



In response to enquiry from NHS Forth Valley

Closed-system transfer-devices for limiting exposure to cytotoxic anti-cancer drugs in healthcare professionals, patients and visitors

What were we asked to look at?

NHS Forth Valley asked us to review the evidence on the effectiveness of closed-system transfer-devices (CSTDs) in reducing the risk of exposure to hazardous anti-cancer drug treatments in healthcare professionals (all relevant staff groups including pharmacy, nursing and cleaning staff), patients and their visitors.

Why is this important?

Individuals who come into contact with anti-cancer drugs during their manufacture, transportation, distribution, administration and disposal, can be exposed to low dose cytotoxic effects from leaks, spills and aerosol dispersion of the drugs. Exposure to cytotoxic drugs can have short-, medium- and long-term adverse health effects. CSTDs are designed to mechanically prohibit the transfer of environmental contaminants into the system, and the escape of hazardous drug or vapor concentrations outside the device. Therefore, implementation of CSTDs may reduce the risk of exposure to cytotoxic drugs.

What was our approach?

We produced an Evidence Synthesis to assess the published evidence on the clinical effectiveness and cost effectiveness of CSTDs, including a review of guidelines for the safe handling of hazardous drugs.

What next?

NHS Forth Valley and other health boards may use the findings of this evidence synthesis to inform the development of practice recommendations for implementation of CSTDs when handling hazardous anti-cancer drugs.

Key points

- It was not possible to reach robust conclusions on the effectiveness of closed-system transfer-devices (CSTDs) in reducing the risk of exposure to hazardous anti-cancer drug treatments.
- CSTDs may be effective at preventing exposure when used as part of a wider set of safe-handling adherence protocols. There is continued uncertainty about the incremental benefits of CSTDs in limiting exposure over and above those achieved by other safe-handling practices, such as wearing double chemotherapy gloves and wearing eye and face protection.
- The evidence reviewed consisted of one moderate quality systematic review (which included 23 non UK based observational studies of low quality).
- There were no statistically significant differences in any of the outcomes examined by the systematic review: detection of exposure in urine, proportion of surfaces contaminated, and quantity of surfaces contaminated. The only significant reduction was in the quantity of surface contamination with Cylophosphamide in pharmacy areas in CSTD groups compared to control groups (based on two uncontrolled before-after studies; and five cross-sectional studies). However, the clinical importance of this reduction is unknown.
- Four studies reporting a range of guidelines for the safe-handling of hazardous drugs recommended implementation of training, personal protective equipment (PPE), CSTDs, medical surveillance and other safety measures, largely based on expert consensus.

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Definitions

Antineoplastic: Blocking the formation of neoplasms (growths that may become cancer)¹.

Cytotoxic drug: A substance that kills cells, including cancer cells. These agents may stop cancer cells from dividing and growing and may cause tumors to shrink in size¹.

Carcinogen: Any substance that causes cancer¹.

Genotoxic: Denoting a substance that by damaging DNA may cause mutation or cancer².

Teratogenic: Causing congenital anomalies or birth defects².

Literature search

A systematic search of the primary and secondary literature was carried out between 16-17 April 2019 to identify systematic reviews, health technology assessments and other evidence based reports. The Medline and Embase databases were searched for primary studies, systematic reviews and meta-analyses.

Key websites were searched for guidelines, policy documents, clinical summaries, economic studies and ongoing trials.

Concepts used in all searches included: Closed system transfer devices, closed system drug transfer devices, CSTDs, adherence, compliance, barriers, facilitators. A full list of resources searched and terms used are available on request.

Introduction

Legislation in the UK requires employers to assess risk and protect workers' health and safety.³ Individuals who come into contact with cytotoxic drugs during manufacture, transportation, distribution, administration and disposal are exposed to low doses of cytotoxic drugs over many years.³ Hazardous drugs, which include cytotoxic drugs, are defined as drugs which are carcinogenic, genotoxic, teratogenic, and those that can result in reproductive toxicity, and organ toxicity at low doses.⁴ Cytotoxic drugs, or antineoplastic agents, have anti-tumour and immunosuppressive functions and are used to treat cancer and disorders such as rheumatoid arthritis and multiple sclerosis.³ Cytotoxic drugs are administered in a range of settings including hospitals, specialist oncology units, hospices, care homes, charitable organisations, and domestic homes.³

