescription/orders are analysed, 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.	I	ISOPP section 11; QuapoS 3.5; ASCO/ONS						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

V. PREPARATION

V.1 Management and Organisation

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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")	I	Suva; USP <800>; ASHP ; ISOPP Section 6; QuapoS 1.6						
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 centralised in order to minimise the risks of contamination and limit the number of people exposed. The preparation area should be located away from breakrooms and refreshment areas.	I	Suva; ASHP ; USP <800>; OSHA; BPP 7.3; ISOPP Section 6; QuapoS 2.1						
42	Access to preparation areas is restricted to authorised personnel involved in preparation of cytotoxic medicines and wearing appropriate personal protective equipment.		I	Suva; ASHP ; USP<800>; OSHA; ISOPP Section 6; QuapoS 2.1						
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 microbiolgical integrity of the product will be maintained for the established conservation period	i	ISOPP Section 6; QuapoS 3.4						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

V. PREPARATION (Continue)

V.2 Preparation area of parenteral medicines

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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.	E	BPP; QuapoS 2.1, ASHP						
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	e	QuapoS 3.4						
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.	i	BPP; QuapoS 2.1; ISOPP Section 6; ASHP; WHO GMP						
47	The preparation room surfaces are designed to minimise 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.	i	Suva; ASHP; BPP 7.3; ISOPP Section 6; QuapoS 2.1;WHO GMP						
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	e	Suva; QuapoS 2.1						
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	i	Suva; OSHA; ISOPP Section 6; BPP; NIOSH; QuapoS 2.2; ASHP; WHO GMP						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

V. PREPARATION (Continue)

V.2 Preparation area of parenteral medicines (continue)

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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.	e	ISOPP section 6; BPP 7.3; ASHP; QuapoS; USP <800>;WHO GMP						
51	A pass-through hatchenables the transfer of cytotoxic preparations between the cytotoxic prepration room and the external environment.	Ideally distinct from the staff airlock.	e	ISOPP section 6; BPP 7.3; ASHP; QuapoS; USP <800>;WHO GMP						
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.	e	ISOPP section 6; BPP 7.3; ASHP; USP <800>;WHO GMP						
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).	i	Suva; BPP 7.3; ISOPP Section 6; WHO GMP						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

V. PREPARATION (Continue)

V.3 Hygiene and protective equipments

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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 jewelery, wrist-watches or makeup.	I	ASHP; BPP; NIOSH; WHO GMP						
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		e	Suva; USP <800>; NIOSH; ASHP ; WHO GMP						
56	During compounding, gloves are regularly changed or are immediately replaced when torn, punctured or directly contaminated.	According to recommendations, gloves should be changed every 30 minutes.	I	Suva; ASHP; USP <800>; NIOSH						
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")		e	Suva						
58	Appropriate measures are used to avoid insects or other animals entering preparation areas.		i	BPP						
59	The storage and use of leftover cytostatics 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).	I	QuapoS 3.4;						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

V. PREPARATION (Continue)

V.4 Preparation process set up

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
60	Doors and windows are closed during compounding.	In an aseptic area, windows should be sealed anyway	i	Suva; QuapoS 2.2						
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.	I	BPP; ASHP; QuapoS 3.4						
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.	i	BPP; ASHP; ISOPP Section 11						
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.	I	QuapoS 3.4; ASHP						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

V. PREPARATION (Continue)

V.5 Preparation techniques

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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.	e	Suva; USP <800>; QuapoS 3.4						
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.	I	ISOPP Section 11; ASHP						
66	The operator compounds preparations by strictly following the operating instructions.		I	QuapoS 3.6						
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.	i	QuapoS 3.4; ASHP ; OSHA						
68	The operator uses proper working techniques to reduce the risks of chemical contamination or needlestick injuries or cuts.	The operator should for example: either use Luer-lock connections on needles and syringes to minimise the risk of separation in case of overpressurisation 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.	i	Suva; ASHP; ISOPP Section 7; NIOSH						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

V. PREPARATION (Continue)

V.5 Preparation techniques (continue)