Staff who are at risk of exposure include pharmacists and pharmacy technicians, nurses, doctors, surgery theatre staff, and maintenance staff such as cleaners and porters.³ Those who prepare and administer cytotoxic drugs, such as pharmacists and nurses, are most at risk of exposure.⁵ Direct and indirect exposure can occur through dermal contact, inhalation, ingestion and injection.⁶ Cytotoxic drugs can be administered by several methods, including orally, intravenously or intrathecally.⁷ Contamination occurs in 25% of cases of spiking intravenous (IV) bags and 100% of de-spiking IV bags.^{8,9} After de-spiking, the leaking bag must be disposed of, thereby extending the risk of contamination to those who handle disposal and cleaning. When there are spillages, vapours from hazardous drugs can also be

inhaled or absorbed through the skin.⁵ There is also a risk of contamination during handling and disposal of patient waste as drug residue remains.⁴ Patients' families may also be at risk of exposure if there are spillages in patient areas or transfer of cytotoxic drug residue to nurses' hands or clothing.

There are several methods to decrease risk of exposure. The National Institute of Occupational Safety and Health (NIOSH) provided a hierarchy of controls to minimize the risks of exposure to healthcare staff.¹⁰ The hierarchy of controls, from most to least effective and protective, is as follows:

- Elimination (physically remove the hazard)
- Substitutions (replace the hazard)
- Engineering controls (isolate people from the hazard)
- Administrative controls (change the way people work)
- Personal protective equipment (PPE; protect the worker)

Elimination and substitution are most effective at reducing hazards, but this is not an option when administering treatment for patients. Engineering controls, which enclose the substances to prevent exposure, include biologic safety cabinets (BSCs) or compounding aseptic containment isolators (CACIs).¹¹ Closed-systems transfer devices (CSTDs) are supplemental engineering controls.¹¹ Although engineering controls are preferable to administrative controls and PPE because they prevent the worker from coming into contact with hazardous drugs¹⁰, there is uncertainty around the effectiveness of CSTDs. For example, two recent studies have shown that only three commercial CSTDs meet performance-testing standards set by NIOSH for vapour containment.^{12, 13} CSTDs are currently not routinely implemented in Scotland.

There are many guidelines available which recommend safe handling practice for healthcare workers. Guidelines have been issued by organisations such as the Health and Safety Executive (HSE), NHS Pharmaceutical Quality Assurance Committee (NHS PQAC), NIOSH, US Pharmacopeia (USP), American Society of Clinical Oncology (ASCO) and The Control of Hazardous to Health (COSHH) regulations. Recommendations vary across guidelines, which may be a contributing factor to the variation in practice across Scotland, both nationwide and at NHS Board level.

This Evidence Synthesis reviews the evidence base for CSTDs in limiting levels of exposure to cytotoxic anti-cancer drugs in healthcare workers and patients/patient families. Outcomes of interest were environmental contamination, biological exposure levels (for example levels of exposure in urine) and short-, medium- and long-term health effects of exposure. The Evidence Synthesis also examined the cost-effectiveness of CSTDs.

Description of health problem

Most cytotoxic drugs prevent cell division or damage DNA by impeding cell replication, meaning there can be both short- and long-term adverse health effects of exposure.⁷ No 'safe' level of exposure has been identified and the effect of long-term low dose exposure is unknown.^{6, 14}

There can be both acute and long-term health consequences of exposure to cytotoxic drugs. Acute health effects include dermatitis/skin rashes/hypersensitivity, sore throat or cough, irritation of the eyes, hair loss and abdominal pain or vomiting.^{3, 4} Long term effects of exposure include altered blood counts, decreased fertility, fetal loss or fetal abnormalities, and cancer.^{3, 4, 15}

Health technology description

A CSTD is a device for administering drugs that mechanically prohibits the transfer of environmental contaminants into the system and the escape of the hazardous drug or vapor concentrations outside the system.⁴ CSTDs attempt to prevent leaks and spills by providing a leak-proof connection to intravenous infusion or drug vials. CSTDs tend to be needleless systems with infusional tubing and syringes that use luer-lock fittings.¹⁶

The device is connected to the vial or to a syringe for intravenous infusion. The CSTD equalises pressure with a sealed expansion chamber when air or diluent is injected into, or extracted from, the vial¹⁴. The injector is used to attach a syringe to the drug vial access device or into an IV line device on IV tubing¹⁴. This forms dry, leak-proof connections during drug preparation and administration. The drugs are then agitated to mix, or inverted if unstable on agitation.¹⁴ Then the drugs are extracted and a protective cap is placed on the syringe to prevent leaks.¹⁴

Examples of commercial CSTDs available on the market include:

- OnGuard® (B Braun Medical Ltd)
- EQUASHIELD® (Equashield, LLC)
- HALO® (Corvida Medical)
- ChemoClave® (ICU Medical)
- PhaSeal™ (Becton-Dickinson)
- Texium™ (Becton-Dickinson)
- SmartSite VialShield™ (Becton-Dickinson)

Some CSTDs are already in use in NHS Highland for drugs used in non-malignant conditions. The Edinburgh Cancer Centre in NHS Lothian has implemented an ICU Medical closed-system product within cancer services (C McKinnel, Lead Nurse Chemotherapy Quality Oncology, NHS Lothian. Personal Communication, 23 July 2019).

Clinical effectiveness

Four guideline publications were identified^{9, 17-19}, alongside a review of various technologies to reduce occupational exposure to anti-cancer drugs¹⁵, and a Cochrane review.⁵ No additional studies reporting clinical effectiveness of CSTDs compared with only PPE were identified. No studies assessed exposure levels or health outcomes for patients or visitors to the wards.

Conducting randomised controlled trials to evaluate the effectiveness of CTSDs may not be a feasible option because the intervention is usually applied at the group/treatment centre level, instead of at an individual level. Therefore, the inclusion of non-randomised studies was appropriate for this Evidence Synthesis.

Guidelines

NHS PQAC issued guidelines in 2018 on handling hazardous drugs.⁹ The guideline recommended that the practice of de-spiking bags of cytotoxic drugs should be discontinued as it poses an unacceptable risk to staff, patients and visitors. Instead it recommended, that needle-free bags with spike-free connections should be used and remain connected for disposal, or should be spiked with a CSTD to allow for safe disposal. Connections which do not require disconnection should remain in place. Closed system caps should be used with syringes for IVs and only removed immediately before connecting to the patient. Closed system catheters should always be used for cytotoxic bladder installations.

Evidence-based standards for safe handling of hazardous drugs were recently developed by an ASCO expert panel.¹⁷ The ASCO committee endorsed current standards set by USP 800, US Occupational Safety and Health Administration, NIOSH and the Oncology Nursing Society. USP 800 recommends CSTDs for drug preparations and makes them mandatory for drug administration. NIOSH currently recommends CSTDs as supplementing engineering controls (e.g. to be used in biological safety cabinets or compounding aseptic containment isolators). ASCO recommend that policies and procedures should be developed for workplace medical surveillance which monitor environmental contamination and exposure in healthcare workers. It was recommended that validated performance testing protocols for CSTDs are developed.

The American Society for Health-System Pharmacists (ASHP)¹⁸ recommend developing and introducing comprehensive safety programmes in any healthcare setting where hazardous drugs are compounded, prepared, stored, transported and administered. These comprehensive safety programmes should include the use of engineering controls (including CSTDs), training, safe work practices, PPE and medical surveillance where the environment and workers are routinely monitored. Specifically, containment of the environment where hazardous drugs are compounded, prepared and administered should be in place. This includes surface cleaning and decontamination procedure and ventilated engineering controls. CSTDs should be in place as well as PPE.

One study conducted a survey of 37 subject experts representing 24 countries regarding practices for handling monoclonal antibodies, the use of CSTDs, medical surveillance, and measurements of compliance with existing guidelines.¹⁹ According to the survey, CSTDs are used in 19 of the 24 countries. Some countries include CSTDs as part of, or as a supplement to, engineering controls while others including UK consider CSTDs as part of PPE. There are no specific guidelines for the UK but local guidelines for practice follow International Society of Oncology Pharmacy Practice (ISOPP) and HSE recommendations. Compliance is voluntary in the UK and there are no recommended measures of compliance.

All of the included studies which described guidelines for safe handling of hazardous drugs acknowledged that there was a lack of good quality evidence to demonstrate that medical surveillance, CSTDs, engineering controls and alternative duties reduce exposure of cytotoxic drugs to healthcare professionals.^{9, 17-19} All recommended that these measures should or must be implemented based on expert consensus, and that the potential risk of harm was deemed unacceptable.

Systematic review and meta-analysis

A non-systematic review by Vyas et al. indicated that CSTDs are highly effective in reducing surface contamination within pharmacy aseptic manufacturing areas.¹⁵ The use of CSTDs along with pharmaceutical isolators is considered to provide a higher level of protection to nursing staff as the outer surfaces of IV infusion bags prepared using CSTDs are less likely to be contaminated with cytotoxic drugs. This review did not examine the effectiveness of CSTDs in reducing exposure outwith pharmacy preparation areas (e.g. administration in wards).