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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).	e	ASHP; ISOPP Section 7						
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.	e	ASHP						
71	I.V tubing is primed prior to adding the cytotoxic product in the infusion bag.		e							
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	e	BPP 7.6; ASHP						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

V. PREPARATION (Continue)

V.6 Packaging and labeling

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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.	I	BPP						
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	e	BPP 7.6; ISOPP Section 11;						
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).	i	BPP 7.7 et 1.5; QuapoS 3.6; ISOPP Section 11						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

V. PREPARATION (Continue)

V.7 Checking procedure

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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.	I	BPP; ISOPP Section 11						
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. colour, clarity, particle free); and finished pack integrity via a visual inspection.	I	BPP 7.11; ISOPP Section 11						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

V. PREPARATION (Continue)

V.8 Documentation

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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.	i	BPP; QuapoS 3.6; ISOPP Section 11						
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 authorisation for any deviation from the master formula; and signature of the person responsible of production.	e	BPP; ISOPP Section 11; QuapoS 3.6;						
80	Each preparation is recorded on a preparation logbook	The logbook can also be electronically available	e	BPP						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

V. PREPARATION (Continue)

V.9 Maintenance

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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.	i	Suva; OSHA; ISOPP Section 6 & 21; BPP; NIOSH; QuapoS 2.2; ASHP						
82	Surrounding conditions (microbiological contamination, particulate contamination) are regularly monitored according to a planned monitoring programme.	if cleanroom	i	ISOPP Section 11; USP <800>; QuapoS 3.4						

V.10 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.	e	ISOPP Section 9; USP <800>;						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

VI. ADMINISTRATION

VI.1 Management and organisation

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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.	e	ISOPP section 12						
85	Only trained, entitled personnel are permitted to administer cytotoxic medicines to patients.	See chapter on "Personnel".	I	ISOPP section 2; ASCO/ONC; ASHP; Suva						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

VI. ADMINISTRATION (continue)

VI.2 Hygiene and safety measures

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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.	e	ASHP						
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 jewellery.	I							
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, gloves. If there is a risk of splashing or an aerosol, protective googles and a mask are also recommended.	e	Suva; USP <800>; NIOSH; ASHP						
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.	I	Suva; OSHA						
90	After administration of the chemotherapy, staff wash their hands with soap and water.		I	Suva; OSHA						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

VI. ADMINISTRATION (continue)

VI.3 Documentation

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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 standardised/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.	e							
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.	I	ASCO/ONS						
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.	I	ASCO/ONS						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

VI. ADMINISTRATION (continue)

VI.4 Work practices

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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.	E	OSHA; ASHP						
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 retropriming) are possible as far as the risk of exposure of the healthcare personnel is minimized during the administration	e	OSHA; ASHP; NIOSH						
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 aerolization	i	OSHA; ASHP; NIOSH; Suva						
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.	I	ISOPP Section 9						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

VII. INCIDENT MANAGEMENT

VII.1 Surface contamination

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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.	I	ISOPP Section 14, Suva, QuapoS 4.2, USP<800>, ASHP						
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.	i	ISOPP Section 14, Suva, QuapoS 4.2, USP<800>, ASHP						
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.	I	ISOPP Section14, Suva, QuapoS 4.2, USP<800>, ASHP						
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.	I	ISOPP Section14 , Suva, QuapoS 4.2, USP<800>, ASHP						
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.)	I	ISOPP Section14,SuvaQuapoS 4.2, USP<800>, ASHP						
103	Spill kits are replaced as soon as possible in case of future incidents.	Ideally, a replacement kit should be available in advance.	i	ISOPP Section14						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

VII. INCIDENT MANAGEMENT (continue)

VII.2 Staff contamination

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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.	I	ISOPP Section 14, Suva, QuapoS 4.2, ASHP						
105	The equipment and materials for managing the emergency treatment for chemical contaminated staff are located in areas where cytotoxic medicines are preprared, administered	Close proximity of an emergency shower or water supply. For eyes, a sterile isotonic solution (0.9% sodium chloride) is recommended	I	ISOPP Section 14; ASHP						
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.		I	ISOPP Section 14; QuapoS 4.2						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