A Cochrane systematic review and meta-analysis evaluated exposure to hazardous drugs, environmental contamination, and short-, medium- and long-term adverse health effects of exposure in healthcare professionals involved in any stage of administering cytotoxic drugs.⁵ The objective of the Cochrane review was to examine the effects of CSTDs for infusional hazardous drugs plus safe handling compared with safe handling alone for reducing staff exposure to hazardous drugs. There were 23 non-UK observational cluster studies (N=358 hospitals) included within the review, which were of low quality. Of those 23 studies, 13 were uncontrolled before-after studies, nine were cross-sectional studies and one was an interrupted time series study.

The majority of studies reported using the PhaSeal™ device (13 studies). The Tevadaptor (one study), SpikeSwan (one study) and other CSTDs (five studies) were also specified. Two studies did not report which type of CSTD was used. The differences in proportion of people or samples that were positive for exposure or contamination between CSTDs and control groups are reported in Table 1, presented as a risk ratio (RR).

There were no statistically significant differences in either the proportion of people exposed or the proportion of surfaces contaminated between CSTD and control groups. The RR for proportion of contaminated samples in patient areas was estimated from only one cross-

sectional study across a number of different drugs (5-fluorouracil, Cytarabine, Gemcitabine, Irinotecan, Docetaxel, Paclitaxel, Vinorelbine, multiple drugs). The risk ratio for many of the drugs tested on surfaces within pharmacy areas was calculated from one cross-sectional study (Irinotecan, Docetaxel, Paclitaxel, Vinorelbine, multiple drugs) and two further cross-sectional studies (Cytarabine, Gemcitabine). Where subgroup analysis could be conducted to determine if there were differences across CSTDs, the proportion of contaminated surfaces was no different between commercial CSTDs.

Table 1. Proportion of people or samples positive for exposure or contamination between CSTDs and control groups

N studies	N participants/ samples	Drug	Risk Ratio (CSTDs vs. control group)	95% Confidence Intervals	I ²
Outcome: Detection of exposure in urine					
2 (uncontrolled before-after)	20 participants; 2 hospitals	Cylophosphamide	0.83	0.46 to 1.52	0%
1 (uncontrolled before-after)	14 participants; 1 hospital	Cyclophosphamide & ifosfamide	0.09	0.00 to 2.79	-
1 (cross-sectional)	36 participants; 4 hospitals	Cyclophosphamide, gemcitabine & ifosfamide	Not estimable	-	-
Outcome: proportion of surfaces contaminated in pharmacy areas					
13 (7 uncontrolled before-after; 6 cross-sectional)	2937 samples; 338 hospitals	Cylophosphamide	0.89	0.78 to 1.01	35%
9 (3 uncontrolled before-after; 6 cross-sectional)	2332 samples; 304 hospitals	Ifosfamide	0.94	0.74 to 1.19	8%
6 (1 uncontrolled before-after; 5 cross-sectional)	1781; 280 hospitals	Methotrexate	0.84	0.58 to 1.22	0%
3 (1 uncontrolled before-after; 2 cross-sectional)	1008 samples; 106 hospitals	5-fluorouracil	0.65	0.43 to 0.97	0%
2 (cross-sectional)	780 samples; 84 hospitals	Cytarabine	0.72	0.18 to 2.86	0%
2 (cross-sectional)	780 samples; 84 hospitals	Gemcitabine	0.96	0.60 to 1.54	0%
1 (cross-sectional)	493 samples; 83 hospitals	Irinotecan	0.36	0.10 to 1.33	-
1 (cross-sectional)	493 samples; 83 hospitals	Docetaxel	Not estimable	-	-
1 (cross-sectional)	493 samples; 83 hospitals	Paclitaxel	0.57	0.04 to 9.06	-
1 (cross-sectional)	493 samples; 83 hospitals	Vinorelbine	1.72	0.16 to 18.73	-
1 (cross-sectional)	287 samples; 1 hospital	Ganciclovir	0.01	0.00 to 27.11	-
1 (cross-sectional)	109 samples; 1 hospital	Multiple drugs	0.87	0.43 to 1.77	-

Outcome: proportion of surfaces contaminated in patient care areas					
5 (cross-sectional)	1535 samples; 279 hospitals	Cylophosphamide	1.01	0.86 to 1.18	0%
5 (cross-sectional)	1535 samples; 279 hospitals	Ifosfamide	1.44	0.91 to 2.28	20%
5 (cross-sectional)	1535 samples; 279 hospitals	Methotrexate	1.00	0.55 to 1.85	0%
1 (cross-sectional)	460 samples; 83 hospitals	5-fluorouracil	1.09	0.53 to 2.23	-
1 (cross-sectional)	460 samples; 83 hospitals	Cytarabine	0.59	0.01 to 24.53	-
1 (cross-sectional)	460 samples; 83 hospitals	Gemcitabine	1.13	0.55 to 2.33	-
1 (cross-sectional)	460 samples; 83 hospitals	Irinotecan	0.44	0.03 to 6.15	-
1 (cross-sectional)	460 samples; 83 hospitals	Docetaxel	0.59	0.01 to 24.53	-
1 (cross-sectional)	460 samples; 83 hospitals	Paclitaxel	0.59	0.01 to 24.53	-
1 (cross-sectional)	460 samples; 83 hospitals	Vinorelbine	Not estimable	-	-
1 (cross-sectional)	33 samples; 4 hospitals	Multiple drugs	2.38	0.69 to 8.23	-

The mean differences in quantity of contamination for pharmacy and patient areas between CSTD and controls groups are reported in Table 2. The quantity of contamination of Cylophosphamide on surfaces in pharmacy areas was lower in the CSTD group compared with the control group. There were no other differences in quantity of surfaces contaminated between CSTD and control groups. The RR for proportion of contaminated samples in pharmacy and patient areas was calculated from only one cross-sectional study for 5-fluorouracil, Cytarabine, Gemcitabine and Irinotecan.

Table 2. Mean differences of quantity of contamination in pharmacy and patient areas

N studies	N participants/ samples	Drug	Mean difference (CSTD vs control)	95% Confidence Intervals	I ²
Outcome: quantity of contamination in surface samples from pharmacy areas					
7 (2 uncontrolled before-after; 5 cross-sectional)	1793 samples; 282 hospitals	Cylophosphamide	-49.34 pg/cm ²	-84.11 to -14.56	0%
6 (1 uncontrolled before-after; 5 cross-sectional)	1749 samples; 280 hospitals	Ifosfamide	-0.32 pg/cm ²	-6.58 to 5.94	11%
6 (1 uncontrolled before-after; 5 cross-sectional)	1749 samples; 280 hospitals	Methotrexate	-3.09 pg/cm ²	-13.80 to 7.61	0%
1 (cross-sectional)	493 samples; 83 hospitals	5-fluorouracil	256.00 pg/cm ²	-461.56 to 973.56	-

1 (cross-sectional)	493 samples; 83 hospitals	Cytarabine	-0.60 pg/cm ²	-15.67 to 14.47	-
1 (cross-sectional)	493 samples; 83 hospitals	Gemcitabine	-32.70 pg/cm ²	-102.43 to 37.03	-
1 (cross-sectional)	493 samples; 83 hospitals	Irinotecan	-18.27 pg/cm ²	-56.89 to 20.35	-
Outcome: quantity of contamination in surface samples from patient care areas					
5 (cross-sectional)	1535 samples; 279 hospitals	Cylophosphamide	-13.34 pg/cm ²	-36.01 to 9.32	0%
5 (cross-sectional)	1535 samples; 279 hospitals	Ifosfamide	3.59 pg/cm ²	-3.45 to 10.63	0%
5 (cross-sectional)	1535 samples; 279 hospitals	Methotrexate	0.10 pg/cm ²	-0.57 to 0.78	0%
1 (cross-sectional)	460 samples; 83 hospitals	5-fluorouracil	-43.90 pg/cm ²	-141.51 to 53.71	-
1 (cross-sectional)	460 samples; 83 hospitals	Cytarabine	-0.20 pg/cm ²	-0.79 to 0.39	-
1 (cross-sectional)	460 samples; 83 hospitals	Gemcitabine	0.47 pg/cm ²	-1.77 to 2.71	-
1 (cross-sectional)	460 samples; 83 hospitals	Irinotecan	-0.05 pg/cm ²	-0.15 to 0.05	-

The Cochrane review found that owing to the low quality of evidence available, no firm conclusions could be drawn about CSTDs being beneficial or harmful in addition to safe handling practices. When measuring the quantity of surfaces contaminated in the pharmacy area, Cylophosphamide contamination was reduced in the CSTD group compared with the control group. It is unclear how meaningful a decrease of 49.34 pg/cm² Cylophosphamide would be for minimising risks of adverse health outcomes, particularly when there was no significant reduction of any other cytotoxic drugs. There is continued uncertainty regarding the applicability of studies examining the effect of CSTDs in pharmacy areas to administration and patient care areas.