VII. INCIDENT MANAGEMENT (continue)

VII.3 Extravasation

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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.	I	ISOPP Section 14; QuapoS 4.3						
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.	e							
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.	i	ISOPP Section 14; QuapoS 4.3						

VII.4 Quality assurance

110	All incidents involving cytotoxic medicines are reported, monitored, analysed, recorded and any corrective measures applied are followed up on and evaluated.	All incidents must be reported on a incident report form. Its causes should be analysed in order to avoid future repetition.	e	ISOPP Section 14 , USP<800>, ASHP						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

VIII. WASTE MANAGEMENT

VIII.1 Waste disposal

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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.	I	ISOPP section 15; QuapoS 4.1; USP <800>; BPP 7.10; ASHP; OSHA; Suva						
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 differenciate between slightly contaminated (traces of cytotoxics) and heavily contaminated (leftovers, expired vials, etc) waste	I	ISOPP section 15; QuapoS 4.1; USP <800>; BPP 7.10; ASHP						
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, exept when disposing waste.	I	ISOPP section 15; QuapoS 4.1; BPP 7.10; ASHP; OSHA; Suva						
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	I	ISOPP section 15; OSHA; Suva						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

VIII. WASTE MANAGEMENT (continue)

VIII.1 Waste disposal (continue)

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
115	Only trained personnel handle cytotoxic waste containers; they wear approriate personal protective equipment.	a minima :Gloves	e	ISOPP section 15; QuapoS 4.1; ASHP; OSHA						
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.	E	ISOPP section 15; OSHA						
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	i	WHO; QuapoS 4.1						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

VIII. WASTE MANAGEMENT (continue)

VIII.2 Patients'excreta

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
118	Trained personnel handle the excreta (vomit, urine, faeces, 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)	E	ISOPP section 15; OSHA; QuapoS 4.9; NIOSH						
119	Contaminated linen should be placed in a bag clearly identified and forwarded to the laundry	See chapter on "Cleaning".	E	ISOPP Section 15; QuapoS; OSHA						
120	Mattresses and pillows are protected with plastic covers and wiped-down between patients.		e	QuapoS 4.9;						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

IX. CLEANING

IX.1 Management and Organisation

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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.	e	ISOPP Section 15; QuapoS; OSHA						
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.	e	Suva; ISOPP section 13; QuapoS 3.4; NIOSH						

IX.2 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 splashproof gown. (note: for cleaning up accidental spills, see chapter on "Incidents")	e	Suva; ISOPP Section 13; NIOSH; USP <800>						
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.	E	ISOPP Section 13; Suva; QuapoS 3.4						
125	Cleaning is only carried out using moistened materials.	No vacuum cleaners, no dry sweeping.	I	Suva;						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

IX. CLEANING (continue)

IX.2 Cleaning practices (continue)

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
126	Staff washes their hands thoroughly with soap immediately after cleaning activities.		I	ISOPP Section 13						
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.	I	ISOPP Section 13						
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	I	ISOPP Section 13						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

IX. CLEANING (continue)

IX.3 Laundry

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
129	Contaminated, reusable protective clothing (gowns) and linen soiled with patient excreta are placed in clearly labelled laundry bags and are washed separetely from other clothing.	Laundry should start with a cold prewash cycle and then continue using the normal washing process	E	ISOPP section 16; QuapoS 4.9; BPP 7.10						
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	resitant gloves, gown with long sleeves	e	ISOPP section 16; QuapoS 4.9, OSHA						

1	No activity
2	Discussed and considered but not implemented
3	Partially implemented in some or all areas
4	Fully implemented throughout
n.a	Not applicable in the context

X. PATIENT COUNSELING

	ITEMS	ADDITIONAL INFORMATION	PRIORITY	REFERENCES	1	2	3	4	N.A	COMMENTS
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.	i	ASCO/ONS; QuapoS						
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.	I	ASCO/ONS; QuapoS						
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.		I	ASCO/ONS						
134	Any patient counseling session is documented and added to the patient's file.		e	ASCO/ONS						