The systematic review and meta-analysis did have some limitations. The review excluded 29 simulation studies that looked at the effect of CSTDs when used in laboratory conditions, rather than real working practice conditions. Simulation studies comprise a large proportion of the evidence base that finds CSTDs to be effective. Their exclusion from the review, but acceptance for purposes of device performance testing and certification, including that of engineering control technologies under which CSTDs are classified, is a point of contention.

With a view to capturing all relevant information within this Evidence Synthesis, simulation studies which were not included within the Cochrane review are presented here. The majority of simulation studies did not investigate leakage and exposure but other parameters such as microbiological contamination and preparation time. Table 3 summarizes the main findings from a sub sample of simulation studies that are relevant to this Evidence Synthesis.

There is also some doubt surrounding the assumed homogeneity of performance and efficacy amongst different CSTDs as they can be sub classified by the types of containment and mechanical interfaces involved. For example, authors may have included devices described by the manufacturer as a 'closed-system transfer-device', yet only the EQUASHIELD, HALO and PhaSeal meet the performance standards set by NIOSH for vapour containment.¹³ Another study found that only the EQUASHIELD and PhaSeal met the NIOSH vapour containment performance standards.¹²

Table 3. Simulation studies excluded from the Cochrane review but deemed relevant to this Evidence Synthesis

Author	Study title	Main finding(s)
De Ausen <i>et al</i> (2013)	Leakage from closed-system transfer devices as detected by a radioactive tracer.	The volume of leakage was significantly less with PhaSeal than with OnGuard and ChemoClave when pharmacists and pharmacy technicians used the three CSTDs and (99m)Tc as a tracer.
Favier <i>et al</i> (2012)	The PhaSeal® system: impact of its use on workplace contamination and duration of chemotherapy preparation.	Major reduction in the contamination of the work environment when using the PhaSeal® system for drug preparation. Reduction rates higher than 93% were obtained, whatever the type of other protection used.
Garrigue <i>et al</i> (2016)	Safe Cytotoxic Drug Preparation Using Closed-system Transfer Device: Technical and Practical Evaluation of a New Device (Vialshield/Texium) Comparatively to a Reference One (Phaseal)	Fluorescein leakage assessment confirmed that PhaSeal is a performing closed system with a dry connection. Spike Swan showed fluorescein leaks. Fluorescein drops were visible on the connection sites of the VialShield/Texium.
Gomez-Alvarez <i>et al</i> (2016)	Evaluation of two closed-system drug transfer device in the antineoplastic drug elaboration process	Local contamination was reduced 21% and 75% in closed-systems Icu Medical® and Care Fusion® respectively. For the Care Fusion® closed system, local contamination was significantly lower than the standard system to the vial, syringe and final package, while Icu Medical® closed-systems only was significantly lower in the connection to the vial.
Gonzalez Haba-Pena <i>et al</i> (2016)	Comparative study of preparation of hazardous drugs with different closed-system drug transfer devices by means of simulation with fluorescein.	A syringe connector is needed to guarantee a closed system. Anchoring spikes did not show higher advantages as compared with supporting vial spikes. Fleboflex® solutions with Luer bags were more efficient than ChemoCLAVE® and show similar safety. However, connections of these closed systems were not leak-tight.

Jorgenson <i>et al</i> (2008)	Contamination Comparison of Transfer Devices Intended for Handling Hazardous Drugs	Titanium tetrachloride was selected to simulate the escape of vapor from each product. The second evaluation concentrated on the “dry connections” between the vial and syringe during drug preparation and between the syringe and access port during administration. Fluorescein sodium was selected to simulate contamination with the dry connections between the vial and syringe and between the syringe and access port. The two studies found that only one of the five devices tested met the criteria or definition of a CSTD.
Le Garlantezec <i>et al</i> (2011)	Evaluation of the performance of transfer devices in a closed system using a radioactive solution of [(99m)Tc]	Teva® and Cardinal® devices were more efficient according to the ability to transfer one solution from a vial to another one with a low dead volume and low-level contamination in and around the manipulation area.
Nygren <i>et al</i> (2008)	Spill and Leakage Using a Drug Preparation System Based on Double-Filter Technology	The handling system, Tevadaptor™, was tested using a modification of an independent test method based on the use of Technetium m-99 as tracer substance. The test results showed that the spill was <100 nl for all 75 preparations and was <1 nl for 70 of the preparations. This is comparable with other tested drug-handling system, e.g. isolators, PhaSeal™. The test shows that the Tevadaptor drug-handling system has similar performance as drug-handling systems regarded as closed systems.
Quereau Lamerie <i>et al</i> (2012)	Multiple-test assessment of devices to protect healthcare workers when administering cytotoxic drugs to patients	No cytotoxic contamination was detected when using Phaseal, Tevadaptor or the Clave extension set with Spiros, Pchimx with a cap or Connect Z devices. For mechanical tests, all devices complied with the norm. The ergonomic study revealed differences between the devices for potential cytotoxic contamination risk only, but not for handling.
Rupp K, Tyler T. (2017)	Assessment off a new closed system drug transfer device at 17 U.S. cancer centers.	In total, 204 wipe samples were collected and analyzed for cyclophosphamide and fluorouracil by an independent laboratory. Cyclophosphamide and fluorouracil were detected in 74% of the baseline wipe samples, with levels of contamination ranging from less than the limit of detection to 3.88 ng/cm ² and 0.36 ng/cm ² for fluorouracil and cyclophosphamide, respectively. After the simulated administration, only 2% of the wipe samples were at or above the level of detection, with 0.003 ng/cm ² for fluorouracil and 0.002 ng/cm ² for cyclophosphamide. This difference in samples demonstrated a statistically significant difference when comparing baseline to the closed system drug transfer device (P <.001)
Vyas <i>et al</i> (2016)	Evaluation of a closed-system cytotoxic transfer device in a pharmaceutical isolator	Surface contamination from cytotoxic infusion preparation in a pharmaceutical isolator was significant and could transmit cytotoxic residues to patient and public areas via infusion surfaces. The frequency and amount of contamination were reduced by the CSTD.

Cost effectiveness

CSTD usage could potentially be associated with cost savings, through a reduction in the cost of administering drugs, or through lower levels of drug wastage from multi-dose vials or a combination of both.

Six studies which explored CSTD-related cost savings were identified, five of which were included in the Cochrane review.⁵ None were UK based or controlled. Since none of the studies included personnel costs (i.e. time spent on preparation and administration expected to be lower with CSTD) as part of their calculations, any savings were based on the potential of CSTDs to maintain drug sterility for longer and reduced wastage through total extraction of liquid contents from vials. The Cochrane review concluded that it was difficult to ascertain whether CSTDs lead to cost savings due to variability in the methods for calculating costs, and because the results of individual studies varied from a potential cost saving of \$642,656 (approx. £506,000) to an additional cost of \$221,818 (approx. £175,000).

Calzado-Gomez et al (2017) compared the volume of drug loss during preparation and the equipment costs of eight different CSTDs.²⁰ The cost of drug loss was calculated by first measuring the differences in weight between full and empty vials using the different CSTDs, and then applying the 'cost per ml lost' to utilisation data for 71 different preparations used within one year at a Spanish hospital. The Care Fusion Smartsite[®], Care Fusion VM04[®], and the BD-Phaseal[®] systems had the least volume of drug loss in 10 ml, 20 ml and 30 ml vials respectively. Although the two Care Fusion systems had the lowest equipment costs, the most cost-effective CSTD based on annual usage was the BD Phaseal[®], with an annual budgetary reduction of €255,668 (approx. £229,000).

Budget impact

Based on the available data, it is not possible to estimate the financial impact of CSTD implementation across Scotland. This owes largely to the uncertainty surrounding a number of variables affecting the choice of CSTD equipment across NHS Boards or cancer centres. The choice of device may depend on factors such as preferences over ease of use, compatibility with other equipment (e.g. infusion pumps), or features of the individual components involved.

Local variation in CSTD utilisation is expected to be contingent on several factors such as: the average number of chemotherapy cycles per patient, the number of appointments per cycle, proportion of appointments for multiple IV regimens, installation of CSTD infusion pumps in wards, and the number of treatments which include a drug bolus. These uncertainties make it challenging to predict total scale up costs.

It is acknowledged that a proportion of spend on CSTD devices could potentially be offset through savings made from reduced usage of other protective equipment and disposable items. A recent business case from NHS Lothian Cancer services, where a four week trial of the ICU Medical CSTDs in two cancer wards was conducted, found that nearly 90% of the

total spend on CSTDs was offset (C McKinnel, Lead Nurse Chemotherapy Quality Oncology, NHS Lothian. Personal Communication, 23 July 2019). This owed largely to a substantial reduction (or elimination) in use of consumables such as gloves, aprons and saline bags. The likelihood of such savings being made will depend on local variations in good practice and adherence protocols.

Organisational issues/context

Clear guidelines to set standards for safe handling of PPE and use of engineering controls are essential to reduce the risk to staff who prepare and administer cytotoxic drugs but can only be effective if there is adherence to recommended practice. Four cross-sectional survey studies were identified which described nurses' adherence to safety guidance and perceived barriers to engaging in safe practice.

The studies illustrated that there is variation in adherence to recommended practice. Self-reported practice of always wearing chemotherapy gloves, washing hands after removing gloves, and replacing damaged gloves immediately when contaminated was very high among nurses.^{21, 22} A very high proportion of nurses also reported always using a needleless system and luer-lock device for needleless systems, syringes, needles, infusion tubing and pumps.²¹ In another study, nurses reported that a needleless system was used 41% of the time.²² Self-reports of always wearing tight gowns with closed front and cuffs were moderate (58-62%).^{21, 22}

Where they were available, adherence to additional safety measures was reported to be at a low level. One study found that only 25% of nurses reported using CSTDs and another study reported 45% of nurses always use CSTDs.^{21, 22} It has been reported that a high proportion of nurses never wear double chemotherapy gloves (59-62%), never wear eye and face protection (78-85%), never wear a respirator (91%-95%), never wear shoe covers (93%) and never wear head covers (94%).^{21, 22}

The most frequent barriers for non-compliance with safe handling practice were: the belief that skin exposure was minimal; that safe handling procedures were not part of the protocol; PPE was not readily available in work areas or provided by employers; that other staff members do not use PPE; that nurses perceive that PPE is uncomfortable and too hot to wear; and that PPE interferes with job duties.²¹⁻²⁴

Higher self-efficacy (confidence in ability to carry out behavior) for using safe handling is related to engaging in more precautionary behaviours.^{23, 24} Higher perceived risk, more perceived barriers and higher perceived conflict of interest are correlated with lower engagement in precautionary behaviours.^{23, 24} Higher workplace safety climate and interpersonal influences were correlated with more precautionary behaviours.^{23, 24} The number of patients treated per day is an important determinant of whether or not safe handling was adhered to. The higher the number of patients treated, the less likely it was for nurses to adhere to safe handling practice.^{23, 24}

Identified research gaps

Conducting controlled before-after studies, uncontrolled before-after studies, case-control studies, cohort studies and interrupted time series to assess exposure in healthcare professionals would improve the quality of the evidence base. Studies that evaluate short- and long- term health outcomes of healthcare workers who regularly use CSTDs to administer cytotoxic drugs are still required, as are studies investigating the impact of progressive changes in practice on exposure levels (e.g. introduction of central production). This would improve the quality of the evidence base and help support clearer guidance on the safe use of CSTDs.

The evidence base could also benefit from evaluating CSTDs using the NIOSH Laboratory Test Performance Protocols for CSTDs.^{25, 26} Studies conducted in the UK would improve the applicability of the evidence base to NHSScotland.

Conclusion

There is a lack of good quality evidence on the clinical effectiveness of CSTDs. The evidence on clinical effectiveness is limited to one moderate quality Cochrane Review that included 23 low quality observational studies, all of which were in non-UK settings. The quantity of surfaces contamination with Cylophosphamide was reduced in pharmacy areas in CSTD groups compared to control groups. However, the clinical importance of this reduction is unknown. The PhaSeal and EQUASHIELD demonstrated the greatest efficacy compared with other commercial CSTDs.

Four other studies described guidelines for safe handling of hazardous drugs that recommended implementation of training, PPE, CSTDs, medical surveillance and other safety measures. Despite the lack of good quality evidence, these measures were recommended by experts on the basis that the risk of harm from cytotoxic drugs was deemed unacceptable. Adherence to safe handling practice beyond wearing chemotherapy gloves, such as wearing double chemotherapy gloves, wearing eye and face protection and using CSTDs may vary across different centres. Some factors, including higher perceived risk of exposure, clear safe handling protocols, higher self-efficacy, a workplace climate that promotes safety, and lower workloads, increase the likelihood of engaging in safe handling practice.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

The process for producing evidence synthesis has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on

www.healthcareimprovementscotland.org

References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network www.knowledge.scot.nhs.uk, or by contacting your local library and information service.

A glossary of commonly used terms in Health Technology Assessment is available from htaglossary.net.

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